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Multivariate methods for genetic association testing for immune traits in maternal pig breeds

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“All Models are wrong, but some are useful.”

George E. P. Box

Dedicated to my grandmother Nina

Meiner Großmutter Nina

Abstract

In pig breeding immune traits are considered to serve as potential biomarkers for pig's health-competence. A limited number of published studies indicate medium to high heritabilities (h^2) for several immune traits. Genetic variance and covariance components of immune traits were estimated in chapter 3 to examine the quantitative genetic background of these traits. For this purpose, blood samples were collected for Landrace (LR) (n=611) and Large White (LW) (n=544) piglets and their biological dams (n=298, 272, respectively) in a short period around birth. Immune profile was covered by 22 traits including immune cells, red blood cell characteristics, and cytokines. Maternal impacts on piglet's immune profile were investigated as well as close phenotypic and genetic-based relationships in a multivariate approach. Immune traits showed low to high breed-specific h^2. Strong positive genetic correlations (r_g) were estimated among red blood cell characteristics (0.77 to 0.99) as well as among cytokines (0.48 to 0.99). The litter impact on piglet's immunity was examined and strengthened already observed breed differences. In LR h^2 (0.22 to 0.15) and litter effect (c^2) (0.52 to 0.44) for IFN-γ decreased after statistical consideration of maternal impact. In LW a decrease in h^2 (0.32 to 0.18) for IFN-γ and an increase in c^2 (0.54 to 0.56) was observed.

The development of selection strategies requires deep investigations with appropriate statistical genome-wide association study approaches to explore the joint genetic foundation for health biomarkers. Consideration of previously established r_g between immune traits were used to identify pleiotropic genetic markers. For this reason, several univariate (uv) and multivariate (mv) genetic association testing methods were applied on immune traits in chapter 4. Mv GWAS approaches detected 647 associations for different mv immune trait combinations that were summarized to 133 quantitative trait loci (QTL). SNPs for different trait combinations (n=66) were detected with more than one mv method. Most of these SNPs are associated with red blood cell related immune trait combinations. With uv methods shared markers were not observed between the breeds, whereas mv approaches were able to detect two conjoint SNPs for LR and LW.

Most immune traits are heritable and are promising to cover global breed-specific immunocompetence in animals. With uv and mv approaches, the joint genetic background of immune traits was demonstrated by revealing immune relevant potential candidate genes. Investigated traits can be used to gain a breeding-based health improvement in piglets whereby special attention has to be laid on the relationship between immunocompetence and further performance characteristics.

Zusammenfassung

In der Schweinezucht werden Immunmerkmale als potenzielle Bioindikatoren der Gesundheitskompetenz betrachtet. In einer begrenzten Anzahl von Veröffentlichungen wurden für eine Reihe von Immunmerkmalen mittlere bis hohe Heritabilitäten (h^2) geschätzt. Im Rahmen dieser Arbeit wurden, wie in Kapitel 3 beschrieben, genetische Varianz- und Kovarianzkomponenten geschätzt. Dazu wurden in einem kurzen Zeitraum um die Geburt Blutproben von Landrasse (n=611) und Large White (n=544) Ferkeln und ihren biologischen Müttern (n=298 bzw. 272) entnommen. Das Immunprofil wurde durch 22 Merkmale einschließlich Immunzellen, Erythrozyten-Charakteristika und Zytokinen abgedeckt. Die Auswirkungen der Mutter auf das Immunprofil des Ferkels sowie vorherrschende, enge, phänotypische und genetische Beziehungen wurden in einem multivariaten (mv) Ansatz untersucht. Immunmerkmale zeigten niedriges bis hohes rassespezifische h^2. Es wurden starke positive genetische Korrelationen (r_g) zwischen den Merkmalen der roten Blutkörperchen (0,77 bis 0,99) sowie zwischen den Zytokinen (0,48 bis 0,99) geschätzt. Der Wurfumwelteffekt (c^2) auf die Immunität der Ferkel wurde untersucht und verstärkte bereits beobachtete Rassenunterschiede. In LR betrugen die h^2 (0,22 bis 0,15) und c^2 (0,52 bis 0,44) für IFN-γ nach statistischer Berücksichtigung des maternalen Effekts. Bei LW wurde eine Abnahme von h^2 (0,32 bis 0,18) und eine Zunahme von c^2 (0,54 bis 0,56) beobachtet.

Die in Kapitel 3 festgestellten r_g wurden zur Identifikation von pleiotropen, genetischen Markern genutzt. Aus diesem Grund wurden verschiedene univariate (uv) und mv genetische Ansätze angewendet. Deren Anwendbarkeit und Aussagefähigkeit wurden in Kapitel 4 untereinander empirisch verglichen. Mv Ansätze detektierten 647 Assoziationen für verschiedene Immunmerkmalskombinationen, wovon 66 SNPs mit mehr als einer mv Methode nachgewiesen werden konnten. Mit uv Methoden wurden keine gemeinsamen Marker zwischen den Rassen beobachtet, während mv Ansätze zwei gemeinsame SNPs zwischen LR und LW aufweisen konnten.

Für die meisten Immunmerkmale wurde eine moderate bis hohe, rassespezifische h^2 festgestellt. Mit uv und mv Ansätzen konnte der gemeinsame genetische Hintergrund von Immunmerkmalen untersucht und potenzielle, immunrelevante Kandidatengene aufgedeckt werden. Immunmerkmale können zu einer züchterischen Verbesserung der Gesundheit von Ferkeln beitragen. Hierbei sollten allerdings die Beziehungen der Immunmerkmale zu weiteren Leistungsmerkmalen in Betracht gezogen werden.

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List of abbreviations

AAMP	Angio associated migratory cell protein
AGT	Aangiotensinogen
APP	Acute-Phase-Protein
BAS	Basophils
BFN	Biological functional network
BIMBAM	Bayesian linear regression uv approach
BLUP	Best linear unbiased prediction
BN	Bayesian network
c^2	Common litter effect
CCA	Canonical correlation analysis
CRISPR/Cas9	Clustered regularly interspaced short palindromic Repeats/CRISPR-associated protein 9
DNA	Desoxyribonucleic acid
DTH	Hypersensitivity
EOS	Eosinophils
FDR	False discovery rate
GV	Genetic variant
GWAS	Genome-wide association study
h^2	Direct genetic effects/heritability
HAP	Haptoglobin
HEWL	Hen egg white lysozyme
HIR	High immune response
HMG	Hemoglobin
HMT	Hematocrit

HWE	Hardy-Weinberg equilibrium
HYSS	Herd-year-season-sex effect
IBS	Identity-by-state
IFN	Interferone
IgG	Immunoglobulin G
IL	Interleukin
LIR	Low immune response
LR	Landrace
LW	Large White
LYM	Lymphocytes
m^2	Maternal genetic effect
MAF	Minor allele frequency
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MHC	Histocompatibility complex
MON	Monocytes
mv	Multivariate
mvBIMBAM	Mv Bayesian linear regression approach/ mv Bayesian imputation-based association mapping
NEU	Neutrophils
NK	Natural killer cells
PC	Principal component
PCA	Principal component analysis
PLT	Platelets
PMN	Polymorphonuclear neutrophils

PNDK	Paroxysmal nonkinesiogenic dyskinesia domain containing
PRRSV	Porcine reproductive and respiratory syndrome virus
PRRSV	Porcine respiratory syndrome virus
QTL	Quantitative trait loci
RBC	Red blood cells
r_g	Genetic correlation
r_p	Phenotypic correlation
SLA	Swine leucocytes antigen
SNPs	Single nucleotide polymorphisms
TATES	Meta analysis/ Trait-based association test that uses extended Simes procedure
TLL1	Tolloid like 1
TLR	Toll-like receptors#
TMBIM1	Transmembrane BAX inhibitor motif containing 1
TNF	Tumor necrosis factor-α
uv	Univariate
WBC	White blood cells

Chapter 1. General introduction

1.1. Challenges in sustainable pig breeding

The requirements for the management of animal products are complex and challenging. This includes the economic point of view, legal constraints, demands of the consumer and understanding of the stock farmers. One important challenge for animal scientists is to reconcile the interests of various actors from today's perspective. The systems of livestock production are currently being massively criticized. In 2015, 83% of Europeans believed the welfare of farmed animals should be better protected than it is now (European Commission, 2017). Animal breeding research can provide a sustainable contribution to improve the livestock production systems regarding profitability, human nutrition, environmental load, resource management, and animal welfare. This results in a need to design genetic strategies that support the balance between the single factors. Genetic improvement of production traits is desirable, but possible genetic antagonisms between production traits and any other characteristics require specific attention.

Since improved data recording and processing (Best Linear Unbiased Prediction (BLUP), computing power, biotechnological approaches) become more effective, strong and sufficient focus was set on production traits in pig's selection. Initially, major progress was seen in carcass traits, growth rate, and meat quality while reproductive characteristics had little attention (Merks 2000). As pig production increased, improvements in litter size were achieved through better management, nutrition and implementation of genetic selection for litter size. This course of action led to a lack of balance between fitness, animal welfare and production traits (Prunier et al. 2010). The selection for high leanness, feed efficiency, and litter size may have resulted in correlated responses in the abilities of pigs to overcome immune challenges (Rauw et al. 1998; Knap and Rauw 2008). The reproductive endocrine system is directly impaired as a result of resource-demanding, adverse environmental conditions that compromise immune response traits. As a consequence, the adaptive ability to deal with intense stress is significantly (Knap and Rauw 2008). Therefore, nowadays breeding progress is emphasized on increase in performance, improving the quality of the animal product, health status, as well as environment and resource compatibility (Merks et al. 2012).

Until now, the mechanisms involved in porcine immunity have not been fully understood. Quantitative information on the genetic variation of immune related health traits within genotypes is needed. Literature information for unchallenged pigs is scarce because immune traits are difficult to measure and to quantify on a large number of animals with various genetic backgrounds. Besides, immune traits are quantitative traits where the expression is influenced by the genome and environmental effects. Additionally, many gene locations are involved in

the expression of quantitative traits. Usually, such complex traits are characterized by a low heritability (Mangino et al. 2017). Maintaining balanced homeostasis requires a high level of interaction between the distinct immune traits. The genetic relationship between the traits and to performance characteristics needs to be assessed continuously in order to reveal the genetic mechanism. The uncovered common genetic basis can help to understand the system governing the balance of immune cells in peripheral blood of protective immunity. As a consequence, it is important to develop suitable statistical analysis methods to explore such complex relationships.

Multivariate models are commonly used to estimate phenotypic, genetic and environmental variances, covariances, and correlations for multiple traits in animal breeding programs. In cases where traits are correlated, a multivariate model can gain more accuracy than a univariate model benefiting from connections in the data due to residual covariance between the traits. Furthermore, traits with low heritabilities benefit more when analyzed together with traits with high heritabilities in a multivariate analysis (Isik et al. 2017). Whereas multivariate methods are common in estimating genetic parameters or breeding values these methods are rarely used in genome-wide association studies (GWAS). Against this background it should be particular worthwhile to investigate the applicability and meaningfulness of multivariate methods for the statistical analysis of immune traits.

1.2. Scope of this thesis

The objective of this thesis was to analyze and discuss the prospects of application of multivariate methods paying special attention to the presumed low heritable and complex porcine immune traits. To achieve this goal, genetic parameters of immune traits were estimated. In order to examine the impacts of the maternal effects on the offspring's immunity genetic and environmental influences are taken into consideration during the statistical analysis. As a way to identify pleiotropic genetic markers associated with immune traits, multivariate approaches for genome-wide association tests were applied.

Chapter 2 introduces the genetic foundation of porcine immune traits. The benefit of the immunocompetence of the piglet and the dam are discussed. The application of univariate and multivariate genome-wide association methods to analyze the genetic foundation of desired traits is introduced.

This thesis includes two studies: Figure 1 gives an overview of all performed analysis steps in the studies.

In the first study, in chapter 3 the quantitative genetic background of immune traits was conducted. Data sets of purebred LR and LW subset pig populations from 2010 to 2017 were

provided by the German breeding organization Bundeshybridzuchtprogramm (BHZP) GmbH. From each litter, one male and one female piglet, as well as, their biological dam were chosen for blood sample collection. Blood samples of piglets were collected on average around 45 days after birth. From the biological dams of all phenotyped piglet's blood was sampled in a short period *postpartum* (7 days). Complete blood count, haptoglobin and cytokines were examined as immune traits to characterize immunocompetence. In order to elaborate on the genetic potential for the dam's immunocompetence, genetic and environmental influences are taken into consideration during the analysis. The genetically correlated immune traits and networks are accessed through the application of principal component analysis.

In the second study, in chapter 4, different genome-wide association approaches were used to identify genes and genetic markers for immune traits. The detection of pleiotropic single nucleotide polymorphisms in immune traits of piglets from two maternal lines was carried out using multivariate approaches besides a univariate frequentist and Bayesian approach. We empirically compared the results obtained using principal component analysis, canonical correlation analysis, meta-analysis, and a multivariate Bayesian linear regression approach with those obtained using univariate tests.

The general discussion included in chapter 5 aims to debate the gain of knowledge and further challenges due to the application of multivariate approaches on immune traits. Moreover, a possible way to implement immune traits into selection strategies is presented.

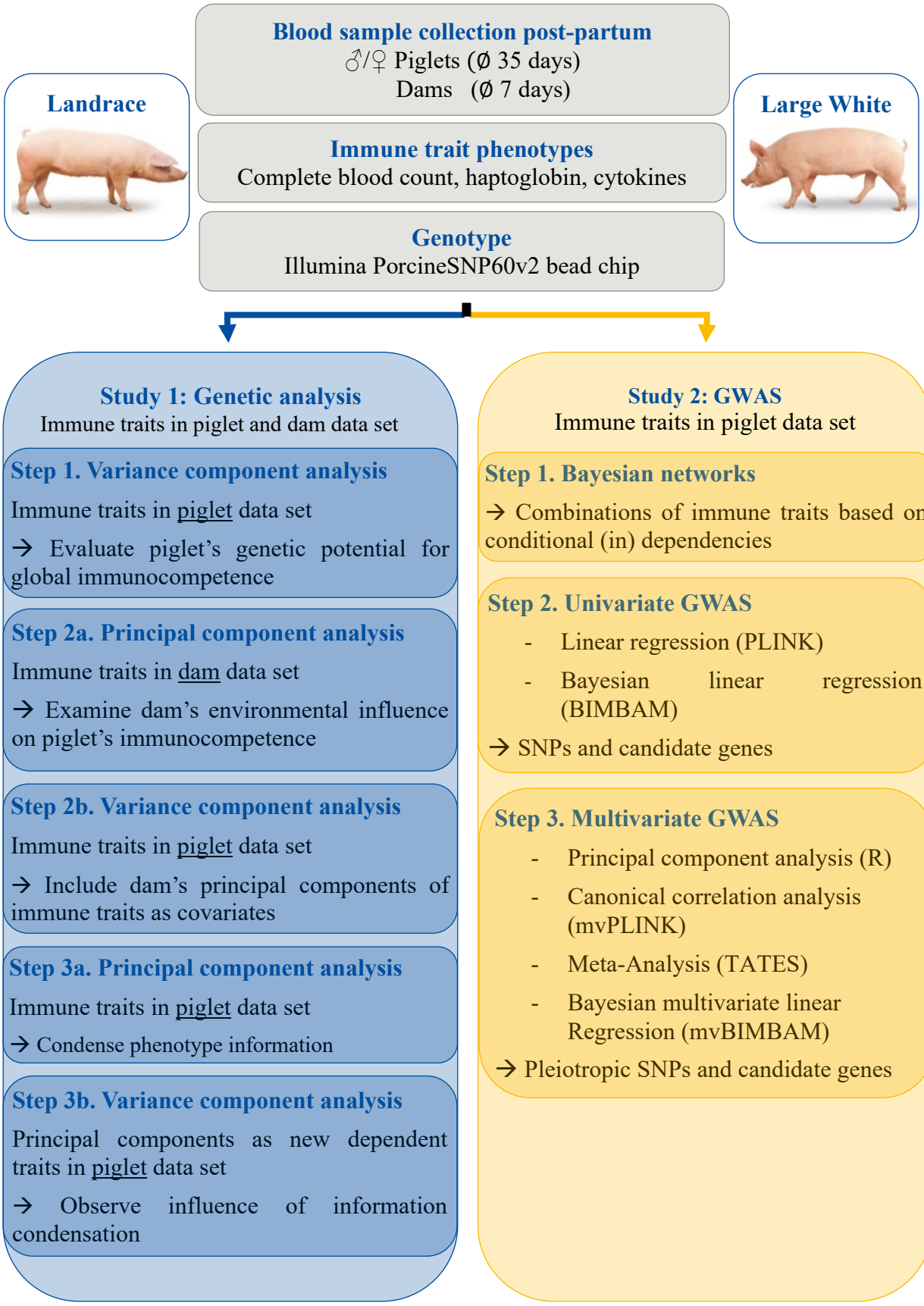

Figure 1: Workflow of the studies included in this thesis

GWAS= Genome-wide association study, SNP= Single nucleotide polymorphism

Chapter 2. Literature review

2.1. Immunocompetence

The animal production sector is actively searching for appropriate solutions to the issue that new phenotypes are needed due to the requirements of pork value chain partners and consumer expectations. Sometimes there seems to be a disconnect between selection for efficiency of production and animal welfare. Selection for high production efficiency may result in undesired correlated responses in other traits for example litter size and piglet survival (Rauw et al., 1998). The motivation is to avoid such adverse effects with different strategies. Moreover, the emergence of antibiotic resistance and society's demands for healthier, sustainable livestock production systems require specific solutions for various disciplines including animal breeding. Health-related traits can be incorporated into pig breeding programs in order to produce healthier, resilient, and disease-resistant pigs.

Direct and indirect breeding approaches can be used to improve animal robustness and disease resistance (Colditz & Hine, 2016; Knap, 2005; Viney et al., 2005; A. H. Visscher et al., 2002). Direct methods require exposure to pathogens and can therefore intend the genetic susceptibility to specific disease incidences. However, this type of method is information-intensive, time-consuming, expensive, and is considered critical against the background of animal welfare legislation. The alternative and indirect approach focuses on global animal immunocompetence. However, in this case, detailed knowledge of the different elements of immunocompetence and components of the immune system is required. Immunocompetence has been defined by Wilkie and Mallard (1999) as “the ability of the body to produce an appropriate and effective immune response when exposed to a variety of pathogens”. A more detailed definition is used by Knap and Bishop (2000) as a broad sense to indicate the capability of the host to launch an immune response of sufficient specificity and magnitude, roughly indicating the effective quality of the host's immune system. The immune system can be assessed immunologically by measuring the immune traits. Humoral and cellular components of the immune system are considered biologically relevant parameters to value immunocompetence (Viney et al., 2005; A. H. Visscher et al., 2002). It is possible to categorize these traits into innate and adaptive immunity, although there are also traits considered bridges between the two types (Tizard, 2013; Zimmerman et al., 2012).

2.2. The innate and adaptive immune systems

The immune system has two functional divisions: innate and adaptive. The innate immune response contains phagocytic cells (macrophages, neutrophils) and the production of various cytokines, chemokines, and proteins. Besides providing antimicrobial protection, they recruit cells through inflammatory processes and activate the adaptive immune system. The adaptive

immune system includes B and T cells, cytokines, and antibodies providing a pathogen-specific memory (Calder, 2007). Immune responses to infection include both innate and adaptive actions involving different cell types, mediators, and chemical agents (Figure 2) (Zimmerman et al., 2012). The immediate defensive response to the rapid destruction of invaders is the task of innate immunity. More slowly process, adaptive immunity develops when foreign antigens bind to B or T cell antigen receptors and trigger strong defensive responses. Communication within one of the immune systems as well as between the innate and adaptive immune systems is brought about by direct cell-to-cell contacts involving cell surface proteins and the production of chemical messengers (e.g. cytokines) which send signals from one cell to another. Each cytokine can have multiple activities on different cell types (Tizard, 2013). Way of example, tumor necrosis factor α (TNF-α), interleukin (IL) 1, and IL-6 are among the most important cytokines produced by monocytes and macrophages. These cytokines activate neutrophils and monocytes to initiate bacterial and tumor cell killing, increase adhesion molecule expression on the surface of neutrophils, stimulate T- and B-lymphocyte proliferation, initiate the production of other proinflammatory cytokines and acute phase protein synthesis in the liver (Calder, 2007) (Figure 2).

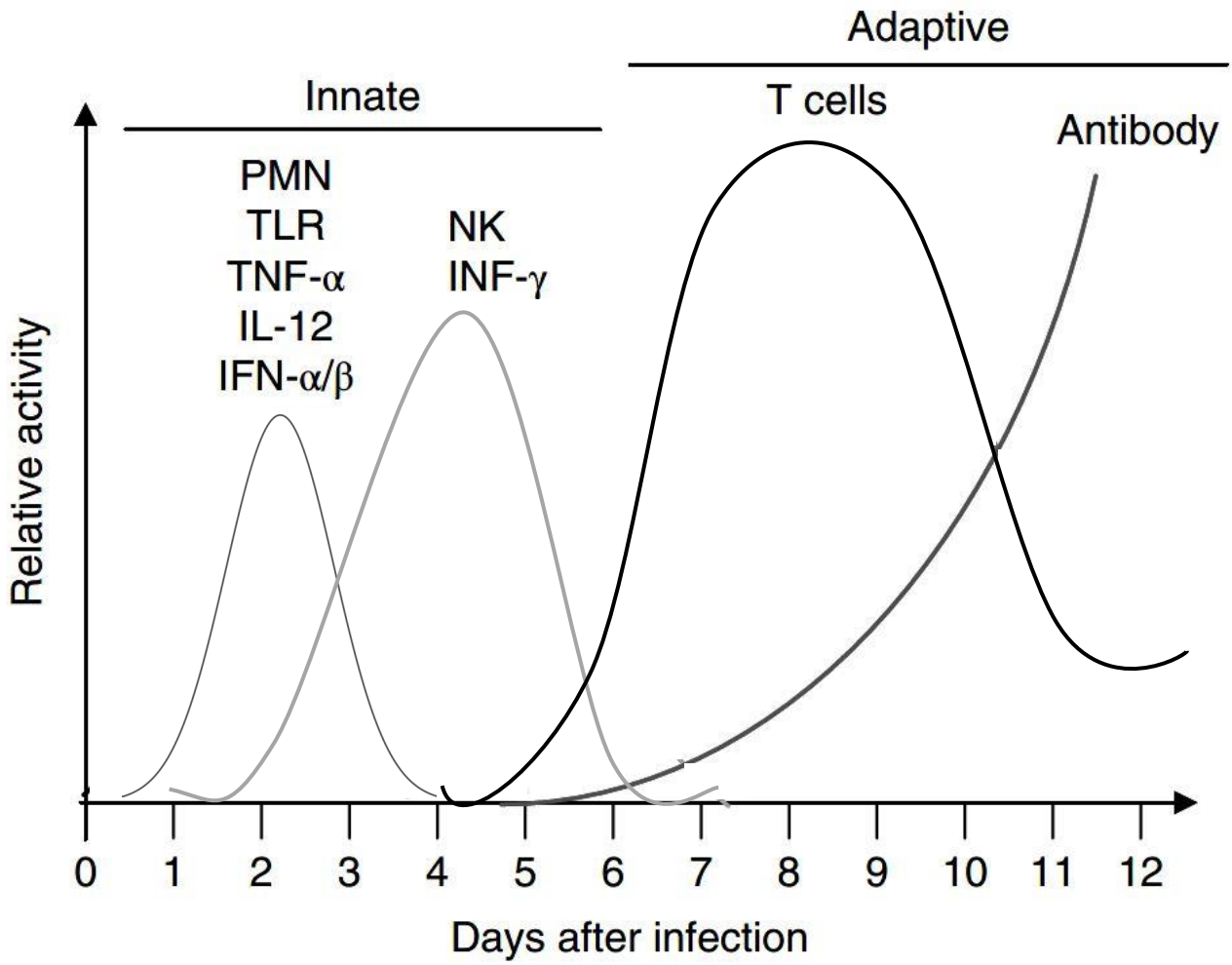

Figure 2: Mobilization of the innate and adaptive immune response (Zimmerman et al., 2012) PMN= Polymorphonuclear neutrophils, TLR= Toll-like receptors, TNF-α= Tumor necrosis factor α, IL= Interleukin, IFN= Interferon, NK= Natural killer cells

2.3. Opportunities of breeding for immunocompetence

The most important element of animal breeding is to determine the breeding goal. Breeding goals and selection indexes determine how genetic improvement should be achieved. For all species, the breeding goal has shifted from being primarily production-driven to being more balanced on a equivalent improvement of production, efficiency, health, and functional traits (Berghof et al., 2018). Piglet production is primarily determined by the number of weaned piglets per sow. In response, breeding organizations have focused on improving litter size, leading to an increase in the number of piglets born alive. This course of action resulted in higher amounts of piglet losses (Alonso Spilsbury, 2007; Baxter et al., 2013; Edwards, 2002; Grandinson et al., 2010; Hellbrügge et al., 2008; Heuß et al., 2019; Rutherford et al., 2013). Previous studies have stressed the multifaceted causes of piglet mortality between the genetic, nutritional, management, and stock persons interventions. Piglet survivability is particularly important in the period between conception and weaning. Genetically, the complex relationship between direct genetic (h^2), maternal genetic (m^2), and common litter (c^2) effects are presumed to determine individual immune system and piglet survival (

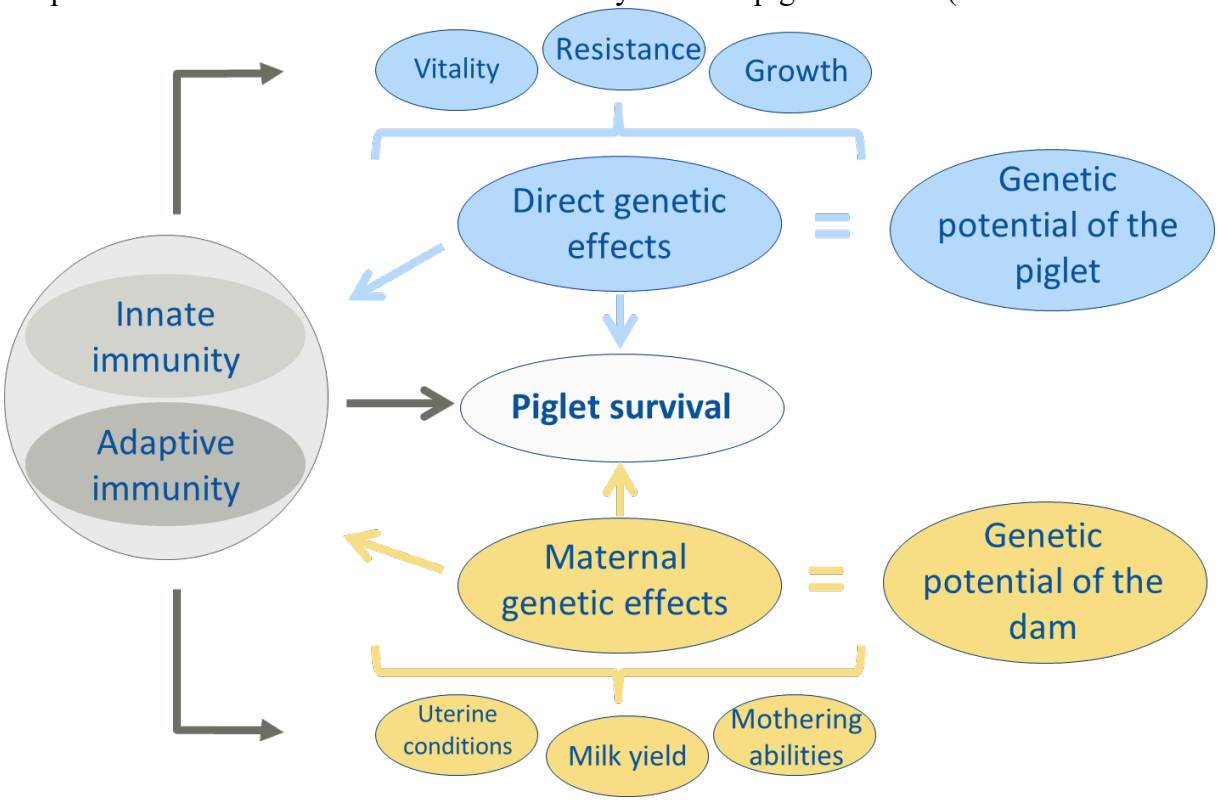

Figure 3) (Knol, Leenhouwers, & van der Lende, 2002; Roehe et al., 2010).

The selection of traits directly related to production performance has greatly improved over the past few decades in commercial pig breeds, while health-related traits have traditionally played a minor role (Ernst & Steibel, 2013). New challenges face the pig production industry due to the emergence of antibiotic resistance and society's demands for healthier livestock products (Berghof et al., 2018). As one of the most important factors contributing to productivity,

profitability, and welfare, animal health is influenced by several factors, including the co-infection of pathogens such as viruses or bacteria, environmental stressors, and management practices. To produce pig populations with more resilient, well-being and disease-resistant, health-related traits have become an emerging and challenging development in pig breeding programs (Cheng et al., 2014). To enhance animal robustness and disease resistance, breeding approaches have mainly focused on direct and indirect methods (A. H. Visscher et al., 2002; P. M. Visscher et al., 2012). To target the genetic resistance/susceptibility to specific diseases, direct methods usually require exposure to the infectious agents (Knap & Bishop, 2000).

There are several challenges associated with this approach, including cost, time, animal welfare, and information requirements. It is possible to determine the global immunocompetence of animals without signs of infection using an indirect approach, but comprehensive knowledge of the different components of the immune system is required (Knap & Bishop, 2000; A. H. Visscher et al., 2002). The immunocompetence of an individual can be measured based on immune traits as these traits are considered biologically relevant (A. H. Visscher et al., 2002). Hence, genetic markers that link health-related traits to disease resistance and robustness may contribute to a proper breeding of pigs.

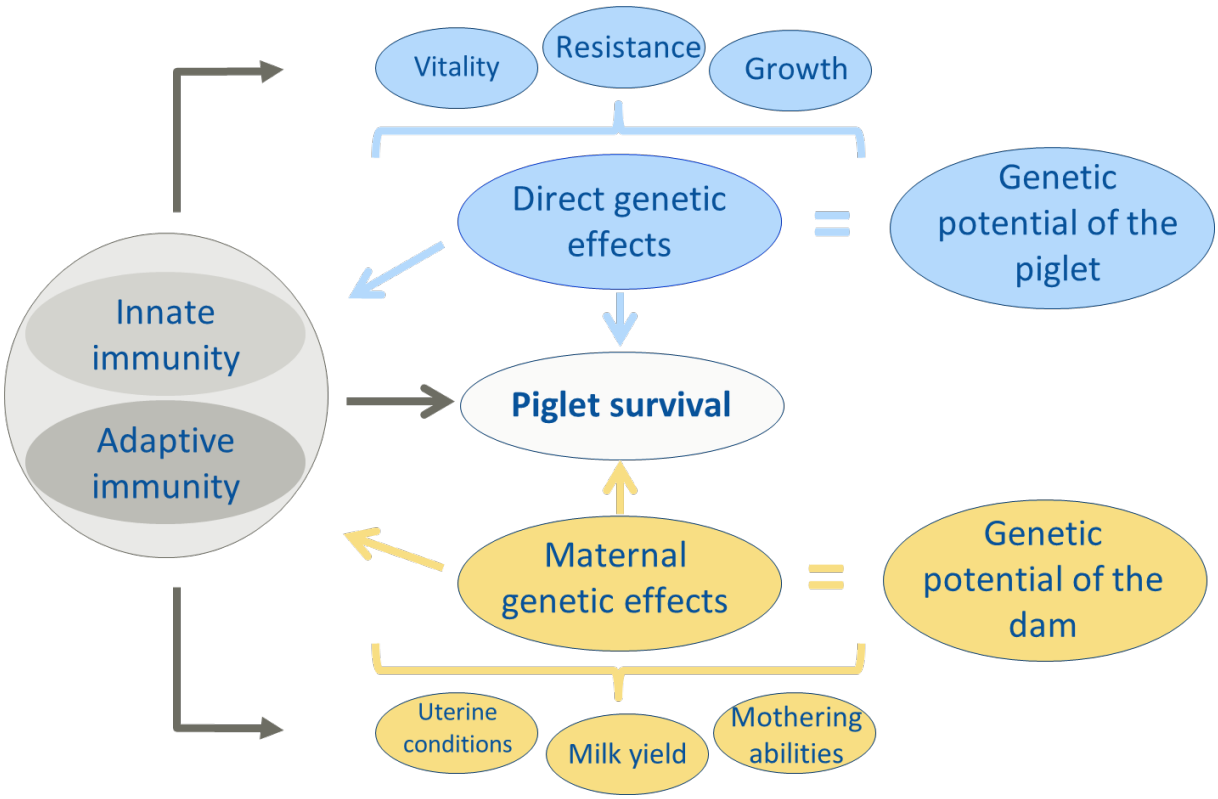

Figure 3: Presumed network of immunity and piglet survival (modified according to Roehe et al. (2010) and Heuß (2019)

The genetic potential of piglet survival at the piglet's level can be described as h^2 for this trait (Roehe et al., 2010). The genetic capability of the dam to rear vital piglets and contribute to piglet survival is represented as m^2 (Knol, Leenhouwers, & van der Lende, 2002; Roehe et al., 2010). It refers to an inheritance pattern for certain genes in which the genotype of the mother directly determines the phenotype of her offspring (Brooker, 2012). Furthermore, genetic effects can simultaneously influence the immune system and therefore, would have an indirect impact on piglet survival. Quantitative genetic studies of piglet survival traits at the sow or piglet level showed mostly low h^2 and considerable environmental influence (Heuß, 2019).
Immune-related traits can be used as further biomarkers for general immunocompetence and piglet survival. To reach that goal, relationships within individual components of the immune system and the contribution of the immune system to piglet survival as well as further performance characteristics have to be well examined.

2.4. Fetal immunity in pigs and maternal genetic potential for immunocompetence

All components of the innate and adaptive immune systems of the pig develop in utero and are functional at birth. However, they are less efficient than in an adult pigs (Hammerberg et al., 1989). Since the newborn piglet has not yet been exposed to an antigen, humoral and cell-mediated immune responses to infectious agents and stressors have to be developed after exposure to antigens. After exposure, it will take seven to ten days for a primary antibody or cell-mediated immune response to develop (Zimmerman et al., 2012). During this critical period of susceptibility, resistance to infection depends on passive-mediated immunity transferred from the sow to the piglet via colostrum. Neonatal pigs have been shown to absorb colostral lymphocytes from their intestinal tract into the bloodstream (Tuboly et al., 1988; Williams, 1993). After 24 hours absorbed cells derived from colostrum were found in the liver, lungs, lymph nodes, spleen, and gastrointestinal tissue. Their direct functional impact on the piglet's immune system is not fully understood, yet. However, piglets that had absorbed the colostral lymphocytes had higher lymphocyte blastogenic responses to mitogens than control piglets (Williams, 1993). The mechanism of how the passively transferred lymphocytes transmit clinically significant cell-mediated or antigen-specific immunity from the sow to the piglet is not well examined, yet.

The epitheliochorial placenta in the sow prevents the transfer of maternal antibodies to the fetuses before birth, so piglets receive antibodies only postnatally through colostrum and milk (Matías et al., 2017). Additionally, neonates have limited ability to synthesize antibodies endogenously (Brambell, 1970). Therefore, maternal immunoglobulins, immune cells, and modulators provide a primary form of immune defense for offspring early in life. Maternal effects occur when offspring phenotype is determined not only by its genotype and environment but also determined by maternal genotype and phenotype (Kirkpatrick & Lande, 1989). Colostrum components protect neonates from disease, support immune system development, induce tolerance, immune priming, antigen neutralization, and the development of immune memory (Bandrick et al., 2008). Contrariwise, maternal-derived antibody-mediated immunity has been shown to downregulate endogenous immunoglobulin synthesis (Klobasa et al., 1981). The role of maternal cellular mediated immunity in the development of the newborn's animal immune status has remained unclear. Maternal colostral labeled cells cross the neonatal intestinal epithelium and migrate to several immune tissues (Tuboly et al., 1988). By practicing a protective effect in the digestive tract and leading to partial tolerance, they may stimulate the immune system of the newborn piglet. Although m^2 effects only influence the performance of growing pigs shortly and indirectly, they may offer opportunities for genetic improvement. Therefore, in chapter 3 the evaluation of the genetic potential of the sow for piglets' immunocompetence by estimating c^2 and consideration of the environmental impact of the dam's immune profile is further described.

2.5. Genetic foundation of immune traits

Previous genetic studies have provided knowledge about genetic differences in immune-related traits which are presented in Table 1 (Clapperton et al., 2009; Edfors-Lilja et al., 1998; Flori, Gao, Laloë, et al., 2011; Hermesch & Luxford, 2018). Heritability, as h^2 for white blood cells (WBC) (e.g. neutrophiles, lymphocytes, monocytes, eosinophils, basophils) can be characterized as moderate to high (0.40 to 0.80). Hereby, obvious breed differences should be noticed. Red blood cells (RBC) and their characteristics (mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)) demonstrate a moderate h^2 (0.41-0.62). Haptoglobin, as an acute phase protein, has scattered values of h^2 from 0.14 to 0.55. Flori, Gao, Laloë, et al. (2011) estimated low h^2 for cytokines (0.00-0.11), except IL-10 (0.35) and IL-12 (0.51). In general, innate immunity shows a slightly greater genetic variance (0.14-0.72) than adaptive immunity (0.22-0.61). Estimations of h^2 are very diverging between previous studies. Discrepancies among the described results can be caused by the number of analyzed animals or investigated breeds. Furthermore, research

designs differ in sampling periods, immune challenges, and statistical methods for variance component estimation. The genetic variability of immune traits is further described in chapter 3.

Table 1: Heritability estimates for immune-related traits found in different studies (continued)

Immune traits	**Edfors-Lilja et al. (1994)**	**Henryon et al. (2006)**	**Clapperton et al. (2008)**	**Clapperton et al. (2009)**	**Flori, Gao, Oswald, et al. (2011)**	**Mpetile et al. (2015)**	**Ponsuksili et al. (2016)**	**Bovo et al. (2019)**
n	**220**	**4204**	**500**	**606**	**443**	**518**	**591**	**843**
Breed	**Swedish Yorkshire**	**Duroc, Landrace, Yorkshire**	**Large White**	**Large White, Landrace**	**Large White**	**Yorkshire**	**Landrace**	**Italian Large White**
WBC	0.44 (0.29)	0.25 (0.05)	0.24 (0.15)	0.28 (0.11)	0.73 (0.20)	0.23 (0.19)	0.23	0.31 (0.07)
Neutrophils		0.22 (0.04)			0.61 (0.20)	0.31 (0.21)		0.24 (0.07)
Lymphocytes	0.24 (0.21)	0.24 (0.05)			0.72 (0.21)	0.15 (0.19)	0.49	0.31 (0.06)
Monocytes		0.22 (0.04)	0.52 (0.17)	0.26 (0.13)	0.38 (0.20)	0.36 (0.20)		0.15 (0.04)
Eosinophils		0.30 (0.05)			0.80 (0.21)	0.58 (0.12)		0.14 (0.06)
Basophils						0.12 (0.19)		0.19 (0.06)
Platelets					0.56 (0.19)	0.11 (0.23)	0.39	0.31 (0.06)
RBC					0.43 (0.20)	0.62 (0.25)	0.41	0.36 (0.07)
Hemoglobin						0.56 (0.13)	0.40	0.36 (0.06)
Hematocrit					0.57 (0.03)	0.06 (0.14)	0.34	0.27 (0.06)
MCV						0.47 (0.24)	0.69	0.39 (0.07)
MCH						0.37 (0.24)	0.67	0.40 (0.06)
MCHC						0.04 (0.16)	0.67	0.24 (0.06)

Immune traits	**Edfors-Lilja et al. (1994)**	**Henryon et al. (2006)**	**Clapperton et al. (2008)**	**Clapperton et al. (2009)**	**Flori, Gao, Oswald, et al. (2011)**	**Mpetile et al. (2015)**	**Ponsuksili et al. (2016)**	**Bovo et al. (2019)**
n	**220**	**4204**	**500**	**606**	**443**	**518**	**591**	**843**
Breed	**Swedish Yorkshire**	**Duroc, Landrace, Yorkshire**	**Large White**	**Large White, Landrace**	**Large White**	**Yorkshire**	**Landrace**	**Italian Large White**
IFN-γ					0.00 (0.17)			
IL10					0.35 (0.19)			
IL12					0.51 (0.20)			
IL1-β					0.12 (0.19)			
IL4					0.15 (0.18)			
IL6					0.11 (0.19)			
IL8					0.00 (0.17)			
TNF-α					0.00 (0.19)			
Haptoglobin		0.14 (0.07)		0.20 (0.11)	0.55 (0.21)			

WBC=white blood cells, RBC=red blood cells, MCV= mean corpuscular volume, MCH= mean corpuscular hemoglobin, MCHC= mean corpuscular hemoglobin concentration, IFN-γ = interferon-γ, IL= interleukin, TNF-α= tumor necrosis factor-α. The standard error is presented in parentheses

Correlations between the various players within the immune system show a complex network of associations following biological relationships. Clapperton et al. (2008) investigated the relationships between immune parameters and growth performance. Negative correlations between some of the investigated leucocyte blood cells and daily gain were found under lower health status on farms, whereas, monocytes and an acute phase protein showed a negative correlation with the average daily gain under high health conditions on farms. Genetic correlations (r_g) from Flori, Gao, Laloë, et al. (2011) are mostly weak, except between subtypes of WBC like monocytes, neutrophils, and lymphocytes (0.4). Furthermore, a positive relationship between haptoglobin and pro-inflammatory cytokines such as IL-8 and TNF-α is described by a r_g above 0.4. Moreover, genetic markers for a share of neutrophils and lymphocytes in swine are found in the same regions as quantitative trait loci (QTLs) for cytokines interferon (IFN) and IL-10 (Lu et al., 2011), indicating close genetic-based relationships between immune cells and mediators. Such interrelations provide indications for a pleiotropic genetic structure that can be further analyzed with multivariate statistical approaches as described in chapters 3 and 4.

2.6. Detection of immune-relevant QTL and genetic markers

To explore the additive genetic background of immune-related phenotypes genome-wide association studies (GWAS) and QTL mapping can be used. The basis of QTL mapping is the association between genetically determined phenotypes for quantitative traits and molecular genetic markers such as single nucleotide polymorphisms (SNPs). In this approach, the identification of QTLs at the sites of already known markers is realized (Gondro et al., 2013). Several QTL studies revealed markers for red and white blood cells (Cho et al., 2011; Edfors-Lilja et al., 1998; Gong et al., 2010; Reiner et al., 2007, 2008; S. Yang et al., 2009; Zou et al., 2008) as well as cytokine (Uddin et al., 2011) across all chromosomes.

Pig QTL Database (Hu et al., 2019) supplies information about 3236 QTLs for traits related to immune capacity and 2900 QTLs for blood parameters. These subcategories are combined into a superset of QTLs about health, which comprises 6761 QTLs. For example, MCV is placed in an overall top 17 QTL associations in the whole Pig QTL Database with 558 observed QTLs for this blood parameter. The Figure 4 demonstrates an example of a cytogenetic map for all the pig chromosomes with detected QTLs influencing the health trait and blood parameter mean corpuscular Vvlume (MCV). distribution of QTLs across all of the *Sus Scrofa C*hromosomes (SSC) illustrates the polygenic structure of immune and health-related traits.

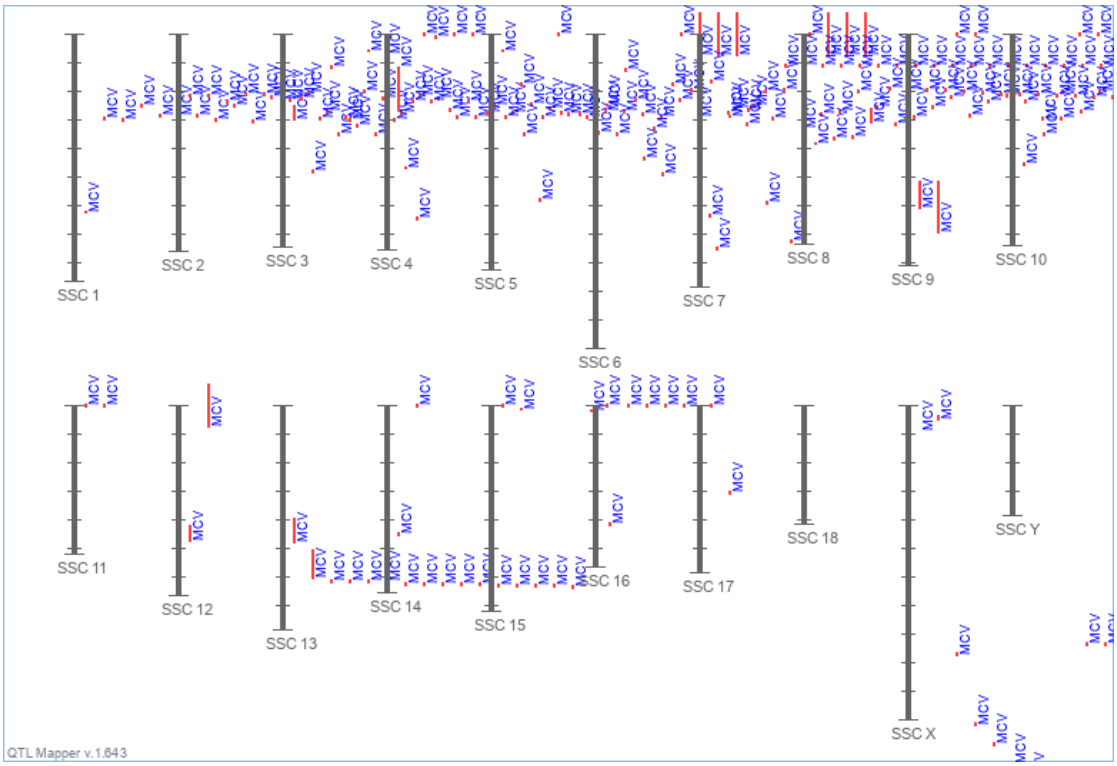

Figure 4: Cytogenetic map of the pig with all QTLs influencing mean corpuscular volume (MCV) adapted from Pig QTL Database (animalgenome.org, 2019)
Red QTL lines represent significant and light blue lines for suggestive statistical evidence

GWAS studies serve to detect variants, in particular, SNPs, at genomic loci that are associated with a complex trait in a population. GWAS are based upon the principle of linkage disequilibrium (LD) at the population level, whereby LD represents the nonrandom association between alleles at different loci. In general, loci that are placed closer together have stronger LD than loci that are far apart on a chromosome. The strength of the statistical association between alleles at two genome loci depends e.g. on their allele frequency (P. M. Visscher et al., 2012). Usually, GWAS studies are realized in three steps: (1) find study objects with sufficient variation for the phenotype of interest, (2) utilize desoxyribonucleic acid (DNA)-chip to identify alleles at adequate SNP genome positions, and (3) identify statistically different SNPs based on allele frequencies. Typically, the results of a GWAS as the statistical difference with the SNPs are visualized by a Manhattan plot. An example of such a conception is given in Figure 5, where each dot represents a genetic marker. The x-axis illustrates all porcine chromosomes and the y-axis quantifies the significance value for the detected associations.

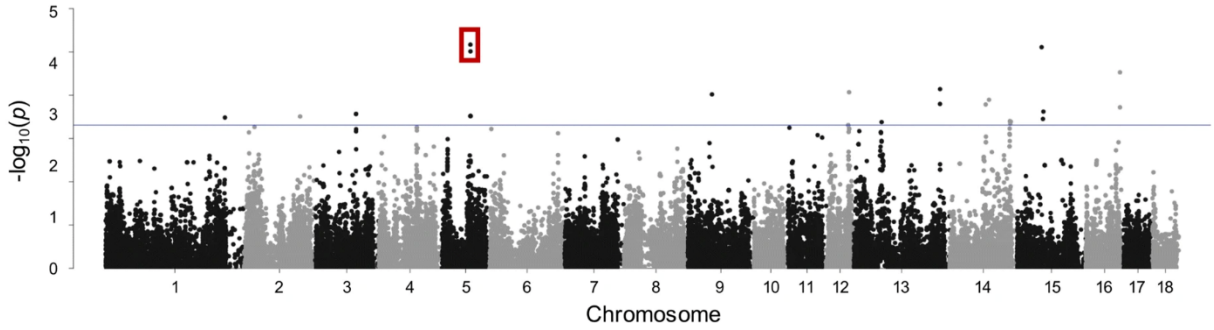

Figure 5: Manhattan plot of whole-genome association analysis for hemoglobin in Large White modified according to Dauben et al. (2021)

Manhattan plot is focusing on a putative pleiotropic region SSC5 illustrated in a red box. This region can be found between 65.8 to 65.9 Mega base pairs and include SNPs like ASGA0025952 and H3GA0016570. Genome-wide significance is computed with a Bonferroni correction with an adjusted p-value < 0.05 and is indicated by a blue line (Dauben et al., 2021)

Since 2007 the detection of loci associated within a GWAS has resulted in new biological knowledge about common diseases and other complex traits. The proportion of genetic variation explained by significant SNPs is usually very low (< 10%). However, for many diseases like type 2 diabetes, multiple sclerosis and Crohn's disease the proportion of explained genetic variance is substantial, reaching from 10 to 20%. In addition, GWAS discoveries for common diseases and complex quantitative traits have given important biological insights with direct clinical relevance. The combination of large sample sizes and stringent significance testing has led to a large number of robust and replicable associations across populations and species (P. M. Visscher et al., 2012).

Methodology development to increase the statistical power of GWAS is important for heterogeneous traits, especially in studies with small sample sizes. Previous GWAS successfully identified genetic markers as SNPs associated with different phenotypes such as RBC- and WBC-related traits (Ballester et al., 2020; Bovo et al., 2020; Bovo et al., 2019; Luo et al., 2012; Ponsuksili et al., 2016; Wang et al., 2013; F. Zhang et al., 2014; Z. Zhang et al., 2013) and cytokines like IFN and IL-10 (Dauben et al., 2021; Lu et al., 2013) (Table 2). Results of detected SNPs and candidate genes helped to clarify, verify and reveal several QTLs for immune related traits. GWAS application with univariate approaches and detected SNPs as well as candidate genes for immune traits is further described in chapter 4.

Normally, detected SNPs are distributed over the whole porcine genome and explain only a small amount of the variation for the trait of interest. In addition, immune traits are difficult to measure and quantify in a large number of animals with various genetic backgrounds. Therefore, it is crucial to develop methods where immune traits can be analyzed jointly to increase statistical power to detect genetic variants and explore the presumed biological-genetical structure.

Table 2: Overview of published porcine GWAS studies performed for hematological traits and cytokines

Reference	Inter alia traits*	Pig population	N
univariate GWAS			
Luo et al. (2012)	RBC, HMG, HMT, MCV, MCH, MCHC	LW x Minzhu F2	430
Wang et al. (2013)	RBC, HMG, HMT, MCV, MCH, MCHC, PLT, WBC, NEU, LYM, MON	Large White, Landrace, Songliao Black	421, 68, 79
Lu et al. (2013)	IFN-γ, IL-10	Landrace, Yorkshire, Songliao Black	68, 415, 79
Z. Zhang et al. (2013)	RBC, HMG, HMT, MCV, MCH, MCHC, WBC, PLT, LYM, MON	White Duroc x Erhualian F2	1912
F. Zhang et al. (2014)	ERY, HMG, HMT, MCV, MCH, MCHC, PLT, WBC, LYM	Sutai	436
Ballester et al. (2020)	RBC, HMG, HMT, MCV, MCH, MCHC, PLT, WBC, NEU, LYM, MON, EOS, HAP	Duroc	432
Dauben et al. (2021)	RBC, HMG, HMT, MCV, MCH, MCHC, PLT, WBC, NEU, LYM, MON, EOS, BAS, HAP, IFN-γ, IL-10, IL-12, IL-1β, IL-4, IL-6, IL-8, TNF-α	Landrace, Large White	534, 461
Univariate GWAS, Bayesian univariate GWAS			
Ponsuksili et al. (2016)	RBC, HMG, HMT, MCV, MCH, MCHC, PLT, WBC, LYM	Landrace	591
Univariate GWAS, Bayesian univariate GWAS, multivariate GWAS			
Bovo et al. (2019)	RBC, HMG, HMT, MCV, MCH, MCHC, PLT, WBC, NEU, LYM, EOS, BAS, MON	Large White	843

GWAS= genome-wide association study, RBC=red blood cells, HMG= hemoglobin, HMT= hematocrit, MCV= mean corpuscular volume, MCH= mean corpuscular hemoglobin, MCHC= mean corpuscular hemoglobin concentration, PLT=platelets, WBC=white blood cells, NEU= neutrophils, LYM= lymphocytes, EOS= eosinophils, BAS= basophils, MON= monocytes,

IFN-γ = Interferon-γ, IL= Interleukin, N=Number of animals, *overlapping traits with own studies in chapters 3 and 4

2.7. Multivariate approaches for QTL detection

Generally, GWAS are performed on a single phenotype of interest, in an univariate (uv) trait manner. In recent years, a variety of multivariate (mv) methods have been proposed to analyze multiple phenotypes simultaneously to investigate their joint association with an SNP (Galesloot et al., 2014; Porter & O'Reilly, 2017; Salinas et al., 2018; Vroom et al., 2019b). Since mv information is increasingly available and pleiotropy is a common phenomenon within and between traits, the development of powerful mv analysis procedures is needed to detect an associated SNP.

The association between complex traits and genome-wide SNP markers is typically analyzed in a uv manner for each trait. Mv analyses, on the other hand, could provide several advantages if multiple, correlated traits are analyzed together. In uv analyses, the additional information provided by the covariance between traits is ignored; in a mv analysis, however, it increases the power in the presence of genetic correlation between the traits. An additional advantage of mv procedures is that many of them can test a single trait for association with a set of variables. In comparison to analyzing all traits separately, this reduces the number of tests performed (Zhu & Zhang, 2009). Furthermore, when pleiotropy is present, where a single genetic variant affects multiple traits, a mv GWAS is more appropriate than a cross-trait comparison using uv analyses (Galesloot et al., 2014).

Considering different conceptual classifications for mv methods (Galesloot et al., 2014; Vroom et al., 2019b; Q. Yang & Wang, 2012) the methods can be distinguished by their statistical properties in regression-based (direct), transformation-based (indirect), and composition test (uv-based). According to this classification, regression-based methods model the effects of the genetic variant directly on the traits without changing the general format and nature of the trait data. On the contrary, transformation-based methods are based on the reduction of the trait dimension. In the first step, initial traits are modified than in the second step transformed traits are regressed on the genetic variant. Uv-based composition tests combine the p-values or test statistics obtained from uv analyses to test a mv hypothesis for example in a meta-analysis (Figure 6).

Combination tests have the challenge of interpreting phenotypic correlations between p-values or test statistics resulting from associated traits in the phenotypical context within which they are conducted.

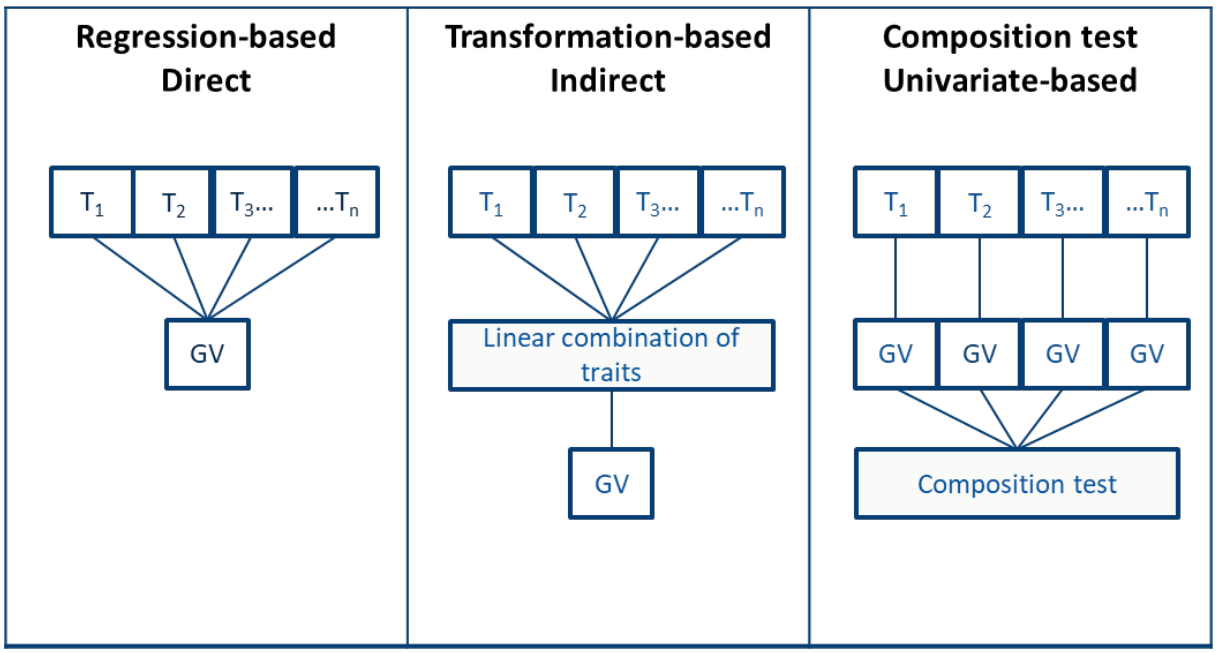

Figure 6: Conceptual classifications for multivariate methods were modified according to Galesloot et al. (2014)

T1, …Tn= trait, GV=genetic variant. Statistical properties of multivariate methods can be distinguished in regression-based (direct), transformation-based (indirect), and composition-based (univariate-based)

Mv genetic association methods, regardless of their statistical foundation, need to deal with a significant correlation between the simultaneously modeled traits dependent on the tested GV. Different methods are used to accomplish this. Combination tests use a correction factor or permutation. Regression-based tests implement two solutions: either traits are treated as predictors (e.g. MultiPhen) or residual trait correlations are accommodated in a background covariance matrix (e.g. MANOVA, GEE, LMM). Transformation-based tests explicitly incorporate the covariance between the traits into the new variates. Thus, for the selection of a suitable mv method to apply to immune traits, several types of mv GWAS approaches were available: uv-based, indirect, and direct mv methods. Representative approaches of each type were selected subjectively in the study included in chapter 4. In the following sections, the

subjective selected mv methods are introduced briefly. Details about the statistical background of the methods are given in the original literature (Everitt & Hothorn, 2011; Ferreira & Purcell, 2009; Scutari, 2010; Servin & Stephens, 2007; Stephens, 2013; van der Sluis et al., 2013; Weller et al., 1996).

Beyond the described methods in this section, there are also further software extensions, packages, and approaches which perform mv GWAS e.g. GEMMA (Zhou & Stephens, 2014b), WOMBAT (Meyer, 2007), aSPUset (Kim et al., 2016), GUESS (Bottolo et al., 2013), BMTME (Montesinos-Lopez et al., 2016). Multi-SNP GWAS methods aim to increase power by reducing the residual variance by including other genetic variants as predictors in the model (Galesloot et al., 2014). However, reviews and studies of mv GWAS approaches state that there is no one most powerful method and that the different existing methods should be viewed as complementary (Galesloot et al., 2014; Porter & O'Reilly, 2017; Zhou & Stephens, 2014b). Except for the recent study from Bovo et al. (2019), mv GWAS methods have not been applied to porcine immune traits, yet. In the study from Bovo et al. (2019), in addition to an uv GWAS, a Bayesian method and a mv GWAS have been applied to hematological traits for slaughtered Italian LW pigs. Thus, the importance of gaining a deeper understanding of the performance of mv methods to identify strategies of analysis to maximize discovery potential and pleiotropic genetic structure is highlighted. It is important to mention that in the comparison studies the predictor of interest is the genetic variant, i.e. SNP. However, in practice, even more, complex factors and additional covariates such as sex, age, and genetic principal components are standardly included in the statistical model to consider all biological influences and to correct for population stratification.

2.7.1. Principal component analysis

A commonly used indirect method is the principal components analysis (PCA). PCA, as a mv technique, analyzes a large amount of data and aims to reduce its dimensionality while preserving as much of its original variation as possible. To achieve this, the original variables are transformed into linear combinations, called the principal components (PCs). The PCs are uncorrelated and are ordered so that the first few of them account for most of the variation in the original variables (Everitt & Hothorn, 2011). PCs derived from the components of the eigenvectors of the phenotypic covariance matrix which explain the largest proportion of the original phenotype are then used in place of the original phenotypes (Weller et al., 1996). PCA is among the oldest forms of mv analysis, having been introduced originally by Pearson (1901) and independently by Hotelling (1933) . It remains a popular method for displaying mv data in

a lower dimensional space and for simplifying other analyses of the data because it provides a convenient way to display mv data.

2.7.2. Canonical correlation analysis

Canonical correlation analysis (CCA) is applied to two sets of variables (phenotypic measurements and the genetic variant) to extract a number of independent pairs of variables that explain as much covariance between the two sets (Ferreira & Purcell, 2009). Whenever there are multiple variables in each set, the objective of CCA is to find the linear functions of the variables in one set that are maximally correlated with the linear functions of the variables in the other set. The process of finding coefficients that define the required linear functions is similar to the PCA. Nevertheless, this technique isn't as widely used as other mv techniques, perhaps because the results of such an analysis are frequently difficult to interpret. As with PCs, the coefficients of each original variable in each canonical variate can be interpreted by looking at the coefficients of each original variable. Using canonical variates to interpret the original variables may provide insight into how the two sets are related to each other. The variances and covariances of the original variables in the two sets may differ considerably, which affects the sizes of the coefficients in canonical variates.

2.7.3. Meta-analysis

Meta-analytical approaches compute a single summary statistic across study populations or phenotypes. For example, TATES (trait-based association test that uses the extended Simes procedure) requires the phenotype correlation matrix and the P-values obtained from uv GWAS analyses to calculate associations across the traits. By combining the uv phenotype-specific GWAS results as p-values, TATES generates one trait-based p-value. Using a method described by Li et al. (2011), an eigenvalue decomposition of the correlation matrix between the p-values associated with phenotypes is used to estimate the effective number of p-values. After transforming this trait correlation matrix to the eigen-decomposition of this p-value correlation matrix, the uv p-values are weighted according to this matrix. A minimum of these weighted p-values is chosen as the corrected p-value for the joint association (van der Sluis et al., 2013).

2.7.4. Bayesian multivariate approaches

Direct methods, for example, Bayesian multivariate approaches with the software SNPTEST or mvBIMBAM can be applied for multi-trait analyses. MvBIMBAM (mv Bayesian imputation-based association mapping) performs Bayesian mv regression to test for association and to partition the phenotypes according to the SNP-effect in the same step (Servin & Stephens, 2007;

Stephens, 2013). Bayes Factors were employed to assess the association between each phenotype group and the genetic variant. Analyses are based on mv regression models, with inputs (n x d) matrices of d phenotypes for each individual. According to the mvBIMBAM approach, response variables are grouped into three categories based on their statistical association with genetic variants: undirect, direct, and indirect. A set of models runs through partitions of the coordinates.

2.7.5. Trait networks and structural equation models

It is computationally intensive to realize all possible mv combinations for all immune phenotypes. Interaction between variables can be modeled with networks, paths, and graphs. The Bayesian network (BN) provides conditions for determining dependencies and independencies among variables (Scutari et al., 2014). Therefore, with a BN it is also possible to uncover conditional dependencies among immune traits.

BNs are graphical representations of probability distributions over a set of variables. Pearl (1988) has extended conditional independence (of random variables) to disjoint node subsets by assuming the different random variables are independent. Accordingly, in the BN approach, the graphical structure of the network was learned using model selection algorithms, and then the local distribution function parameters were estimated based on the learned structure. Different types of algorithms can be used to obtain the model from the network structure (Scutari, 2010). A score-based structure learning algorithm is a general heuristic optimization technique for solving the problem of learning the structure of a BN. An output of this algorithm is a graphical structure that shows how well the BN fits the data set, measured by a score.

Using structural modeling such as a BN, a mv modeling strategy is developed that accounts for recursive effects (effects from one phenotype are passed onto another) and simultaneous (reciprocal) structures among its variables, unlike standard mv statistical methods (Goldberger, 1972). Using SEM-GWAS, Momen et al. (2019) were also able to partition the source of the SNP effects into direct and indirect effects, allowing a better understanding of the relevant biological mechanisms. However, mv GWAS without structural equation modeling does not take into account network structure between phenotypes, estimating overall SNP effects across phenotypes, rather than combining direct and indirect SNP effects.

2.8. Accessing genetic pleiotropy

According to the literature contributing to Pig QTL Database (Hu et al., 2019), most of the detected genetic markers for health-related traits explain small amounts of phenotypic variance, are distributed across the porcine genome, and show polygenic genetic structure by being linked

to further genomic areas. Sharing the same genetic foundation between hematological traits, showed that pleiotropic QTLs are common in hematological traits like hematocrit, RBC, and MCV (F. Zhang et al., 2014). Pleiotropy refers to a single gene or genetic variant that affects multiple, different, phenotypic traits (Solovieff et al., 2013). In the context of complex traits, which are influenced by many small genetic effects across the genome (P. M. Visscher et al., 2012), pleiotropy can be considered at the SNP level. Identifying pleiotropic SNPs can lead to a greater understanding of the underlying biological network between complex traits, and identify biological pathways enriched for effects on clusters of traits for further investigation.
Pleiotropy can arise in different forms, and distinguishing between them is important for understanding the biological implications. Several types of pleiotropy are distinguished further in biological, mediated, and spurious pleiotropy. Biological pleiotropy occurs when one gene has a direct effect on at least two different traits. Spurious pleiotropy is defined as a genetic variant falsely identified to be associated with more than one phenotype, whereas mediated pleiotropy exists if one phenotype is causally related to another phenotype (Solovieff et al., 2013). In chapter 3 moderate to high r_g (0.4-0.8) between immune traits like hematological parameters and cytokines, which were measured in LR and LW piglets and their biological dams, are described. Consideration of close relationships between multiple immune traits can be used to boost statistical power to detect joint SNPs, which was applied in chapter 4. Most mv GWAS methods are not optimized for the detection of pleiotropic genetic variants. Furthermore, these approaches do not require a pleiotropic effect to gain power over the uv approach. However, mv GWAS methods have the potential to further describe the pleiotropic effect of a genetic variant on multiple complex traits, which was done in chapter 4.

Chapter 3. Genetic parameters of immune traits for Landrace and Large White pig breeds

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3.1. Abstract

Improving the immunocompetence towards pathogens represents a desirable objective of breeding strategies to increase resilience. However, the immune system is complex and the genetic foundation of the underlying components is not yet clarified. In the present study, we focused on 22 blood parameters of 1144 Landrace (LR) and Large White (LW) piglets at the age of six to seven weeks. The immune profiles covered immune cells, red blood cell characteristics, and cytokines. Genetic parameters based on pedigree information along with possible environmental effects were estimated. Litter effects play an important role in the expression of immune parameters of their young progenies. Hence, litter impacts on the piglet's immune profile including the immune parameters of the dam itself were investigated by different models. To incorporate the complexity of the immune network, the data were further investigated with a principal component analysis.

Immune traits showed low to high breed-specific heritabilities (h^2). Strong positive genetic correlations (r_g) were estimated among red blood cell characteristics (0.77 to 0.99) as well as among cytokines (0.48 to 0.99). Neutrophils and lymphocytes illustrated a high negative r_g (-0.96 to -0.98). The litter impact on piglet's immunity was examined and strengthened already observed breed differences. In LR h^2 (0.22 to 0.15) and litter effect (c^2) (0.52 to 0.44) for IFN-γ decreased after statistical consideration of maternal impact. In LW a decrease in h^2 (0.32 to 0.18) for IFN-γ and an increase in c^2 (0.54 to 0.56) was observed. Here, sufficient correlations were detected within various immune traits and functional biological networks of principal components. Most immune traits are heritable and are promising to cover global breed-specific immunocompetence in pigs. The analysis of immune traits has to be extended in order to find an optimal range and to characterize relationships between immunity as well as performance to gain an improved immune system without accidental losses in productivity.

Keywords: Variance components, immune traits, maternal impacts, principal component analysis, pig.

3.2. Introduction

In pig breeding programs the development of breeding strategies to increase resilience represents a desirable objective. Improving immunocompetence towards pathogens could contribute to achieving this challenging goal. However, the immune system is very complex, and little is known about the genetic foundation of its parameters. Some genetic studies provide insights into the genetic variability of the immune parameters in pigs (Ballester et al., 2020; Bovo et al., 2019; Clapperton et al., 2009; Clapperton et al., 2008; Edfors-Lilja et al., 1998; Flori, Gao, Laloë, et al., 2011; Henryon et al., 2006; Hermesch & Luxford, 2018; Mpetile et al., 2015; Ponsuksili et al., 2016). From this can be concluded that immune responsiveness and disease resistance are quantitative traits regulated by the effects of numerous genes influenced by a variety of environmental factors (Mallard et al., 1992). However, the number of observations, the underlying breeds as well as non-genetic effects like the time of blood sampling, housing conditions including the hygienic farm concept, and infection pressure are very divergent. As a result, heterogeneous and non-consistent environmental as well as genetic parameters have been reported. Moreover, various studies (Flori, Gao, Laloë, et al., 2011; Mallard et al., 1992) have postulated, that animals bred for high production output could be more susceptible to pathogens.

Against this background, we focused on the immunocompetence of purebred Landrace (LR) and Large White (LW) piglets, raised under the definable condition of two nucleus farms with high hygienic status. Within these herds, piglets were born under comparable conditions with low infection pressure. Authors of already published variance component studies for health-related traits (Clapperton et al., 2005; Hermesch & Luxford, 2018; Ponsuksili et al., 2016) pointed out that traits which tend to represent the immunocompetence should be effortless to measure and to reproduce without any impairment, disease symptoms, or inflammatory and pathological signs. Therefore, for the purpose of this study pigs were not treated in any way. Our evaluation represents the first step towards a deeper insight into the genetic foundation of immune traits of breeding animals.

Many influences on a piglet's immune system have been described in the literature (Zimmerman et al., 2012). During the first days of life, maternal effects have a strong impact on the piglet's innate and adaptive immunity and thus, have an influence on the piglet's survival (Heuß et al., 2019). Passive maternal-derived humoral and cellular immunity provide additional essential protection for newborn piglets, who receive antibodies only postnatal through the colostrum (Bouma et al., 1998). Colostrum and milk serve primarily to transfer systemic and local protection due to maternal-derived humoral and cellular immunity and to influence the

development of systemic and mucosal immunity through provided hormones, antimicrobial proteins, and growth factors (Bandrick et al., 2008; Salmon et al., 2009; Zimmerman et al., 2012). Moreover, maternal genetic effects influence piglet survival directly (Knol, Ducro, et al., 2002; Roehe et al., 2010). Therefore, research on the maternal and litter impact requires an emphasis on neonatal immunity development. Since piglet mortality mostly occurs during early development, even maternal and litter effects of short duration may have important consequences (Grindstaff et al., 2003). Furthermore, a low genetic correlation between the transfer of maternal antibodies and the offspring's adult reproductive rate and some components of the immune response has been observed e.g., in chickens (Biozzi et al., 1982; Martin et al., 1990). In pigs, maternal influences have been shown to modulate offspring's birthweight, farrowing, pre-weaning, and total piglet survival (Knol, Ducro, et al., 2002; Roehe et al., 2010). It is well known that the immune system is a high-dimensional complex network with key nodes along with highly expressed relationships between the participating components. To incorporate these expected dependencies, multivariate (mv) approaches seem to be a promising analysis option. Principal components analysis (PCA) allows reducing correlated traits into a set of uncorrelated variables called principal components (PCs). This statistical method detects patterns in the data by their similarities and differences and compresses the data information (i.e., by reducing the number of dimensions) without much loss of information (Hair, 2009; Weller et al., 1996).

The objectives of this study were to estimate the genetic parameters of immune traits, to investigate the genetic associations between these traits by PCA, and to examine the impacts of the dam's immune profile on their offspring's immunity.

3.3. Material and Methods

3.3.1. Animals and phenotypic measurements

Data sets of purebred LR and LW subset pig populations were recorded from 2010 to 2017 and were provided by the German breeding organization Bundeshybridzuchtprogramm (BHZP) GmbH as been already described in Dauben et al. (2021). The animals within the nucleus populations were kept under high hygienic conditions and reflect the genetic diversity of both populations concerning their different breeding objectives. From each litter, one male and one female piglet, as well as, their biological dam were chosen for blood sample collection. Animals were apparently healthy and average in physical development. Blood samples of piglets (LR: n=611 and LW: n=533) were collected on average around 45 days (32-60) after birth by puncturing the *Vena jugularis* and were collected in three 7.5ml monovette containing Ethylenediaminetetraacetic acid. As an additional trait, piglets were weighed individually after blood sample collection. From the biological dams (LR: n=298 and LW: n=272) of all phenotyped piglet's blood was sampled in a short period *postpartum* (7 days). The blood sample collection period for piglets (45 days after birth) was chosen because at this age piglet's immunity is still under development (Tizard, 2013) and the importance of maternal antibodies decreases. For dams, the recorded immune profile should characterize the postnatal passive immune transmission from sow to the progeny.

Complete blood count (red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, white blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, band and other remaining cells) was performed with an ADVIA® 2120 hematology system, a flow cytometry-based system, and a pig-specific setting, as described by Harris et al. (2005). Besides, serum haptoglobin was measured in 0.5 ml serum. Peroxidase activity of the haptoglobin-hemoglobin complex was carried out by a spectrophotometric method. Hematology analysis and haptoglobin were measured in an external laboratory of synlab.vet GmbH immediately after blood samples arrived on the same day.

Cytokine levels (interferon-γ, interleukin-10, interleukin-12, interleukin-1β, interleukin-4, interleukin-6, interleukin-8, tumor necrosis factor-α) in serum samples were analyzed with a Porcine Cytokine/Chemokine Multiplex Magnetic Bead Panel (Merck KGaA) enabling the simultaneous measurement of multiple cytokines. Immunoassay of serum samples was performed using 22 plates according to the manufacturer´s protocol. These fluorescence intensity measurements were performed using Luminex® 200 with xPONENT 3.1 software in

the external laboratory of the Flow Cytometry Core Facility, Medical Faculty, University of Bonn. A general overview of all investigated immune traits in piglets and dams as well as their summary statistics are presented in the results section 3.1 . Cytokines were measured in the detectable concentration ranges with the chosen assay quantification method. High standard errors for the mean values are caused by a high reported variation range of the cytokines. To consider low values and the resulting left-skewed distribution of the raw cytokine and haptoglobin measurements, observations were log-transformed. Records of piglet's and dam's immune traits were excluded when they met at least one of the following criteria: Haptoglobin ≤ 0.01 mg/ml, Neutrophils =0%, Lymphocytes ≤ 10%, Band cells ≥ 20%, Cytokine's bead count < 50. In total, measurements from at least 522 LR piglets and 456 LW piglets as well as 261 LR dams and 231 LW dams were used for further analysis.

3.3.2. Statistical analysis

Variance component analysis of immune traits

Variance components of immune traits were estimated by using an animal model 1 as follows:

$$y_{ijk} = fix_i + a_{ij} + c_{ik} + e_{ijk} \quad (1)$$

The estimation of the genetic parameters was performed within a breed for immune traits (y_{ijk}) of the complete blood count, haptoglobin, and cytokines. Model 1 includes all relevant fixed effects (fix_i), given as the class effects parity (PAR_i:1-4), herd-year-season-sex ($HYSS_j$: 1-12). Moreover, age (age_{ijkl}) and weight (wt_{ijkl}) and interaction between age and weight $(age \times wt)_{ijkl}$ at the time of sample collection were included in the model as covariates. Porcine Cytokine/Chemokine Multiplex Magnetic Bead Panel method requires the quantification of samples distributed among 22 analytical plates. Therefore, pl_k was included as a random term for cytokine immune traits.. The effects breed (LR or LW) or sex (boar or sow) were not included as main factors in the model because of the hierarchical classification of these effects within HYSS classes. To quantify differences between breeds or sexes, linear contrasts between relevant HYSS classes were constructed and tested via a series of Tukey-Tests. We used the fixed part of model (1) (fix_i) to analyze the impact of fixed effects within and between the two breeds. In the combined data set, linear contrasts were used to present potential effects of breed and farm. Because in the investigated combined data set most herds kept only one breed and one sex, the interpretation of linear contrasts between breeds and sex is impaired because of possible uncorrected environmental effects. The significance levels of

fixed effects included in the statistical model as well as relevant linear contrasts were obtained by a generalized linear model using R (R Core Team, 2019).

In addition, this model was extended by the random, uncorrelated additive genetic (a_{ij}) and litter (c_{ik}) effects. The estimation of the additive genetic effects incorporated the relationship matrix of all piglets (a_{ij}), which could be traced back almost completely up to the 8th generation. Litter effects (c_{ik}) include the litter information of each dam, and it was assumed that, (c_{ik})-effects were independent and identically distributed. As usual heritability (h^2) and litter effects (c^2) were expressed as the ratios of additive genetic variance (σ_a^2): phenotypic variance (σ_p^2) or litter variance σ_c^2:σ_p^2.

With a series of overlapping mv approaches (up to six traits per analysis) phenotypic (r_p) and genetic (r_g) correlations between all immune traits were established applying model 1. Based on the model (1) we have estimated the genetic parameters within a breed. This was motivated by the distinct genetic distance between the LR and LW breeds. This distance was calculated by means of available SNP information and has been published in the work of Dauben et al. (2021). Genetic parameters of each trait were estimated in combination with almost all possible sets of other traits. Identical parameters with their standard errors which were estimated in different mv runs were averaged using the median. In rare cases, the convergence criteria of the REML analysis could not be reached, so some genetic correlations were not estimable. These exceptions occur if the h^2 of one or more traits used in the mv model were close to zero. The calculations were conducted in VCE 5.1 (Kovač & Groeneveld, 2003).

Statistical consideration of maternal effects

In statistical model 1 random litter effects (c_{ik}) were included to take into account mainly the common environment of the littermates. To consider the dam's environmental influences more rigorously, immune traits of the dam were integrated as an environmental effect into the genetic analysis of the piglet data. For this purpose, the highly correlated immune traits of the dam were centered, scaled, and condensed via PCA. This analysis was performed within biological functional networks (BFN) a) immune cells (Cell), b) RBC and haptoglobin (RBC) or c) cytokines (Cyto). In the genetic analysis of the piglet data, resulting first and second dam's PCs which belong to the corresponding BFN as the piglet immune target trait were used as additional covariates in model 1. According to the statistical PCA principles (details are given in Weller et al. (1996)), PCA transformation of n traits resulted in n number of phenotypically uncorrelated variables conducted from the components of the eigenvectors of the phenotypic covariance matrix. Eigenvalue stands for the part of phenotypic variability explained by the

corresponding PC variable. The importance of each immune trait within the different PC can be quantified by their loadings. PCA was conducted in R (R Core Team, 2019).

Multivariate analysis of piglet's immune traits

Similarly, to the above section: statistical consideration of maternal effects, PCA techniques were used to condensate the highly correlated piglet's immune observations within the different BFN and breeds. An overview of PCs within the BFN together with their loading composition for the piglet data set is presented in the results section 3.5. Based on this information, it might be possible to interpret PCs in a summarizing, biological manner. The number of resulting PCs per BFN which were finally used to characterize piglet's immune system derived from eigenvalues of the correlation matrix. Applying Kaiser's criterion (Braeken & van Assen, 2017), PCs with eigenvalues above a threshold of 1.0 were used in the following analysis. Variance components of resulting PCs as new dependent variables were estimated by using the mv approach as has been described in the section above: Variance component analysis of immune traits.

3.4. Results

3.4.1. Immune trait values and influencing factors

The results from the ANOVA after formulating a generalized linear mixed model are shown in the Table S1. For most immune traits in the LR and LW piglet's data set HYSS effect had a significant influence. Age had a breed-specific effect on several phenotypes. In the LR piglet data set age influenced immune traits like MCV, MCH, platelets, WBC, and haptoglobin whereas it only had significant impacts on hemoglobin, hematocrit, MCH, and MCHC in the LW piglet data set. LR and LW immune traits like MCV, neutrophils, lymphocytes, and monocytes were influenced by the weight at the time of blood sample collection. Besides, weight also had a significant impact on RBC, hemoglobin, hematocrit, MCH, MCHC, eosinophils, IL-1 β, and IL-4 for LR piglets. The interaction of the covariates age and weight remained significant for haptoglobin, IL-1β, IL-4 in LR and for RBC, hemoglobin, hematocrit, and MCHC in LW.

Descriptive statistics of phenotypic measurements of all piglets and dams separated by breed are given in the Table S2. The measured band and other remaining cells were excluded from further investigations because these traits showed a phenotypic variance close to zero. Breed differences were investigated by comparing the mean values of the immune traits and by linear contrasts between relevant HYSS classes that were constructed and tested. In total, 14 traits (RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, neutrophils, lymphocytes, basophils, IL-10, IL-12, IL-1β, and IL-8) revealed significant ($p < 0.05$) differences between the breeds. The neutrophil value in LR piglets was 6% higher than in LW (47.64% to 41.48%), whereas the LR lymphocyte value was 7% lower in comparison to LW (45.84% to 52.89%). For the mean values of platelets, WBC, monocytes, eosinophils, haptoglobin, IFN-γ, IL-4, and TNF-α no significant differences between the breeds within the piglets' data set were found.

Within the dams' data set, similar breed contrasts regarding RBC, hemoglobin, hematocrit, platelets, and monocytes means were detected. For example, the neutrophil value in LR dams (58.58%) was 5% higher than in LW (53.85%), whereas the lymphocyte value was 6% in LR (31.43%) was lower than in LW dams (37.46%).

There are possible uncorrected environmental effects in the investigated data set since most herds kept only one breed and one sex. The interpretation of linear contrasts in the combined data set is therefore impaired.

3.4.2. Genetic parameters for immune traits

Heritabilities and c^2 effects for 22 immune traits were estimated within the LR and LW breed applying animal model 1 (Table 3). The h^2 and c^2 estimates were classified as high ($h^2 > 0.40$), moderate ($0.10 < h^2 \leq 0.40$), and low ($h^2 \leq 0.10$) as has been suggested by Flori, Gao, Laloë, et al. (2011). In both breeds, the h^2-estimates for eight traits were categorized as high.

High h^2 were found for MCH and MCV in both breeds and RBC, hemoglobin, hematocrit, and TNF-α within LR. In contrast, h^2 close to zero were found for MCHC in the LR breed and hematocrit, platelets, WBC, eosinophils, basophils, and haptoglobin within the LW breed.

Regarding both breeds moderate to high established c^2 were only present in platelets, monocytes, and cytokines whereas for most immune cells and haptoglobin c^2 values showed almost no variability. Particular high c^2 effects were estimated for the cytokines IFN-γ, IL-10, IL-1β, IL-4, and IL-6 in a range of 0.46 to 0.61 in both breeds.

Table 3: Direct genetic and litter effects for immune variables of Landrace and Large White piglets

Trait	Landrace			Large White		
	σ^2p	h^2±SE	c^2±SE	σ^2p	h^2±SE	c^2±SE
RBC	0.11	**0.41±0.10**	0.05±0.04	0.17	0.36±0.08	0.03±0.03
Hemoglobin	13476.89	**0.41±0.11**	0.08±0.05	17281.73	0.18±0.08	0.09±0.04
Hematocrit	0.001	**0.43±0.11**	0.05±0.04	0.001	0.09±0.06	0.08±0.04
MCV	69.39	**0.53±0.10**	0.09±0.05	72.93	**0.61±0.10**	0.11±0.05
MCH	1.06	**0.41±0.08**	0.04±0.03	0.79	**0.66±0.12**	0.08±0.05
MCHC	2.56	0.02±0.02	0.02±0.02	1.06	0.15±0.07	0.14±0.05
Platelets	264740234.31	0.24±0.08	0.20±0.05	410896818.95	0.01±0.02	0.26±0.05
WBC	472.63	0.18±0.06	0.08±0.04	942.49	0.08±0.07	0.15±0.06
Neutrophils	7575.96	0.25±0.08	0.10±0.04	10465.29	0.12±0.08	0.16±0.05
Lymphocytes	7823.40	0.30±0.08	0.11±0.04	10241.44	0.14±0.08	0.16±0.05
Monocytes	4.67	0.32±0.09	0.03±0.04	9.24	0.17±0.07	0.33±0.06
Eosinophils	5.24	0.22±0.08	0.07±0.04	1.30	0.06±0.05	0.04±0.03
Basophils	0.02	0.22±0.08	0.04±0.03	0.001	0.03±0.04	0.14±0.05
Haptoglobin	0.001	0.18±0.07	0.07±0.04	0.01	0.03±0.03	0.04±0.03
IFN-γ	0.31	0.22±0.08	**0.52±0.06**	0.42	0.32±0.10	**0.54±0.06**
IL-10	0.06	0.24±0.10	**0.56±0.06**	0.15	0.25±0.10	**0.53±0.06**
IL-12	0.001	0.34±0.13	0.36±0.07	0.001	0.18±0.09	0.38±0.07
IL-1β	0.04	0.17±0.09	**0.51±0.06**	0.07	0.16±0.09	**0.46±0.06**
IL-4	0.22	0.19±0.09	**0.52±0.06**	0.40	0.27±0.13	**0.45±0.07**
IL-6	0.08	0.35±0.09	**0.52±0.06**	0.17	0.31±0.10	**0.50±0.06**
IL-8	0.01	0.15±0.08	0.23±0.06	0.02	0.36±0.11	0.17±0.06
TNF-α	0.08	**0.61±0.09**	0.28±0.06	0.07	0.13±0.08	**0.46±0.06**

RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC=white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α, h^2=heritability, c^2=litter effect, σ^2_p=phenotypic variance, cytokines are log-transformed, bold font indicates high h^2 or c^2 above 0.4

3.4.3. Genetic correlations between immune traits

Pairwise r_g and r_p for all mv combinations in LR and LW can be found in Tables S3 and S4. Figure 7 provides a graphical overview of the genetic parameters, where h^2 can be found on the diagonal, r_p under the diagonal, and r_g above the diagonal for LR and LW piglets. The color key from red to blue was chosen to illustrate the classification of positive as well as negative genetic parameters in high, moderate, and low. The ellipses have their eccentricity parametrically scaled to the correlation value and are shaded to display high or low as well as positive or negative correlations. Regarding both breeds, 106 (LR) and 135 (LW) r_g among different immune traits exceeded an absolute value of 0.4. Regarding consistent across-breed correlations, RBC characteristics were highly positively correlated with each other. As expected, particular high positive r_g were found between MCH and MCV (r_g: 0.99 to 0.94, LR and LW, respectively). Furthermore, MCHC was highly positively correlated with monocytes (0.64 to 0.93) and basophils (0.94 to 0.97).

Hemoglobin and hematocrit were highly positively correlated with the cytokines IFN-γ (r_g: 0.71 to 0.43, LR and LW, respectively and r_g: 0.69 to 0.40, LR and LW, respectively) and TNF-α (0.65 to 0.79 and 0.61 to 0.88). In addition, RBC showed high positive correlations with cytokines like IL-1β (0.40 to 0.75) and TNF-α (0.61 to 0.96). Between immune cells, different relationships were found. Neutrophils showed a high positive correlation with WBC (0.62 to 0.72), whereas they showed a high negative correlation with lymphocytes (-0.98 to -0.96). Furthermore, lymphocytes were highly negatively correlated with WBC (-0.71 to -0.58). Between cytokines such as IFN-γ, IL-10, IL-1β, IL-4, IL-6, and TNF-α high positive r_g were estimated. In addition, haptoglobin was highly negatively correlated with cytokines like IL-1β (-0.89 to -0.71), IL-4 (-0.96 to -0.47), and Il-6 (-0.73 to -0.84) in both breeds.

The remaining r_g revealed a contrasting relationship between the two investigated breeds. MCV was highly positively correlated with cytokines like IFN-γ, IL-10, IL-1β, IL-4, and IL-6 in LR piglets (0.42 to 0.66) but was highly negatively correlated in LW piglets (-0.44 to -0.90). MCH showed similar relationships to cytokines IFN-γ, IL-10, and IL-1β within the breeds LR (0.40 to 0.52) and LW (-0.47 to -0.84). A high positive relationship between monocytes, eosinophils, and TNF-α was observed for LR (0.53 to 0.40), whereas in LW high negative estimates (-0.82 to -0.85) could be observed.

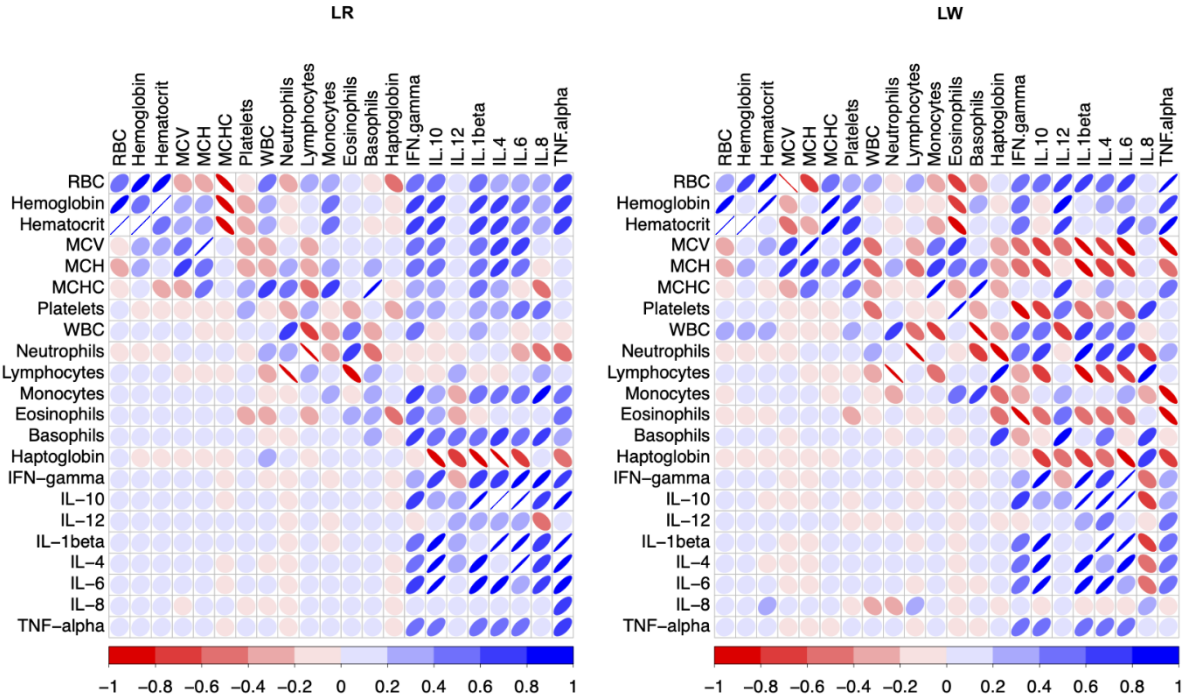

Figure 7: Graphical display of genetic parameters for immune variables in the piglet data set

Heritabilities (h^2) on the diagonal. Phenotypic correlations (r_p) under the diagonal and genetic correlations (r_g) above the diagonal. RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC=white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α, LR=Landrace, LW=Large White

3.4.4. Maternal influences on piglet's immunity

Along with the piglet's genetic effect, we intended to investigate how a dam influences her offspring's immune system through the provided environment. To consider the dam's environmental influences in a more specific way, the first and second immune PCs of the dam were integrated as covariables into the genetic analysis of the piglet's immune traits. As has been described in section: statistical consideration of maternal effects, these PCs of the dam correspond to the BFN of the target immune trait of the piglet. These PCs reflect the specific parts of the immune system of the dam which might operate as an environmental effect for the immune traits of the piglet (Table S5).

In general, these covariables had only negligible consequences for the magnitude of maximum 0.05 for the estimated genetic parameters (Table S6). Within cytokines, the consideration of dam's PCs led to a small, breed-specific shift between h^2 and c^2 effects. For example, in LR h^2 for IL-8 decreased from 0.15 to 0.12 in favor of c^2 effects which increased from 0.23 to 0.24. The exact opposite was observed for LW piglets, where h^2 for IL-8 increased from 0.36 to 0.38 and c^2 decreased from 0.17 to 0.16. In addition, h^2 for RBC (0.41 to 0.36) and MCH (0.41 to 0.29) in LR was lowered after consideration for maternal environmental effect. For all other examined immune traits, the inclusion of immune PCs of the dam into the statistical model has changed h^2 or c^2 as well as r_g estimates only to a minor extent.

3.4.5. Accessing highly correlated immune networks in piglets

Theoretically, PCA aims for a more powerful analysis of the immune traits by reducing the dimension of information and therefore, allowing the detection of key players in immunocompetence. Variance component estimation was performed for PCs as new dependent variables of piglet's immune traits within BFN. According to the BFN and breed, three to four PCs were extracted (Table S7). The loading values for these PC-specific traits indicate how much the respective immune traits contribute to a particular PC. Moreover, the loadings can help to interpret estimated variance component results according to their biological function. Loading values for the first PC of each BFN are also presented as pie charts in Figure 8. We used a threshold of |0.3| to classify the immune trait within a BFN into the classes "contributing" or "not contributing". Within BFN RBC, $PC1_{RBC}$ explains ~37% of the variation in both breeds (LR: 37.23%, LW: 37.49%). This PC is mainly influenced by the directly measured RBC characteristics of hemoglobin, hematocrit, and RBC (Figure 8, Table S7). On the contrary, $PC2_{RBC}$ (LR: 22.43%, LW: 22.84%) is mainly influenced by the calculated ratio MCH and

MCV (only in LR). Within the $PC3_{RBC}$ and $PC4_{RBC}$ which also explain more than 10% of the variation, MCHC and haptoglobin are the main actors (Table S7).

Within the BFN Cells $PC1_{Cell}$ (LW: 35.96%, LR: 35.49%) is dominated by neutrophils and lymphocytes, which were known to be negatively correlated and influenced by the time point of blood sampling (Figure 8). On the other hand, $PC2_{Cell}$ can be characterized by the percentages of eosinophils and WBC (only in LW) (Table S7).

In BFN Cyto $PC1_{Cyto}$ explains most of the phenotypic variation (LR: 68.13%, LW: 60.13%). This PC is similarly influenced by all examined cytokines (Figure 8). Apart from that the chemokines IL-12 and Il-8 are less contributing to $PC1_{Cyto}$ but dominate in $PC2_{Cyto}$ for LW piglets (Table S7).

In general, PCs of the two breeds LW and LR can hardly be compared because their composition based on loading values is partly different. In contrast, we assumed that the variance components of the first PCs of each BFN ($PC1_{Cell}$, $PC1_{RBC}$, $PC1_{Cyto}$) are comparable between the breeds due to similarities in the contribution based on their loading values (Figure 8).

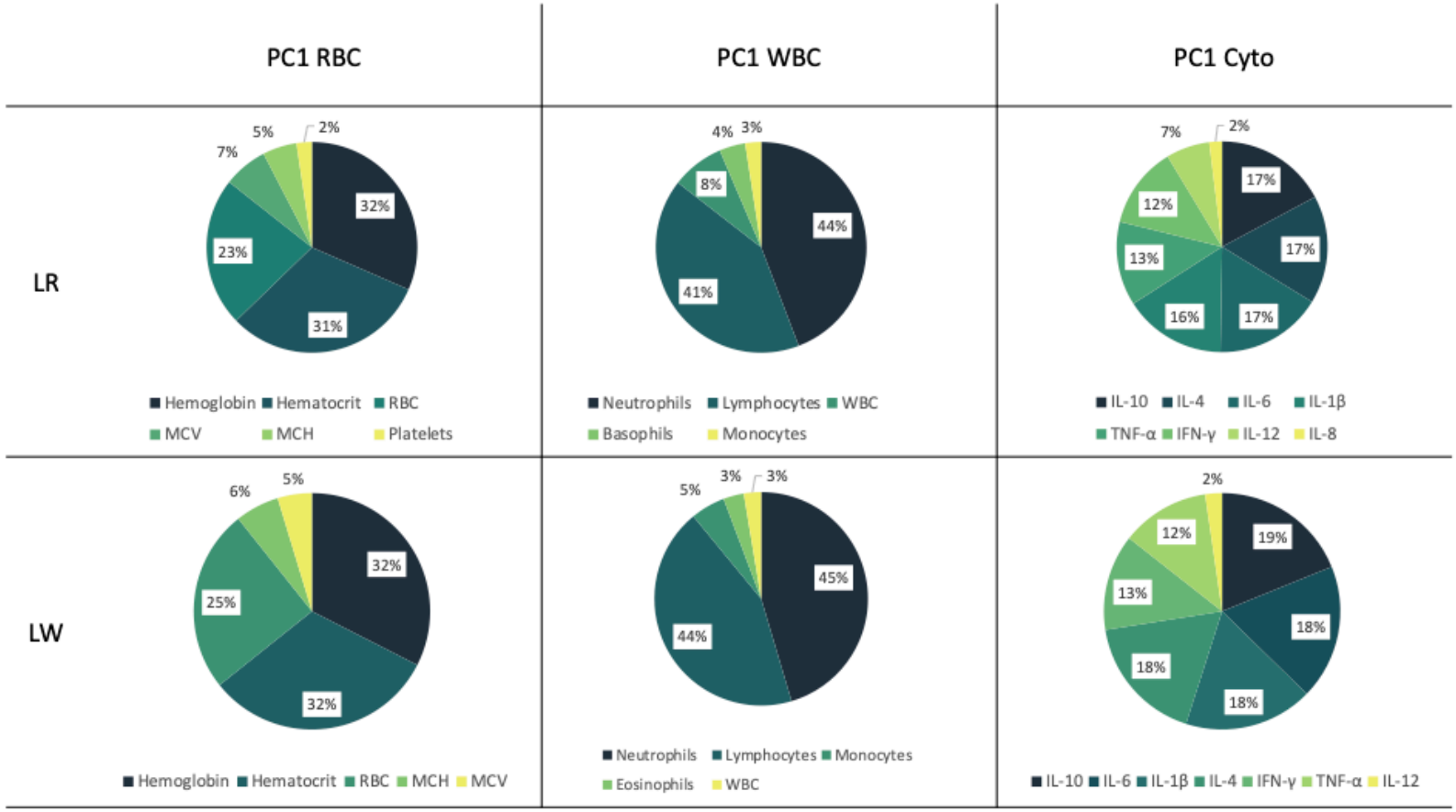

Figure 8: Loading composition for first principal components within piglet's functional biological networks

PC=principal component, LR = Landrace, LW=Large White, RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC=white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α. PCs are estimated within three distinguished biological functional networks like cells (Cell), RBC, and additional RBC characteristics including haptoglobin (RBC), and cytokines (Cyto).

3.4.6. Genetic parameters for condensed immune traits

Estimated h^2 and c^2 for relevant PCs in LR and LW piglets are presented in Table 4. Within the LR BFN Cell, $PC1_{Cell}$ to $PC3_{Cell}$ show moderate h^2 (0.18 to 0.31) and mostly low c^2 (0.04 to 0.06). In contrast to that, in LW only $PC1_{Cell}$ shows a h^2 (0.12) > 0.1 whereas c^2-values are on a slightly higher value (0.10 to 0.16).

For the BFN RBC in LR piglets, moderate ($PC2_{RBC}$, $PC3_{RBC}$) to high ($PC1_{RBC}$) h^2 were estimated in a range of 0.13 to 0.50, whereas c^2-effects were low (0.04 to 0.07). However, for LW piglets $PC1_{RBC}$ showed only a low h^2 (0.07), which is surprising because the composition and loadings of $PC1_{RBC}$ in LW and LR are similar. $PC2_{RBC,}$ $PC4_{RBC,}$ and $PC3_{RBC}$ had moderate to high (0.14 to 0.58) h^2 estimates in LW. Similar to the BFN Cell the estimates for c^2-effects are higher than in LR in a range of 0.11 to 0.15. Within the BFN Cyto, all PC_{Cyto} were moderately heritable (0.27 to 0.32) in both breeds. Similar to the variance component estimation for single cytokines the estimated c^2 values were particularly high for $PC1_{Cyto}$ in a range of 0.45 to 0.56.

Table 4: Direct genetic and litter effects for principal components of Landrace and Large White piglets within biological functional networks

BFN	PC	Landrace			Large White		
		σ^2p	**h^2±SE**	**c^2±SE**	**σ^2p**	**h^2±SE**	**c^2±SE**
Cell	PC1	3.87	0.31±0.08	0.06±0.03	3.53	0.12±0.07	0.16±0.05
	PC2	1.39	0.20±0.08	0.12±0.05	1.19	0.05±0.04	0.10±0.04
	PC3	0.98	0.18±0.07	0.04±0.03	0.85	0.04±0.04	0.14±0.05
RBC	PC1	3.89	**0.50±0.10**	0.05±0.04	3.61	0.08±0.08	0.12±0.05
	PC2	2.82	0.35±0.08	0.04±0.03	3.28	**0.58±0.11**	0.11±0.05
	PC3	1.04	0.13±0.06	0.07±0.04	0.86	0.17±0.06	0.11±0.05
	PC4					0.14±0.06	0.15±0.05
Cyto	PC1	6.10	0.32±0.10	**0.53±0.06**	10.69	0.27±0.09	**0.57±0.06**
	PC2				0.88	0.32±0.10	0.30±0.06

BFN = Biological functional network, PC=Principal component, σ^2p=phenotypic variance, h^2=heritability, c^2=litter effect, BFN Cell=immune cells, RBC=Red blood cells, and RBC characteristics, Cyto=cytokines, bold font indicates high h^2 or c^2 over 0.4 value

3.4.7. Genetic correlation between PCs of biological functional networks

In an additional step, a mv approach provided r_p and r_g between relevant PCs of LR and LW piglets applying model 1. According to the PCA principles, the phenotypic correlation between PCs within a BFN should be close to zero (Weller et al., 1996), so only the genetic correlation of PCs among BFN was estimated. All estimates can be found in the Table S8. Graphical representation of the genetic parameters h^2, r_p, and r_g for PCs in BFN is given in Figure 9.

As has been described in the previous section 3.4.5 breed-specific comparison of PCs is difficult because their loading composition is partly different. However, in general, many estimated genetic relationships for PCs in BFN Cell, RBC, and Cyto were characterized as high in both breeds.

In LR, high positive r_g were observed between $PC3_{Cell}$ and $PC1_{RBC}$, as well as $PC2_{Cell}$ and $PC2_{RBC}$. Between the BFN Cell and Cyto, all r_g were characterized as high (0.51 to 0.68), except for the relationship between $PC1_{Cell}$ and $PC1_{Cyto}$, which was only moderately (0.17).

In LW, high estimated r_g were detected between $PC4_{RBC}$ and all PCs in the BFN Cell (0.89 to -0.84). In addition, $PC2_{Cell}$ and $PC2_{RBC}$, as well as $PC3_{Cell}$ and $PC2_{RBC}$ show high negative r_g (-0.89 to -0.64). Between the BFN Cell and Cyto, all r_g were characterized as moderate to high (0.36 to -0.93). Further, between $PC1_{Cyto}$ and $PC2_{RBC,}$ a high negative (-0.70) r_g was observed. However, the r_g was highly positive (0.89) between $PC1_{Cyto}$ and $PC3_{RBC}$.

In addition, we observed that the first PCs of each BFN ($PC1_{Cell}$, $PC1_{RBC}$, $PC1_{Cyto}$) can be compared between the breeds due to similarities in the contribution based on their loading values (Figure 8). Therefore, breed differences were observed for high r_g between $PC1_{Cyto}$ and $PC2_{Cell}$. In LR, $PC1_{Cyto}$ and $PC2_{Cell}$ were high positively correlated (0.51), whereas in LW they were high negatively correlated (-0.93). $PC1_{Cyto}$ and $PC1_{RBC}$ were high positively correlated in LR (0.68) whereas in LW this relationship was described as moderate (0.24).

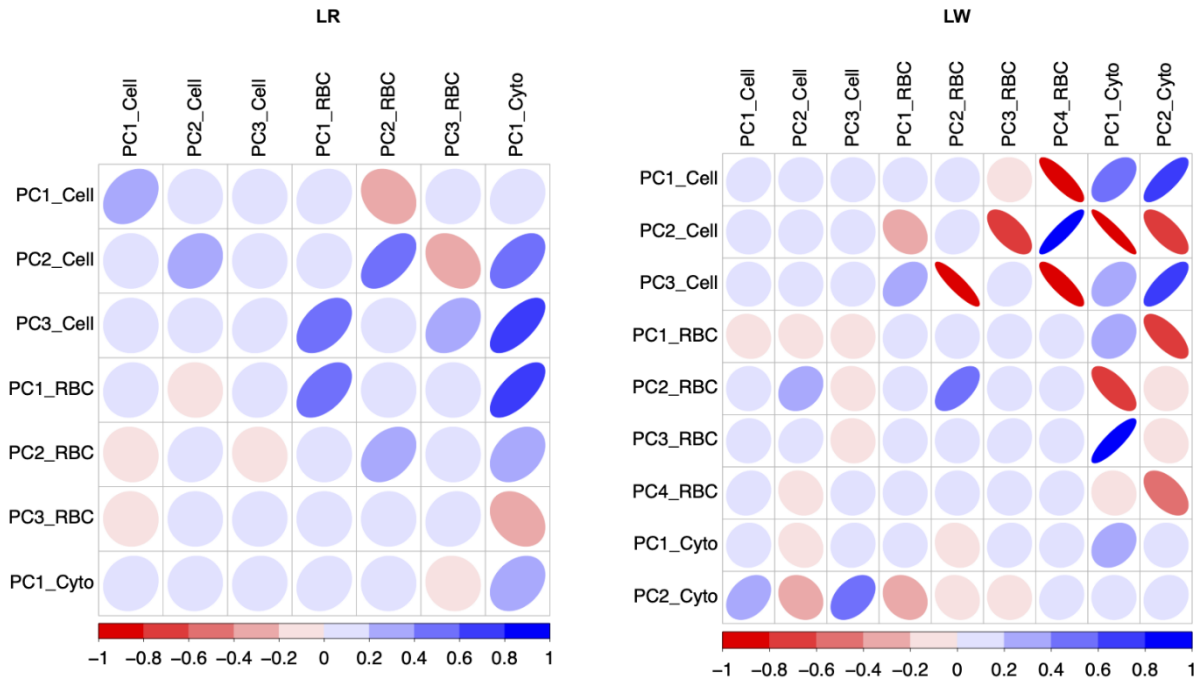

Figure 9: Graphical display of genetic parameters for condensed variables in the piglet data set

Heritabilities (h^2) on the diagonal. Phenotypic correlations (r_p) under the diagonal and genetic correlations (r_g) above the diagonal. PC=Principal component, LR = Landrace, LW=Large White, PCs are estimated within three distinguished biological functional networks like cells (Cell), RBC and additional RBC characteristics including haptoglobin (RBC), and cytokines (Cyto).

3.5. Discussion

In this study, the genetic background of immune traits and their complex relationships were investigated. For this purpose, 22 immune traits were analyzed in LR and LW piglets together with their biological dams. Genetic parameters were estimated and a mv approach using a PCA was initiated. The extension of the animal mixed model for additional covariate of dam's PC allowed the investigation of environmental influences on piglet's immunity.

The comparison of phenotypic mean values between the breeds showed clear differences and was also confirmed by the neutrophil to lymphocyte ratio. Friendship et al. (1984) have reported that within the feeder, finisher pigs, and sows the number of lymphocytes exceeded the number of neutrophils, except for growing pigs. The numbers of neutrophils are expected to exceed lymphocytes in piglets because neonates were assumed to develop their adaptive immune systems (Farmer, 2015). In addition to the age, farm, physiological status (lactating or pregnant sow) of the pig can influence the hematological profile. Lactating sows had higher neutrophil and lower lymphocyte values than pregnant sows (Ježek et al., 2018). Breed differences for immune traits phenotypic values (e.g., neutrophil to lymphocyte ratio) are also reported for other breeds and will be explained further. Clapperton et al. (2005) demonstrated differences in innate immune traits between Meishan and LW pigs. Meishans had higher neutrophil and monocyte counts and lower lymphocyte counts. At the current state, it is not possible to characterize which ratio is beneficial for a stable or advantageous immune system; still, such differences in immune traits may have implications in the resistance to pathogen infection in these breeds.

3.5.1. Environmental effects affecting the immune traits

As described in the method section, the estimation of genetic parameters was realized for the LR and LW piglets separately. The selection for the suitable environmental correction was achieved by including relevant significant fixed effects into the statistical model based on ANOVA results. Published reference studies (Ježek et al., 2018; Ponsuksili et al., 2016) have described significant influences of sex, breed, farm, physiological status, and parity for hematological profiles and cytokines. Our results partly confirm already published influencing factors. Discrepancies can be explained by the chosen blood sampling period and the investigated breeds. Finally, relevant effects based on literature and our results were included in the statistical model 1. Further, the environmental impact of the biological dam was analyzed and described in detail.

3.5.2. Genetic foundation of immune traits for piglets

The inclusion of immune traits in a selection program requires these traits to be heritable across generations. Our study confirms previous findings reporting a genetic foundation for immune traits with h^2 estimates for several immune traits within the published range (Clapperton et al., 2009; Clapperton et al., 2008; Edfors-Lilja et al., 1998; Flori, Gao, Laloë, et al., 2011; Hermesch & Luxford, 2018; Mpetile et al., 2015; Ponsuksili et al., 2016). Moderate h^2 was found for RBC in LW piglets as reported by several authors (Flori, Gao, Laloë, et al., 2011; Mpetile et al., 2015; Ponsuksili et al., 2016). High h^2 for MCV were observed in both breeds and have been previously confirmed by Mpetile et al. (2015) in Yorkshire pigs and by Ponsuksili et al. (2016) in LR pigs. MCH showed high h^2, which is comparable to the study of Ponsuksili et al. (2016) for LR pigs but has been in contrast to Mpetile et al. (2015) for Yorkshire pigs. Flori, Gao, Laloë, et al. (2011) have reported h^2 for cytokines, however, their estimates for LW swine were very low. In the current study, there were high h^2 for TNF-α in LR piglets and moderate h^2 estimates for all examined cytokines in LW piglets. Generally, there are numerous differences between these studies. Clapperton et al. (2008) estimated the h^2 of two traits in common (WBC and monocytes) in approximately 500 LW pigs at 30 and 90 kg weight under two environments. Clapperton et al. (2009) evaluated unchallenged and unvaccinated pigs that were either at a farm without major swine pathogens or at a farm where swine pathogens were documented. Flori, Gao, Laloë, et al. (2011) measured many of the same traits as investigated in this study in 443 LW pigs one week after these were vaccinated against *Mycoplasma hyopneumoniae*. However, due to fundamental differences, inter-study results should be interpreted with caution. Variations between LR and LW as well as deviations between study results and the literature can be explained by genetic diversities among the breeds but also by heterogeneous environmental conditions or different effects included in the model. Breed differences described in the present study may be related to various disease resistance traits. In the literature, pigs from Duroc and Yorkshire breeds have been shown generally to be more resistant to clinical and subclinical diseases than pigs from LR and Hampshire breeds (Henryon et al., 2001). Genetic breed variation has also been reported between LR, LW, and Duroc in delayed-type hypersensitivity (DTH) and Immunoglobulin G (IgG) (Kikuchi et al., 2002). Large White showed a significantly higher DTH area than LR and Duroc. In IgG concentration, Duroc was significantly lower than LR and LW. Between LR and LW no statistical difference in IgG concentration was detected. In a comparative study on hematological traits in LR, LW and Chinese Songliao Black pig breeds higher values of lymphocyte count, monocyte count, and hemoglobin were observed for LR piglets in comparison to LW. In contrast, MCH and MCHC

were lower in LR than in LW piglets (Y. Liu et al., 2010). The authors interpret a higher immune trait value as beneficial for the immune capacity. Similar observations have been reported by Wilkie and Mallard (1999). Piglets selected for a high immune response revealed a better response to vaccination. However, for some stimuli such pigs seemed to generate some autoimmune reactions (Mallard et al., 1992; Wilkie & Mallard, 1999). Therefore, it is still necessary to identify an optima for immune traits. Incorporating resilience indicators into breeding programs seem to be promising for producing healthy and manageable livestock (Berghof et al., 2018).

A consistent result of many studies is that pigs from breeds with high levels of reproduction (Meishan, LW) are more resistant to the effects of the Porcine reproductive and respiratory syndrome virus than pigs from lines selected for lean growth rate (Duroc, Pietrain) (Halbur et al., 1998; Petry et al., 2007; Vincent et al., 2005, 2006). However, other factors also influence the outcome of an immune response, for example, environmental factors and stressors (Clapperton et al., 2009; Farmer, 2015). Our results of additive genetic effects suggest that breed-specific selective breeding for immune traits is feasible. It is necessary to note that a sufficient genetic variance is essential for a high h^2. Some of our investigated immune traits i.a. HMT in LR did not meet this requirement, so that it is questionable if a promising genetic response can be achieved in such cases.

3.5.3. Maternal impacts on piglet's immune traits

Besides additive genetic effects, further effects e.g. litter can additionally influence piglets' immune traits. To test this hypothesis c^2 was estimated by including the litter information as an additional random effect into the model during variance component estimation. Results for both breeds showed moderate to high c^2 in common cytokines like IFN-γ, IL-10, IL-4, and IL-6. Above mentioned immune studies consider the litter effect and report similar results.

In addition, several studies describe the maternal impacts on piglet's immunity on an environmental level such as cell and antibody transfer, development of mucosal immunity, and colostrum intake (Bandrick et al., 2008; Hermesch et al., 2017; Salmon et al., 2009). Moreover, besides a low h^2, Rohrer et al. (2014) were even able to estimate moderate maternal genetic effect in their genetic analysis of colostrum intake measured as γ-immunoglobulins complexes bound to ammonium sulfate (immunocrit). There is limited information concerning the impact of immune factors transferred from colostrum and milk to suckling piglets on their immune development. Due to the epitheliochorial placentation of the sow, the passive transfer of antibodies from mother to offspring occurs during colostrum intake only (Farmer, 2015).

Maternal effects can also arise indirectly, whereby an immune trait of the mother would affect some part of the variation in offspring's phenotypic traits (Grindstaff et al., 2003). To consider an environmental impact, PCs of the dam's immune traits were added as an additional covariate into the model. In general, this consideration led to a decrease in h^2 while at the same time causing an increase in c^2 and r_g indicating that it is possible to adjust piglet's immune measurements. The biological dam plays a crucial role in fetal and postnatal piglet survival through the provision of vital resources and by displaying good maternal behavior. The genotype and parity of the dam, as well as the dam's physical condition during gestation and lactation influence piglet survival (Farmer, 2015) and, may have an indirect impact on the piglet's immune system. This statement implies that breeding affords immune traits in piglets that can be accessed through the biological dam.

3.5.4. Close relationships between immune traits imply complexity of piglet's immunity

The immune system is a highly interactive network where the ability to send signals from one cell to another is crucial. Communication within the adaptive immune system and between the innate and adaptive immune systems occurs directly via cell-to-cell contact or by the production of cytokines as mediators (Zimmerman et al., 2012). This leads to the presumption that immune cells and cytokines may be phenotypically or genetically correlated. Furthermore, it is expected that underlying genes may have pleiotropic effects, by influencing several immune traits at the same time (Lu et al., 2011). To investigate this close correlated relationship between examined traits, r_p and r_g were estimated with a mv approach. As expected, a strong positive r_g was observed between cytokines IFN-γ, IL-10, IL-1β, and IL-6 for both breeds. Pro-inflammatory cytokines (IFN-γ, IL-1β, and IL-6) are excreted by T-lymphocytes, monocytes, or macrophages and initiate an inflammatory response to regulate the host defense against pathogens. Anti-inflammatory cytokines (e.g. IL-10) are secreted by macrophages, T- and B-lymphocytes and have an immunoregulatory role by suppressing inflammatory response (Zimmerman et al., 2012). The importance of cytokines is emphasized by their function to alter metabolism. Cytokines IL-1, IL-6, and TNF-α have been found to modulate intermediary metabolism of carbohydrate, fat, protein substrates, regulate hypothalamic-pituitary outflow and act in the periphery and central nervous system (CNS) to reduce food intake (Johnson, 1997). Immune cells, but also microglial cells within the CNS can synthesize various cytokines (IL-1, IL-6, and TNF-α) at the same time (Fontana et al.). Increased mRNA and protein values of cytokines TNF-α, IL-1α, and IFN-γ within CNS have been observed in diseased animals infected with

encephalomyelitis (Renno et al., 1995). Therefore, cytokines demonstrate local effects, but can also act systemically to change animal behavior, metabolism, and neuroendocrine secretions.

Besides cytokines, strong correlations were found between RBC and RBC characteristics. F. Zhang et al. (2014) found moderate to high r_p for several hematological traits such as RBC and RBC characteristics like hematocrit, hemoglobin, MCV, MCHC in Chinese Sutai pigs. Furthermore, genome-wide association analysis for this trait revealed single nucleotide polymorphisms (e.g., ss107842725) located in ENSSSCG00000001232 gene on *Sus Scrofa* chromosome 7 which is associated with hematocrit, RBC, and MCV. Sharing the same genetic foundation between these traits' authors express that pleiotropic quantitative trait loci are common on hematological traits.

MCH amounts to the average hemoglobin level in a RBC (Zimmerman et al., 2012). The established high r_g of MCHC to monocytes cannot be fully explained from the literature. According to a recent mouse model of deep vein thrombosis, monocytes contribute to tissue factor-driven coagulation (Rezende et al., 2014) and for this reason, may be associated with higher MCHC values.

Estimated r_g for immune factors are very rare in the literature for livestock, especially for piglets. Flori, Gao, Laloë, et al. (2011) estimated r_g for components of innate and adaptive immunity and was able to show that these two pillars of the immune system are complementary. However, no clusters of innate or adaptive immunity were revealed and estimated r_g for immune traits were mostly weak. Nevertheless, for the total number of white blood cells and different leucocyte subsets high positive r_g were estimated which is consistent with our results. Estimated relationships highlight a strong connective network within the immune system where selection for several immune traits would affect other immune components and therefore, should be carefully examined.

3.5.5. The multivariate analysis emphasizes compound relationships between immune traits

PCA was chosen as a mv approach to reduce the dimensions of phenotypic immune measurement levels. Genetic parameters for direct immune measurements and PCs as new dependent immune variables are very similar. LR and LW showed consistent moderate to high h^2 and c^2 for RBC characteristics and cytokines and PCs which are composed of these phenotypes according to their loadings. Considering the r_g results for PCs, analog relationships are found as in estimated mv r_g between immune traits. For example, a close relationship was estimated between BFN RBC and Cyto, in detail $PC1_{RBC}$ and $PC2_{Cyto}$ were moderate to highly correlated. According to the loadings, $PC2_{RBC}$ is mostly composed of two immune traits: MCH and MCHC, which express mean hemoglobin and mean hemoglobin concentration. Most investigated cytokines (IFN-γ, IL-10, IL-1β, IL-4, IL-6, TNF-α) contribute variance to the $PC1_{Cyto}$. As for mv direct r_g, this relationship was also observed as a high positive correlation between hemoglobin and the cytokines IFN-γ as well as TNF-α. Stimulation of human WBC with purified hemoglobin led to the release of proinflammatory cytokines IL-8 and TNF-α (McFaul et al., 2000).

The results obtained here demonstrate that PCA is a useful tool to condense information based on a phenotypic covariance matrix. The number of dependent variables can be reduced by applying this technique without losing important information (Weller et al., 1996). PCA provides from an originally large number of immune traits and variables a simpler basis for summarizing the data. A further advantage of a PCA is an appropriate weighting of immune traits within the PCs. Immunocompetence complex data was measured as immune traits in this study where a desirable directionality of an individual immune trait is unknown. PCs consider a proper weighting of these traits. Therefore, they represent an extraction of the desired and undesired direction of immune traits as the weighted sum of the original variables (Everitt & Hothorn, 2011).

3.6. Conclusion

This study investigated the genetic background of immune traits in LR and LW piglets and their corresponding dams through immune profiling. Most of the examined immune traits show moderate to high genetic parameters including h^2, c^2, and r_g. Condensed immune phenotypes as PCs allowed to uncover the complexity of the immune system networks. Most immune traits are heritable and are promising to cover global, but breed-specific immunocompetence in animals. The analysis of immune traits has to be extended to characterize relationships between immunity and performance to gain an improved immune system without accidental losses in productivity.

Chapter 4. Multivariate genome-wide associations for immune traits in two maternal pig lines

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4.1. Abstract

4.1.1. Background

Immune traits are considered to serve as potential biomarkers for pig's health. Medium to high heritabilities have been observed for some of the immune traits suggesting genetic variability of these phenotypes. Consideration of previously established genetic correlations between immune traits can be used to identify pleiotropic genetic markers. Therefore, genome-wide association study (GWAS) approaches are required to explore the joint genetic foundation for health biomarkers. Usually, GWAS explores phenotypes in a univariate (uv), trait-by-trait manner. Besides two uv GWAS methods, four multivariate (mv) GWAS approaches were applied on combinations out of 22 immune traits for Landrace (LR) and Large White (LW) pig lines.

4.1.2. Results

In total 433 (LR: 351, LW: 82) associations were identified with the uv approach implemented in PLINK and a Bayesian linear regression uv approach (BIMBAM) software. Single Nucleotide Polymorphisms (SNPs) that were identified with both uv approaches (n=32) were mostly associated with immune traits such as haptoglobin, red blood cell characteristics and cytokines, and were located in protein-coding genes. Mv GWAS approaches detected 647 associations for different mv immune trait combinations which were summarized to 133 Quantitative Trait Loci (QTL). SNPs for different trait combinations (n=66) were detected with more than one mv method. Most of these SNPs are associated with red blood cell related immune trait combinations. Functional annotation of these QTL revealed 453 immune-relevant protein-coding genes. With uv methods shared markers were not observed between the breeds, whereas mv approaches were able to detect two conjoint SNPs for LR and LW. Due to unmapped positions for these markers, their functional annotation was not clarified.

4.1.3. Conclusions

This study evaluated the joint genetic background of immune traits in LR and LW piglets through the application of various uv and mv GWAS approaches. In comparison to uv methods, mv methodologies identified more significant associations, which might reflect the pleiotropic background of the immune system more accurately. In genetic research of complex traits, the SNP effects are generally small. Furthermore, one genetic variant can affect several correlated immune traits at the same time, termed pleiotropy. As mv GWAS methods consider strong dependencies among traits, the power to detect SNPs can be boosted. Both methods revealed immune-relevant potential candidate genes. Our results indicate that one single test is not able

to detect all the different types of genetic effects in the most powerful manner and therefore, the methods should be applied complementary.

Keywords: Immune traits; Pigs; Multivariate; Genome-wide Association Studies; Immunocompetence; Animal Genetics

4.2. Background

In modern swine breeding conditions, the time around birth is one main critical period for piglet survival (Heuß et al., 2019; Theil et al., 2014). Development of breeding programs to increase general immunocompetence in order to improve piglet survival are desired. Enhancing the piglet's immune capacity can result in further beneficial animal welfare and productivity of pigs. The immune system plays an essential role in the immunocompetence of piglets (Edfors-Lilja et al., 1994). For the progress of selection strategies, basic knowledge of the genetic foundation for phenotypes associated with global immunocompetence is required.

Medium to high heritabilities (h2 0.4-0.8) have been estimated for several immune traits suggesting exceeding potential of the genetic impact (Clapperton et al., 2009; Flori, Gao, Laloë, et al., 2011; Hermesch & Luxford, 2018). GWAS and QTL mapping can be used to explore the genetic background of immune phenotypes. Several QTL studies revealed markers throughout all chromosomes for immune traits related to red and white blood cells (Cho et al., 2011; Edfors-Lilja et al., 1998; Gong et al., 2010; Reiner et al., 2007, 2008; S. Yang et al., 2009; Zou et al., 2008) as well as cytokines (Uddin et al., 2011). Previous GWAS successfully identified numerous genetic markers associated with different phenotypes such as hematological, leucocyte-related traits (Ballester et al., 2020; Bovo et al., 2019; Lu et al., 2013; Luo et al., 2012; Ponsuksili et al., 2016; Wang et al., 2013; F. Zhang et al., 2014; Z. Zhang et al., 2013) and cytokines like interferone (IFN) and interleukins (IL-10) (Dauben et al., 2021; Lu et al., 2013).

Usually, GWAS addresses phenotypes in a univariate (uv) trait manner. However, a variety of multivariate (mv) methods were introduced to analyze multiple traits jointly (Zelterman, 2015). The utilization of mv methods is recommended to increase the statistical power to detect associations (Galesloot et al., 2014; Porter & O'Reilly, 2017; Wang et al., 2013). Previous results show moderate to high genetic correlation (rg 0.4-0.8) between immune traits (Roth et al., 2022) . Consideration of rg between multiple immune traits can be used to identify pleiotropic genetic markers. So far, Bovo et al.

(Bovo et al., 2019) reported uv and mv results for the largest number of 30 hematological and clinical biochemical traits in slaughtered pigs. In these studies, pleiotropic QTL and significant tag haplotypes with effects on multiple blood parameters were detected with mv analysis e.g., a mv Bayesian approach. The aim of this study was to identify genetic markers associated with immune traits. Besides uv GWAS the following mv statistical approaches have been applied and the results have been compared: Principal component analysis (PCA), Canonical correlation analysis (CCA), Meta-analysis (TATES) and one mv Bayesian linear regression approach (mvBIMBAM). Preliminary estimated genetic correlations (Roth et al., 2022) and the construction of biological network assisted the detection of pleiotropic QTL regions. Therefore, a LR and a LW population were investigated in order to identify biologically relevant pleiotropic markers related to health and immunity.

4.3. Results

An overview of the investigated data sets, animals and immune traits can be found in Dauben et al. (2021) and Roth et al. (2022). In brief, piglets of LR and LW were phenotyped for the complete and differential blood count (15 traits), eight cytokines and haptoglobin. The experiment was conducted under mostly practical, but high hygienic conditions and without challenging the animals (Dauben et al., 2021). For the uv and mv analyses performed in this study, data sets of 522 LR and 461 LW piglets comprising 47,292 and 43,730 SNP markers, respectively, were used

4.3.1. Genetic markers identified with uv GWAS approaches

Linear and Bayesian linear regression-based approaches were applied to obtain uv GWAS results (Table S9). In total 401 significant associations were identified with PLINK (LR: 324, LW: 77; adjusted p-value < 0.05). For uv BIMBAM 32 associations were detected in total (LR: 27, LW: 5; BF > 3.02). All SNPs observed with the uv Bayesian approach were also detected by the linear regression approach as implemented in PLINK. These results were mostly associated with immune traits related to red blood cells (RBC), cytokines, and haptoglobin (HAP). The identification of pleiotropic SNPs with uv GWAS is possible when genetic markers are detected across various traits. In total, 75 SNPs (PLINK: 70, 5: BIMBAM) were detected for multiple traits like RBC (RBC, HMG, HMT) and cytokines (IL1b, IL-4, IL-6, IL-10, Tumor Necrosis Factor-α (TNF)) within uv GWAS. Aditionally, the uv GWAS results were compared

across the investigated breeds, however, no overlapping markers were observed between the breeds (Figure S1).

4.3.2. Principal component analysis of the immune traits

Details of the analysis of the PCs within the breeds can be found in the study of Roth et al. (2022). In brief, within BFN red blood cells (RBC), PC1 RBC explains ~37% of the variation in both breeds (LR: 37.23%, LW: 37.49%). This PC is mainly influenced by RBC characteristics of haemoglobin, haematocrit and RBC. On the contrary, PC2 RBC (LR: 22.43%, LW: 22.84%) is mainly influenced by the calculated ratio of mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MCV) (only in LR). Within PC3 RBC and PC4 RBC which also explain more than 10% of the variation, mean corpuscular haemoglobin concentration (MCHC) and haptoglobin are the main actors. Within the BFN cells, PC1 Cell (LW: 35.96%, LR: 35.49%) is dominated by neutrophils and lymphocytes, which were known to be negatively correlated and influenced by the time point of blood sampling. On the contrary, PC2 Cell can be characterized by the percentages of eosinophils and white blood cells (WBC) (only in LW). In BFN cytokines (Cyto), PC1 Cyto explains most of the phenotypic variation (LR: 68.13%, LW: 60.13%). This PC is similarly influenced by examined cytokines. Apart from that, the chemokines IL-12 and Il-8 have less impact on PC1 Cyto but dominate PC2 Cyto in LW piglets. PCs of the two breeds cannot be compared in general because their composition based on loading values differs from breed to breed. In contrast, we assumed that the variance components of the first PCs of each BFN (PC1 Cell, PC1 RBC and PC1 Cyto) are comparable between the breeds due to similarities in the contribution based on their loading values.

4.3.3. Structural multivariate trait combinations

The identification of causal relationships among immune traits before performing mv GWAS helps to reduce extensive computation effort impaired by the realization of all possible mv combinations for all available immune phenotypes. Immune trait combinations of interest were created by performing Bayesian Network (BN) analyses based on the hill-climbing algorithm (Scutari et al., 2019) for all immune traits in LR and LW data sets.

The dependencies among the variables of the structural BN model strings are illustrated in Figure 10 and are presented in Table 5. In total 22 combinations were detected for LR and LW, respectively. In Table 1 the structure of the identified BN is displayed: a local structure is presented in square brackets [] with the first string identifying a node. There are two types of nodes: parents and children. The state input variables, or parents of the node, are listed after a vertical bar "|", separated by colons ":". Children of the node represent the interaction

determined by the conditional probability, derived from two or more parent nodes. One trait combination [HMT|HMG:Mean Corpuscular Hemoglobin Concentration (MCHC)] was identified in both breed-specific networks allowing investigations for trait combinations within as well as across the breeds.

The causal relationships among the phenotypes are also displayed in Figure 10. Each of the nodes (e.g. RBC, white blood cells (WBC), IL10) represents the measured phenotypes. A directed arrow from one node to another means a direct causal effect. For example, in LR, HAP has a direct causal effect on the variable WBC, which in turn affects neutrophils (NEU) and IL1B. To accentuate functional biological networks of phenotypes, nodes are illustrated in different colors. Node frames are highlighted in red when variables are conditionally independent (HAP in LW and LR, PLT in LR). Additionally, colors are used for arrows to indicate parental relationships of the nodes in the structured model learned from the data sets.

Although BNs do not serve as biological patterns, causal relationships between immune traits mostly represent biological functional subsets. Combinations mainly based of WBC, RBC, and cytokine-related clusters. The identified conditionally dependent traits by the network structure were used as mv trait combinations for mv GWAS.

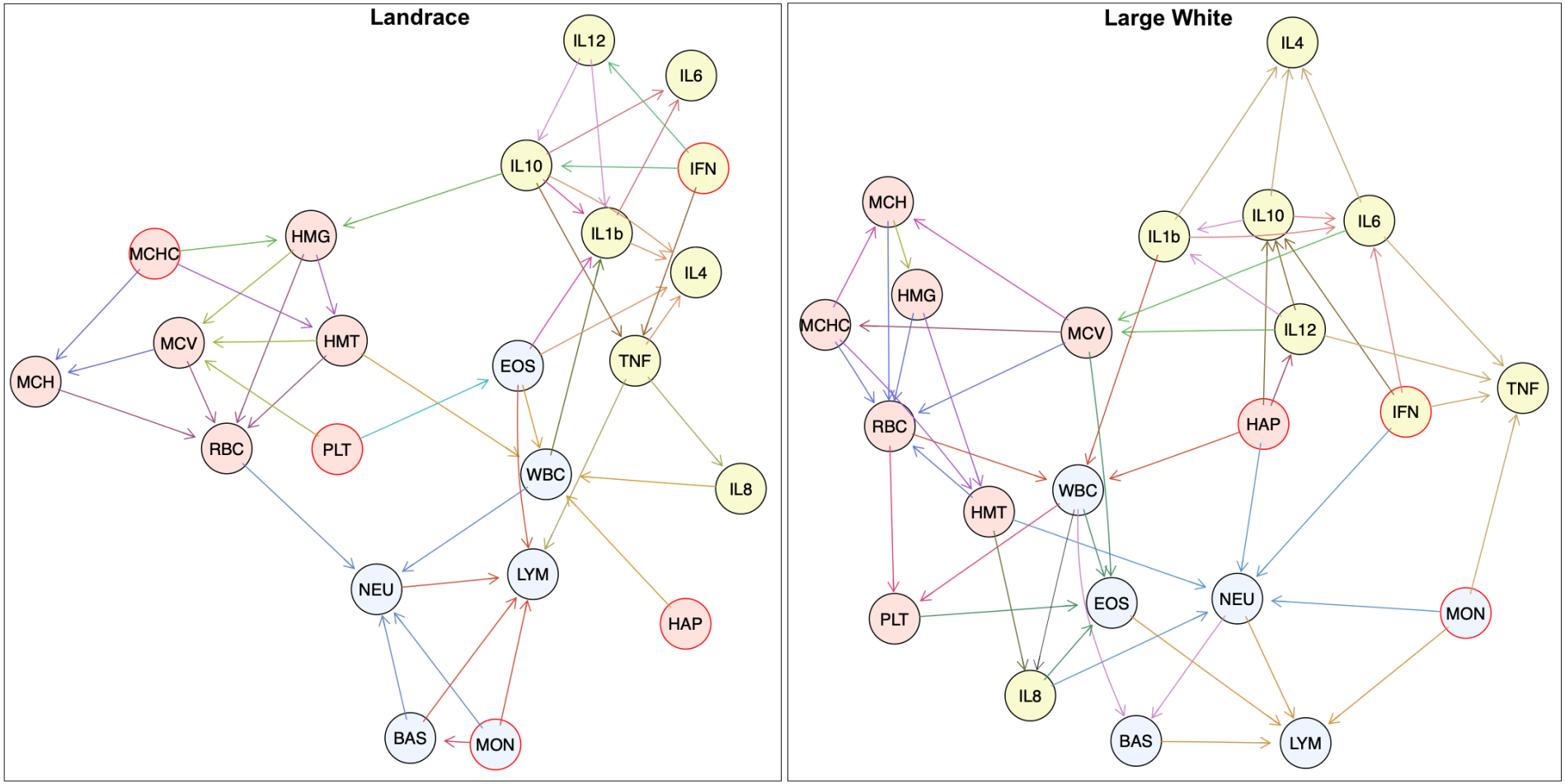

Figure 10: Bayesian network for immune trait residuals

RBC=red blood cells, HMG=hemoglobin, HMT=hematocrit, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, PLT=platelets, WBC=white blood cells, NEU=neutrophils, LYM=lymphocytes, MON=monocytes, EOS=eosinophils, BAS=basophils, HAP=haptoglobin, IFN=interferon-γ, IL=interleukin, TNF=tumor necrosis factor-α. Functional biological networks of phenotypes are illustrated as nodes in pale blue ( ) for WBC, light red ( ) for RBC, and yellow ( ) for cytokines. Node frames are highlighted in red to highlight conditionally independent variables. Colored arrows are used to indicate parental relationships of the nodes in the structured model learned from the data sets.

Table 5: Resulting structural model learned from a causal network

Breed	Conditional independent	Conditional dependent with one parent	Conditional dependent with two parents	Conditional dependent with multiple parents
LR	[MCHC] [PLT] [MON] [HAP] [IFN]	[BAS|MON] [EOS|PLT] [IL8|TNF] [IL12|IFN]	[HMG|MCHC:IL10] [HMT|HMG:MCHC] [MCH|MCV:MCHC] [IL6|IL10:IL1b] [IL10|IFN:IL12] [TNF|IFN:IL10]	[RBC|HMG:HMT:MCV:MCH] [MCV|HMG:HMT:PLT] [WBC|HMT:EOS:HAP:IL8] [LYM|NEU:MON:EOS:BAS: TNF] [NEU|RBC:WBC:MON:BAS] [IL1b|WBC:EOS:IL10:IL12] [IL4|EOS:IL10:IL1b:TNF]
LW	[MON] [HAP] [IFN]	[IL12|HAP] [HMG|MCH] [MCHC|MCV]	[MCV|IL12:IL6] [HMT|HMG:MCHC] [MCH|MCV:MCHC] [PLT|RBC:WBC] [BAS|WBC:NEU] [IL1b|IL10:IL12] [IL8|HMT:WBC]	[RBC|HMG:HMT:MCV:MCH:MCHC] [WBC|RBC:HAP:IL1b] [NEU|HMT:MON:HAP:IFN: IL8] [LYM|NEU:MON:EOS:BAS] [EOS|MCV:PLT:WBC:IL8] [IL10|HAP:IFN:IL12] [IL4|IL10:IL1b:IL6] [IL6|IFN:IL10:IL1b] [TNF|MON:IFN:IL12:IL6]

LR=Landrace, LW=Large White, RBC=red blood cells, HMG=hemoglobin, HMT=hematocrit, MCV= mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, PLT=platelets, WBC=white blood cells, NEU=neutrophils, LYM=lymphocytes, MON=monocytes, EOS=eosinophils, BAS=basophils, HAP=haptoglobin, IFN-γ= interferon-γ, IL=interleukin, TNF-α= tumor necrosis factor-α. Conditional dependencies are indicated as straight line. Local structure is presented in square brackets [] with the first string identifying a node. Parents of the node are listed after "|" and are separated by colons ":". Children of the node represent the interaction determined by the conditional probability, derived from two or more parent nodes. These parental relationships are also indicated in different colors for arrows in Figure 10. The causal network model was assigned in three categories for more comprehensive understanding of the model structure. Conditionally dependent traits identified by the network structure given in [] were used as trait combinations for multivariate genome-wide association study

4.3.4. Genetic markers identified with mv GWAS approaches

Applying uv GWAS, the identification of pleiotropic genomic region is limited, especially in the situation of polygenic inherited traits. Therefore, the following four different mv approaches were applied on immune trait combinations for LR and LW in order to increase the detection power for pleiotropic SNP: PCA, CCA, TATES and mvBIMBAM. In total, 647 significant associated SNPs were detected with mv methods and can be found in the Additional Table S10. PCA was able to detect 98 (9 genome-wide and 89 chromosome-wide significant) and 26 (5 genome-wide and 21 chromosome-wide significant) SNPs associated with the phenotypes for LR and LW, respectively.

CCA revealed a variety of associated SNPs: 416 for LR and 151 for LW. For LR, 72 were genome-wide and 344 were chromosome-wide significant. For LW, 37 were genome-wide and 144 were chromosome-wide significant.

Twenty-eight genome-wide significant markers were determined with TATES for LR while 3 genome-wide significant genetic variants were characterized as significant for LW.

mvBIMBAM detected 8 and 23 genome-wide significant SNPs for LR and LW, respectively.

All detected SNPs with mv methods were summarized to 190 QTLs, by assuming a 1 Mbp interval around significant SNPs. Out of these QTLs, 133 were located within or close located to protein-coding genes. Functional annotation of these QTLs revealed 453 protein-coding genes (Additional Table S10).

4.3.5. Comparison across mv GWAS results

SNPs that are identified with multiple mv methods are of particular interest to characterizing pleiotropy. In total, 66 SNPs were detected for different trait combinations with more than one mv method (Figure 11). Thirty-seven of these SNPs are associated with RBC related immune trait combinations (e.g. [RBC|HMG:HMT:Mean Corpuscular Volume (MCV):Mean Corpuscular Hemoglobin (MCH), HMG|MCHC:IL10, HMT|HMG:MCHC]. Thirteen SNPs are associated with WBC subtypes and 12 with cytokines. For example, SNP ALGA0073579 (rs81442304) was identified with three mv methods CCA, TATES, as well as mvBIMBAM. CCA and TATES associated this SNP with BAS|MON in LR, whereas mvBIMBAM detected this association for cytokines IL-4|IL-10:IL-1b:IL-6 in LW. Currently, this SNP remains unmapped for Sscrofa 11.1. SNPs ALGA0086892 (rs81454413, SSC 15: 116.13 Mbp), ASGA0070586 (rs80818610, SSC15: 120.11 Mbp), and ASGA0070620 (rs80883544, SSC 15: 120.35 Mbp) were detected by all four mv methods in LR for cytokines and a five immune trait combination of WBC, HMT, eosinophils (EOS), HAP, and IL-8. With PCA these SNPs were observed for the second PC in the biological functional network of cytokines (PC2 Cyto).

According to the contribution based on loading values, this PC mainly contains cytokines IL-12 and IL-8 (Roth et al., 2022). These SNPs are located on SSC 15 within an intron region of four Mbp (116.13 to 120.35 Mbp) (Figure 11, Table 6).

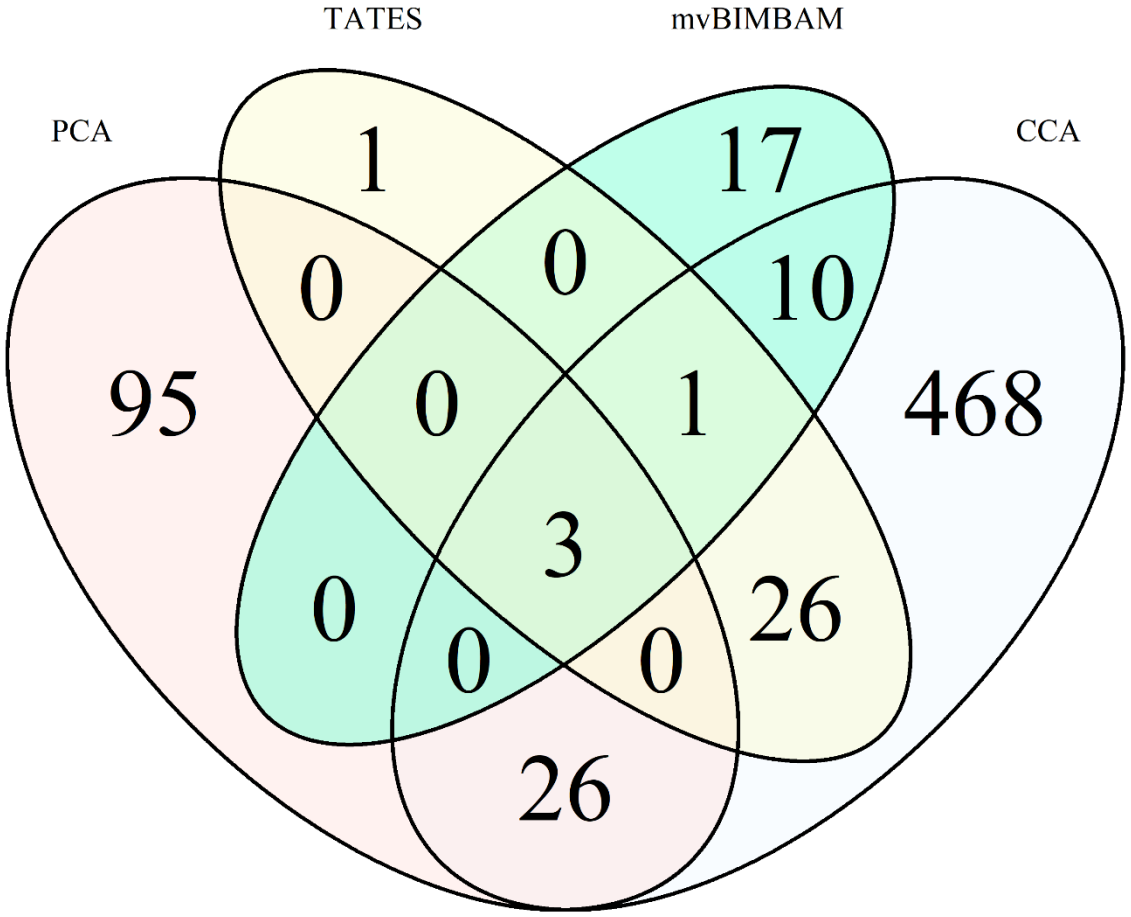

Figure 11: Venn diagram of different methods used to detect significant multivariate associations for both breeds and significance types

PCA=Principal component analysis, CCA=Canonical correlation analysis, TATES=Trait-based Association Test that uses Extended Simes procedure, mvBIMBAM= multivariate Bayesian imputation-based association mapping. Multiple identical significant SNPs for different immune traits within a method are counted once.

Table 6: Selected significant associated genetic markers identified with multivariate methods

Breed	Trait	SSC	SNP	Pos	m/M	MAF	p-value/BF	Method	Gene
LR; LW	BAS|MON, NEU|RBC:WBC:MON:BAS; IL-4|IL-10:IL-1b:IL-6		ALGA0073579		T/C	0.01 and 0.21	0.01/3.22	CCA, TATES, mvBIMBAM	
LR; LW	HMG|MCHC:IL-10, PC4Cell; PLT|RBC:WBC		H3GA0016899		T/C	0.04 and 0.16	0.04	CCA, PCA	
LR	IL-8|TNF, WBC|HMT:EOS:HAP:IL-8, PC2Cyto	15	ALGA0086892	120.1	T/C	0.50	0.04/3.5	CCA, PCA, TATES, mvBIMBAM	SPAG16
LR	IL-8|TNF, WBC|HMT:EOS:HAP:IL-8, PC2Cyto	15	ASGA0070586	120.1	T/C	0.41	0.01/4.77	CCA, PCA, TATES, mvBIMBAM	TNS1, RUFY4, CXCR2, ARPC2, GPBAR1, AAMP, PNKD, TMBIM6
LR	IL8|TNF, WBC|HMT:EOS:HAP:IL-8, PC2Cyto	15	ASGA0070620	120.3	T/C	0.39	0.03/4.04	CCA, PCA, TATES, mvBIMBAM	

SSC=*Sus scrofa* chromosome, SNP=single nucleotide polymorphism, Pos=position [Mbp] m/M allele=minor/major allele, MAF=minor allele frequency, p-value =adjusted p-value after correction for stratification and multiple testing, BF=Bayesian factor, Gene=selected nearest gene within a progressive number of QTL based on ± 1Mbp distance from a significant SNP, LR=Landrace, LW=Large White, BAS=basophils, MON=monocytes, IL=interleukin, HMG=hemoglobin, HMT=hematocrit, NEU=neutrophils, RBC=red blood cells, WBC=white blood cells, PLT=platelets, IFN= interferon-γ, TNF=tumor necrosis factor-α, PC= principal component, Cell/Cyto=biological functional networks within the PCA cell/cytokines, PCA=principal component analysis, CCA=canonical correlation analysis, TATES=trait-based association test that uses extended Simes procedure, mvBIMBAM=multivariate Bayesian imputation-based association mapping.

In addition, 152 markers were identified for multiple mv trait combinations (Table S10). Identical SNPs were mostly shared between immune traits related to functional biological immune trait subsets like RBC (e.g. [HMT|HMG:MCHC], MCH|MCV:MCHC], [RBC|HMG:HMT:MCV:MCH]), WBC subtypes (e.g. [NEU|RBC:WBC:Monocytes (MON):Basophils (BAS)], [Lymphocytes (LYM)|NEU:MON: EOS:BAS:TNF]) and cytokines (e.g. [IL1b|IL10:IL12], [IL4|IL10:IL1b:IL6], [IL6|IFN:IL10:IL1b]). These markers are distributed over all 18 chromosomes. Interestingly, 30% of identical markers are located on *SSC* 5 between 23.93 and 97.48 Mbp and cover 16 QTLs including 20 protein-coding genes (Figure 12).

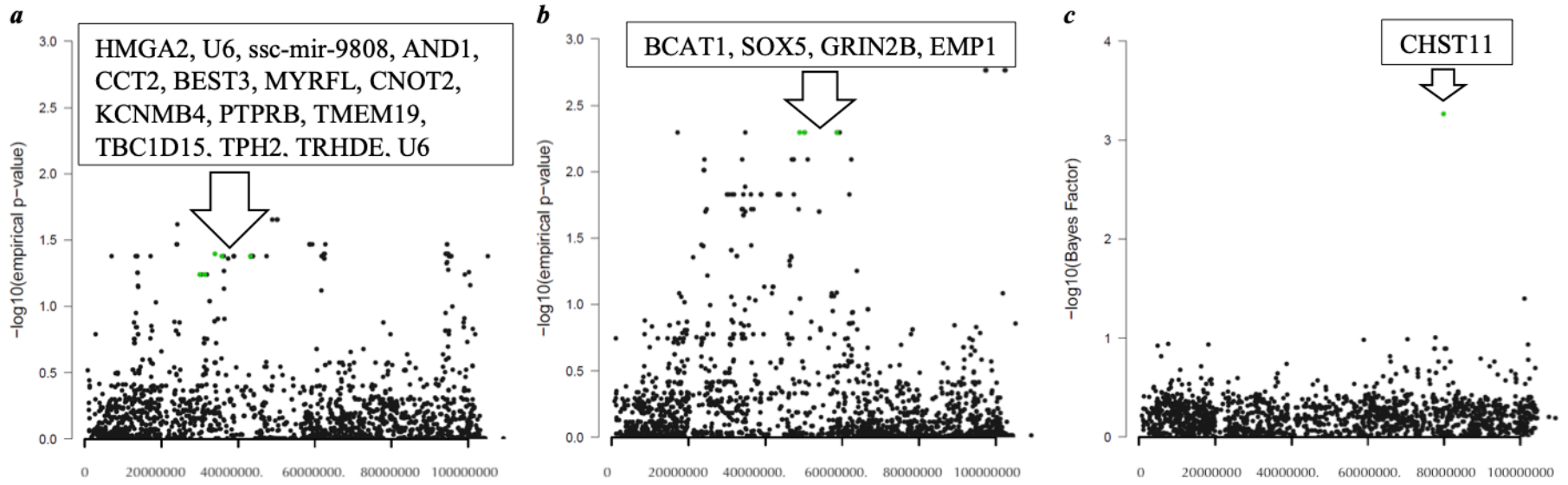

Figure 12: Manhattan plot of SSC5 for multivariate trait combinations a RBC|HMG: HMT:MCV:MCH in Landrace with CCA, b HMG|MCHC:IL10 in Landrace with CCA, and c WBC|RBC:HAP:IL1b in Large White with mvBIMBAM

RBC=red blood cells, HMG=hemoglobin, HMT=hematocrit, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, IL=interleukin, WBC=white blood cells, HAP=haptoglobin, SNPs of interest are highlighted with green color (**a** DRGA0005609, ASGA0025326, ALGA0031690, MARC0021861, DRGA0005776, **b** ALGA0031924, MARC0001027, ALGA0032074, and **c** MARC0013873). Protein coding genes within annotated QTLs between 23.93 and 97.48 Mbp are stated in the box

In addition, mv results were compared across the investigated breeds. In total, 469 markers were identified for LR, whereas 180 were detected for LW applying mv GWAS. Two SNPs, ALGA0073579 (rs81442304) and H3GA0016899 (rs80959576), were repeatedly observed in both breeds (Table 6). These markers were identified by applying mv methods (CCA, TATES, mvBIMBAM) as well as with uv methods.

4.3.6. Comparison between uv and mv GWAS results

In addition, a comparison of the uv and mv results revealed that 204 markers overlap across the methods (Figure 4). All in all, these 204 markers are located near 125 protein coding genes. Filtering the overlapping SNPs for the investigated breeds revealed four interesting genetic variants (ALGA0073579 (rs81442304), H3GA0016899 (rs80959576), DRGA0006061 (rs81303269, *SSC* 5: 79.02 Mbp), ALGA0113815 (rs81342648)) that overlap between uv and mv methods (Figure 13).

CCA revealed, that ALGA0073579 (rs81442304) was significantly associated with [BAS|MON] in LR, whereas, applying mvBIMBAM, this SNPs was observed for cytokines [IL-4|IL-10:IL-1b:IL-6] in LW. Additionally, this SNP was also identified for the trait basophils in LR within uv GWAS using PLINK.

H3GA0016899 (rs80959576) was significantly associated with PC4 Cell in LR. According to the loading value, PLT and HAP mostly contributed to PC4 Cell. Applying CCA allowed to detect this SNP for [PLT|RBC:WBC] in LW. Furthermore, H3GA0016899 was also significantly associated with RBC in LW using an uv GWAS.

The genetic variant DRGA0006061 (rs81303269, *SSC* 5: 79.02 Mbp) was identified for [IL4|EOS:IL10:IL1b:TNF] with CCA in LR, whereas PLINK detected this association for RBC in LW. Currently, the SNP H3GA0016899 is unmapped for *Sscrofa* 11.1, but was previously mapped on SSC 5.

On *SSC* 12, within and intron region of the Regulator of G-protein signalling 9 (RSG9) gene (12.0 Mbp), the SNP ALGA0113815 (rs81342648) was significantly associated with a PC2 Cyto (consisting of cytokines IFN-γ, IL-12, IL-8 specified by the loading value) by applying the PCA approach in LR, whereas PLINK identified this association for IL-4 in LW (Tables S9 and S10).

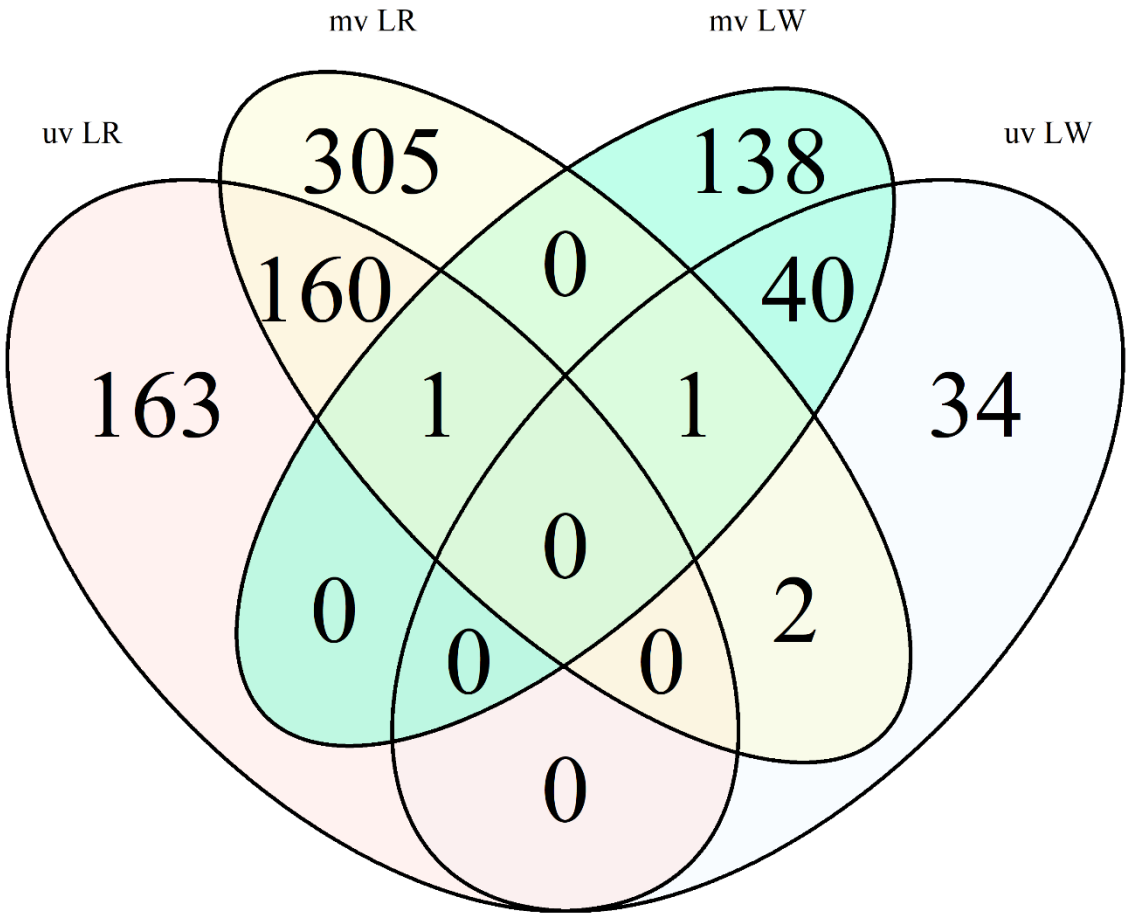

Figure 13: Genetic markers identified with GWAS approaches: Comparison of different association methods for both investigated breeds

Multiple identical significant SNPs for different immune traits within a method are counted a single time. mv=multivariate, uv=univariate, LR=Landrace, LW=Large White

4.4. Discussion

The aim of this study was the detection of genetic markers associated with immune traits applying different approaches of uv and mv GWAS. In total 401 and 647 significant associations were identified with uv GWAS and mv GWAS, respectively. Of particular interest are the created immune networks using BN and PC analyses.

4.4.1. Conditional dependencies of immune networks

For mv analysis 22 available immune phenotypes would result in multiple possible mv combinations, which would require high computational effort. The application of a BN approach allowed to identify conditional dependencies among immune traits and to focus on relevant trait combinations. Usually, BNs do not reflect biological patterns when causal statistical relationships between variables have been detected. However, identified combinations can be classified into biological functional subsets of immune traits. For both pig lines, conditional relationships were identified within RBC-related traits, WBC subtypes, and cytokines. These networks correspond to previous estimated rg results (Roth et al., 2022). RBC were highly correlated with RBC characteristics, like HMT (LR: 0.82±0.05, LW: 0.90±0.09) and HMG (LR: 0.81±0.06, LW: 0.77±0.10). As expected, among further RBC characteristics, a high positive correlation was found between HMT and HMG (LR: 0.99±0.00, LW: 0.97±0.04), MCH, and MCV (LR: 0.99±0.02, LW: 0.94±0.03). Between cytokines such as IFN-γ, IL-10, IL-1β, IL-4, and IL-6 high positive rg were estimated in both investigated pig lines. Immune cells such as MON and EOS were positively correlated to cytokines like TNF-α in LR but showed a high negative correlation in LW. Ballester et al. (2020) constructed a network based on phenotypic correlations for immune traits in Duroc piglets. Although only 13 immune parameters overlap between Ballester et al. (2020) and our study, similar clusters that relied on RBC and WBC subtypes were identified. The detected close relationships in the previous and current studies (Ballester et al., 2020; Bovo et al., 2020; Dauben et al., 2021; Roth et al., 2022) indicate the complexity of piglet's immunity.

As discussed by Roth et al. (2022) the PCA aims for a more powerful analysis of the immune traits by reducing the dimension of information, and therefore allowing the detection of key players in immunocompetence. In that study, PCA was shown to be an effective tool for condensing information based on a phenotypic covariance matrix. Using such a technique can reduce the number of dependent variables without compromising important information (Weller et al., 1996). Furthermore, PCAs provide an appropriate weighting of individual traits. In general, all observed phenotypic and genetic correlations as well as conditional dependencies

among immune parameters, might be helpful to create well-balanced breeding selection strategies to improve the immunocompetence of pigs.

4.4.2. Comparison between uv and mv GWAS results and method performance

Beside one uv frequentist and one uv Bayesian approach, four mv approaches (PCA, CCA, meta-analysis, mv Bayesian linear regression) were applied on two maternal pig lines. Results were empirically compared within and across the methods.

Comparing the uv approaches, identical significant associations were detected. The investigated data sets were also studied by Dauben et al. (2021) using the GenABEL-package in R (Aulchenko et al., 2007) and ASReml Software (Gilmour, 2015). In total, Dauben et al. (2021) identified 25 genome-wide and 452 chromosome-wide significant SNPs (LR: 280, LW: 197) associated with 17 immune relevant traits in both pig lines. Applying PLINK and uvBIMBAM it was possible to identify 433 (LR: 351, LW: 82) significant associations. Comparing the results of both studies, 159 and 15 associations were commonly detected for LR and LW, respectively.

One reason for the different number of significant SNP markers among the studies are caused by the requirement for the multivariate analyses. The number of phenotypes per animals have to be complete. Furthermore, the applied methods to correct for false positives and the determined threshold for genome-wide and chromosome-wide significance differ depending on the applied methodology.

Among the common associations in LR, 49 SNPs were also identified with mv methods in this study. Common results were mostly associated with immune traits related to RBC, cytokines, and HAP e. g. ASGA0070620 (rs80883544, SSC 15: 120.35 Mbp). The SNP ASGA0070620 is located near protein-coding genes such as TMBIM1 (transmembrane BAX inhibitor motif containing 1).

Generally, previous GWAS studies for immune traits focused mostly on uv statistical approaches. The application of mv methods is recommended to increase the statistical power to detect associations (Bovo et al., 2019; Galesloot et al., 2014; Porter & O'Reilly, 2017; Wang et al., 2013) even if the rg between the traits is expected to be weak (close to 0) [25, 26]. Consideration of previously published high rg ($\geq \pm 0.4$) results between multiple immune traits [27] was used to increase GWAS power to identify pleiotropic SNPs. In this study, mv methods revealed a higher number of significant associations compared to uv methods. Moreover, there was a substantial overlap of associations found by several mv methods which have different underlying statistical backgrounds. These results could be used as heuristic arguments, that mv-methods have a higher detection power. However, it should be considered that the number of

approaches differs between the applied methods. For uv analysis, two different approaches were compared, whereas for mv analysis four different mv methods were utilized.

204 SNPs were identified with uv and mv methods. When SNPs are detected with multiple approaches, they provide more certainty for the GWAS results and contribute potential candidate genes. However, 443 associations were exclusively identified with mv approaches. This underlines the importance of considering the correlation among immune traits with mv methods. Common markers for comparable trait complexes were also identified between different mv approaches. Nevertheless, markers match incompletely and only to a small extent. Application and comparison between multiple uv and mv approaches were addressed mostly on simulated data (Galesloot et al., 2014; Porter & O'Reilly, 2017), rather than on immune phenotypes. Recently, Bovo et al. (2020; 2019) reported uv and mv GWAS results for hematological and blood clinical-biochemical traits in LW pigs after slaughtering. Similarly, to our study, one frequentist and one Bayesian approach were applied. In general, the performance of different mv approaches is scenario-specific and sensitive to specific effects like allele frequency, the number of investigated traits, and underlying correlation structures among the traits (Galesloot et al., 2014; Porter & O'Reilly, 2017). Galesloot et al. (2014) concluded that mv methods implemented in software like PLINK, SNPTEST, MultiPhen, and mvBIMBAM performed best in terms of detection power for the majority of scenarios, which is partly consistent with our results.

Furthermore, it has to be mention, that the possibility of chromosome-wide correction for multiple testing was not applied in every approach and was limited to methodology implemented in PLINK and R. For CCA, the highest number of associated SNPs was reported in our analysis. Similar to our results, Galesloot et al. (2014) studied high power for almost all scenarios for the same approach. These authors explain higher power was observed with increasing residual correlation in case of a single QTL trait and when two or all three traits were associated with the QTL with a negative genetic correlation for methods including CCA. Due to trait correlations, test statistic distributions are likely to have longer tails, and therefore a more conservative threshold is recommended to maintain the type I error at 5% (Galesloot et al., 2014). As recommended by Galesloot et al. (2014), we lowered the threshold within the CCA approach (5 % default value to 1 % lowered threshold) and compared the association results empirically once again (results not shown). The number of detected SNPs with CCA lowered to 184 (LR: 144, LW: 40). However, the common three SNPs, which were detected with all four mv approaches, remained in the results for CCA after lowering the threshold.

Zhou et al. (2014b) developed an efficient linear mixed model algorithm for GWAS which is implemented in the software GEMMA and compared this algorithm to those implemented in WOMBAT (Meyer, 2007) and GCTA (J. Yang et al., 2011). Algorithms were applied to different numbers of phenotypes in simulated data as well as human and mouse data sets. Even though the authors reported exceeded improvements in computational time and power, they recommended considering the methods as complementary rather than competing. One single test is not able to detect all the many different types of genetic effects in the most powerful manner. Salinas et al. (2018) described many of the mv methods aimed to detect genetic pleiotropy in an epidemiological context. In their study, specific method selection considering phenotype distribution type and data availability was developed. Therefore, our results contribute to a deeper understanding of the performance power and selection of suitable mv methods.

4.4.3. Comparison of genetic markers between LR and LW

A comparison of results regarding breed differences was realized since GWAS methods were applied to the investigated breeds separately. With uv methods, no overlapping markers were observed, whereas mv methods were able to identify two SNPs shared between LR and LW. These two significant SNPs were currently unmapped. Using the older assembly 10.2 H3GA0016899 (rs80959576) was located on SSC5 (80.17 Mbp) as an intergenic variant and ALGA0073579 (rs81442304) on SSC13 (203.44 Mbp) within the GRIK1 gene, which the function has not been described so far. Thirty-eight SNP listed in table 2 could not be allocated by current assembly SScrofa 11.1 but were mapped under SScrofa 10.2. Therefore, these results should be considered with caution.

Several GWAS and QTL studies for immune competence traits investigated cross-bred (White Duroc x Erthulin F2, LR x Duroc x Yorkshire, LW x Minzhu F2) and pure-bred (Chinese Sutai, LR, LW, Songliao Black, Yorkshire) pigs (Bovo et al., 2019; Cho et al., 2011; Dauben et al., 2021; Edfors-Lilja et al., 1998; Gong et al., 2010; Lu et al., 2013; Luo et al., 2012; Ponsuksili et al., 2016; Reiner et al., 2007, 2008; Uddin et al., 2011; Wang et al., 2013; S. Yang et al., 2009; F. Zhang et al., 2014; Z. Zhang et al., 2013; Zou et al., 2008). Even though the results of these studies reported a few overlapping QTL regions, most of the markers were not shared between the studies. Genetic heterogeneity of the investigated pig populations, differences in the analyzed immune traits, variety of the experimental designs, and therefore, different environmental effects considered in the statistical models during the analysis, might explain the discrepancies among the studies and between the breeds. In the current study, further options

for pre-selection of the breed-specific mv trait combinations can be applied to enable appropriate comparison between the breeds within mv methods.

4.4.4. Identification of pleiotropic genetic variants

When a locus influences several traits at the same time, pleiotropy is responsible for genetic and phenotypic correlations (Pavlicev et al., 2008). Human complex traits have been extensively reviewed and discussed under different definitions of cross-phenotype association (biological, mediated, spurious) (e.g. (Solovieff et al., 2013; van Rheenen et al., 2019)). However, in a joint analysis of complex traits, autocorrelations suggest pleiotropic effects.

The mv GWAS provides a higher level of precision and detection power in mapping pleiotropic QTL than uv analyses (Bolormaa et al., 2014; Jiang & Zeng, 1995; Knott & Haley, 2000; Korsgaard et al., 2003). In particular, this applies when studying traits that are highly correlated or when heritability is low for the trait affected by the QTL (Korsgaard et al., 2003). Nevertheless, correlated traits may lead to correlated sampling errors (Bolormaa et al., 2010). A PC method has been described as a more powerful alternative to a single trait analysis (Gilbert & Le Roy, 2003; Klei et al., 2008). This approach condenses traits of interest into a number of uncorrelated PCs that reflect the underlying (co)variance matrix. According to Mähler et al. (Mähler et al., 2002), it has been suggested to analyze only the first PC since it explains the majority of the variation. It has been demonstrated that the second PC and subsequent PCs can identify the highest phenotypic proportion that can be explained by genetic markers (Aschard et al., 2014). According to the authors, the second and following PCs may contain a substantial proportion of total genetic variation, which normally accounts for a small amount of variance in phenotypic traits. If the QTL effects oppose positively correlated traits, these PCs appear very powerful.

Using the first three PCs, this study determined that a significant portion of the total genetic association could be attributed to these PCs. However, genetic interpretation of the identified association is impossible with this approach, despite higher statistical power. Due to unclear pleiotropy or high linkage between two regions, there is not yet a clear indication of true pleiotropy [40]. This analysis is generally considered a first step in identifying pleiotropic regions, which would require further investigation with more precise models, fine-mapping or molecular experiments to confidently distinguish between the different scenarios.

4.4.5. Functional annotation and identification of potential candidate genes

Using different uv and mv GWAS approaches in this study it was possible to detect a plethora of genetic markers. SNPs were summarized into QTLs, based on their genetic distance of 1 Mbp downstream and upstream, to condense functional information. Annotation was performed

within the characterized QTLs in Sscrofa 11.1 from the Ensembl database (Hunt et al., 2018). QTLs were located within numerous protein-coding genes (uv: 354, mv: 453). 125 protein-coding genes were identified with both methods (uv and mv) and selected immune relevant genes are presented in Table 2 and Table S1 and S2. The SNP ASGA0070586 (rs80818610, SSC 15: 120.11 Mbp), located on SSC 15, was detected applying all four multivariate approaches. In the following, three out of eight candidate genes are discussed. AAMP (angio associated migratory cell protein) plays a positive role in angiogenesis, a physiological process through which new blood vessels are formed from pre-existing vessels (Beckner et al., 2002). PNDK (paroxysmal nonkinesiogenic dyskinesia domain containing) protein is involved in the regulation of neurotransmitter secretion and is associated with pancreatic, ovarian, and breast cancer in humans (Gong et al., 2014; Zhao et al., 2013). In swine, a disruption of expression and pathway of PDNK in response to infection with Actinobacillus pleuropneumoniae bacteria was observed (Reiner et al., 2014). TMBIM1 (transmembrane BAX inhibitor motif containing 1) protein binds to a TNF receptor and thus regulates the degranulation of neutrophils and the reorganization of blood vessels (Deng et al., 2018). Five additional gene were located close to ASGA0070586 (rs80818610, SSC 15: 120.11 Mbp), but a functional immune relevant relationship have not been described yet.

On SSC 14 the marker MARC0013023 (rs80797218) was significantly associated for HMG and HMT using uv PLINK and BIMBAM. In addition, this SNP was also detected applying CCA for the traits HMT, HMG and MCHC applying CCA. Within this region the protein-coding gene AGT (angiotensinogen) is located, that regulates the systemic arterial blood pressure by renin-angiotensin (Schuijt et al., 1999). According to their direct influence on immune traits these protein-coding genes represent potential candidate genes.

Some of the genetic markers detected in this study have been identified in previous association studies for hematological traits. Wang et al. (2013) detected SNPs ALGA0123028 (rs81318039, SSC 3: 71.12 Mbp) and MARC0001946 (rs81288717, SSC 3: 72.97 Mbp) located on SSC 3 for mean thrombocyte volume. These SNPs were identified for immune trait combination [WBC|HMT:EOS:HAP:IL8] in LR. In the study of Lu et al. (2013) MARC0039159 (rs81232385, SSC 5: 44.44 Mbp), located on SSC 5, was significantly associated with IL-10 , which was identified in our study with CCA and PCA for [NEU|RBC:WBC:MON:BAS] and PC3 Cell (LYM, MON, BAS contribute to this PC according to the loading value), respectively. Luo et al. (2012) identified ALGA0047813 (rs81400288, SSC 8: 43.03 Mbp) and MARC0039159 (rs81232385, SSC 5: 44.44 Mbp) on SSC 8 for MCV and MCH, which was observed in our study for the mv trait combination

[RBC|HMG:HMT:MCV:MCH:MCHC] in LW with CCA. ALGA0047813 (rs81400288, SSC 8: 43.03 Mbp), is located within the intron region of the protein-coding gene TLL1 (tolloid like 1). Studies in mice suggest that TLL1 plays multiple roles in the development of the mammalian heart, and is essential for the formation of the interventricular septum. Allelic variants of this gene are associated with atrial septal defect type 6 (Sieroń & Stańczak, 2006). Further investigations of this protein function in pigs are needed, to determine the potential as a candidate gene. Dauben et al. (2021) detected associations for immune traits in the same pig population with a different uv GWAS approach. Identical markers have been identified between this and the current study (LR: 159, LW:15). Noteworthy, 49 SNPs identified in LR were observed with uv and mv methods. Therefore, in this study we were able to confirm associations with our previous results.

4.5. Conclusion

This study evaluated the joint genetic background of immune traits in LR and LW piglets through the application of various uv and mv GWAS approaches. In general, mv GWAS approaches outperformed uv methods and detected genome-wide associations for immune traits. It should be considered that the number of significant associations differs between the applied methods and the possibility of chromosome-wide correction for multiple testing was only feasible in two approaches. When associations were compared across the investigated breeds, no overlapping markers were observed with uv methods, indicating genetic breed differences. It was possible to detect two SNPs in both breeds applying mv GWAS. However, further options for pre-selection of the breed-specific mv trait combinations and cross-validation should be considered to enable appropriate breed comparison. Our results support the observation that one single test is not able to detect all the many different types of genetic effects in the most powerful manner. These analyses are initial steps to detect pleiotropic regions in general. Beside the validation of our results with other data sets, it is necessary investigate the identified associations further applying fine-mapping approaches and the analyses of candidate genes.

4.6. Methods

4.6.1. Statistical analysis of immune traits

Data sets of purebred LR and LW populations were recorded from 2010 to 2017 and were provided by the German breeding organization BHZP GmbH. Animal care, phenotypic measurements, and consideration of environmental effects were described in Roth et al. (2022).

In brief, a total of 611 piglets (♂152/♀307) of LR and 533 piglets (♂134/♀257) of LW were analysed. Animals were a subset of two nucleus populations. From each litter, one male and one female piglet, were chosen for phenotype collection. Blood samples of piglets were collected on average around 45 days (32– 60) after birth by puncturing the Vena jugularis and were collected in three 7.5 ml monovette containing ethylenediaminetetraacetic acid. Complete blood count was performed with an ADVIA® 2120 Hematology system, a flow cytometry-based system, and a pig- specific setting. Besides, serum haptoglobin was measured in 0.5 ml serum. Peroxidase activity of the haptoglobin– haemoglobin complex was carried out by a spectrophotometric method. Cytokine levels (interferon- γ, interleukin- 10, interleukin- 12, interleukin- 1β, interleukin- 4, interleukin- 6, interleukin- 8 and tumour necrosis factor- α) in serum samples were analysed with a Porcine Cytokine/Chemokine Multiplex Magnetic Bead Panel (Merck KGaA) enabling the simultaneous measurement of multiple cytokines. Immunoassay of serum samples was performed using 22 plates according to the manufacturer´s protocol.

GWAS was performed for complete blood count (RBC, haemoglobin, haematocrit, MCV, MCH, MCHC, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, band and other remaining cells), HAP, and cytokines (interferon-γ, interleukin-10, interleukin-12, interleukin-1β, interleukin-4, interleukin-6, interleukin-8 and tumour necrosis factor-α) as immune traits of 1144 LR and LW piglets, corrected for environmental impacts within the breeds. A detailed description of all investigated immune traits, their summary statistics, and processing of the data set can be found in Roth et al. (2022).

4.6.2. Genotyping and quality control of genomic markers

To study genetic associations between measured phenotypes animals were genotyped with a tissue sample via an Ilumina Porcine SNP60 v2 BeadChip (Illumina, San Diego, CA, USA) in an external laboratory (GeneControl GmbH, Poing). Only autosomal markers were used in the different GWAS approaches. Regardless of the selected association method, quality control of genotype data was performed with PLINK (Shaun Purcell, 2010). Genetic markers and animals were excluded when they did not meet the following criteria: Call Rate ≥0.95, Minor allele frequency (MAF) ≤0.01, deviation from Hardy-Weinberg equilibrium (HWE) p-value =0.0001, acceptable Identity-by-state (IBS) threshold ≤0.95. After quality control 47’292 and 43’730 markers, as well as 522 and 461 animals, remained for GWAS for LR and LW, respectively. The position in the genome and the base pair location of each SNP is based on *SScrofa* 11.1. In total, 38 markers show currently no location under this assembly. Using the assembly *SScrofa* 10.2 it was possible to report a chromosome number and a base pair position for 15 markers.

The remaining 22 markers revealed high linkage disequilibrium to other significantly associated SNP (results not shown). The observed regions correspond to the positional information given in the manifest file of the manufacturer.

4.6.3. Correction for environmental effects

The correction for environmental effects was performed within a breed and included all relevant fixed effects: the class effects parity (1–4) and herd-year-season-sex (1–12). Moreover, age and weight and interaction between age and weight at the time of sample collection were included in the model as covariates. Cytokine detection method requires the quantification of samples distributed among 22 analytical plates. Therefore, plate was included as a random term for cytokine immune traits. The effects of breed (LR or LW) or sex (boar or sow) were not included as main factors in the model because of the hierarchical classification of these effects within herd-year-season-sex classes.

4.6.4. Univariate GWAS

After quality control, one frequentist and one Bayesian method were used to analyze immune traits for uv associations with the genotype in a GWAS within each breed data set
The starting point for both approaches is a mixed linear model:

$$y = \mu + Z\alpha + e \quad (1)$$

where y is a vector of phenotype measurement of animals, μ is a vector of the phenotype means of animals carrying the reference genotype, Z is a matrix of genotype covariates (coded as 0, 1, or 2) for SNP markers, α is a vector of random regression coefficients of the SNPs (marker effects), and e is a vector of residuals.

The frequentist association approach in PLINK (Shaun Purcell, 2010) tests each marker for association with the trait of interest since it performs a linear regression analysis with each SNP as a predictor. For Bayesian regression, prior distributions are specified for α and$e$. For vector of residuals e, a prior conditional on the residual variance, σ_e^2, a normal distribution with null mean and covariance matrix $R\sigma_e^2$, is used. In this case, R is a diagonal matrix and σ_e^2 is treated as an unknown with a scaled inverse χ^2 prior (Gondro et al., 2013). Assuming that a SNP j is a Quantitative Trait Locus, then its effect is dependent on two parameters: a_j and $d_j = a_j k_j$: the additive and dominance effect, respectively. An additive effect is given by $k_j = 0$, while $k_j = 1$ and $k_j = -1$ represents a dominant effect. Bayesian linear regression carried out with BIMBAM uses two priors D_1 and D_2 to model this effects (Servin & Stephens, 2007). Bayesian Factors for observed associations were computed as posterior distributions for SNP effects using the prior D_2 averaging $a_j = 0.05,0.1,0.2,0.4$ and $d_j = a_j/4$. Further detailed information

about the utilized uv GWAS approaches can be found in the original literature (Gondro et al., 2013; Servin & Stephens, 2007; Shaun Purcell, 2010).

4.6.5. Principal component analysis

To condensate the estimated highly correlated immune network PCA was applied to immune observation residuals. PCA proceedings steps and results are already published and described in detail in Roth et al. (2022). Before the application of the PCA technique for each breed data set, we split the immune traits of our survey into three biological functional networks as a) Cells, b) RBC (including HAP) and c) Cytokines. This classification was motivated by the strategy to maintain the greatest possible explained variance from the original variables in the constructed PCs. The number of PCs used to characterize immune traits was based on the eigenvalues of their correlation matrix. In order to limit the number of PCs, PCs with eigenvalues lower than 1.0 were excluded (Braeken & van Assen, 2017). As far as possible, loading values of PCs were used to label them roughly and to interpret PCs according to their summarizing biological composition. BFN-specific PCs were then used as new traits during a uv GWAS which was carried out with PLINK (Shaun Purcell, 2010). The output of the association analysis generates an asymptotic significance value (p-value). Received p-values were adjusted for population stratification and multiple testing on genome and chromosome levels.

4.6.6. Learning structures using Bayesian network

The realization of all possible mv combinations for all available immune phenotypes is computationally extensive. Networks, paths, and graphs can model interactivity between variables. BN describe conditional in- and dependence relationships among variables (Scutari, 2010). Therefore, in this study, a BN approach was performed for each breed data set to reveal conditional dependencies among immune traits. Applying this approach, it was possible to set various combinations of immune traits for LR and LW regardless of the applied mv GWAS method.

Briefly, the BN is a graphical representation of a probability distribution over a set of variables (Arbib, 1998; Nagarajan et al., 2013; Scutari, 2010). The conditional independence (of the random variables) and graphical separation (of the corresponding nodes of the graph) have been stretched out to disjoint node subsets by Pearl (1988). Therefore, in the BN approach model selection algorithms were used to learn the graphical structure of the network and then estimate the parameters of the local distribution functions conditional on the learned structure. A hill-climbing algorithm (Scutari et al., 2019) was applied to the immune data set in this study. This Score-based structure learning algorithm is a general heuristic optimization technique to the

problem of learning the structure of a BN. This algorithm attempts to maximize a score that measures how well that BN describes its goodness of fit to the data set, returning a graphical structure as output (Nagarajan et al., 2013). R package bnlearn (Scutari, 2010) was used to obtain BNs for LR and LW immune trait residuals. Residuals of originally measured phenotypes were used to avoid a large number of solutions that need to be computed because of existing cross-classified effects. Resulting conditional dependencies illustrated as parents of the nodes in the network structure were used as trait combinations for mv GWAS approaches.

4.6.7. Multivariate GWAS

GWAS is generally performed on a uv (trait-by-trait) basis by testing each variant at a time. Association analyses that include multiple phenotypes may be more powerful to identify QTL for complex traits, particularly in the case of causal variants that affect multiple correlated traits (Zhou & Stephens, 2014a). In the following, principles and optional parameters of four selected mv GWAS approaches applied in this study within each breed data set are described brieflyGWAS is generally performed on a uv (trait-by-trait) basis by testing each variant at a time. Association analyses that include multiple phenotypes may be more powerful to identify QTL for complex traits, particularly in the case of causal variants that affect multiple correlated traits (Zhou & Stephens, 2014a). In the following, principles and optional parameters of four selected mv GWAS approaches applied in this study within each breed data set are described briefly.

4.6.8. Canonical Correlation Analysis

In the same way that PCA is applied to one set of possibly correlated traits to extract a number of independent variables (PCs) that explain as much variance in the original data set, CCA is applied to two sets of variables to extract a number of independent pairs of variables that explain as much covariance between the two original sets (2009). Thus, CCA represents a mv generalization of the Pearson product-moment correlation (Hotelling, 1992). CCA extracts the linear combination of traits that explain the largest possible amount of the covariation between the marker and all traits. This approach is applied to analyze the association between one SNP and multiple traits, as implemented in --mqfam --mult-pheno procedure for MV-PLINK (Ferreira & Purcell, 2009). The test implies Wilk's lambda (λ) and the corresponding F-approximation. Specifically, $\lambda = 1 - \hat{\rho}^2$, where $\hat{\rho}$ is the canonical correlation between the marker and the traits, calculated as the square root of the eigenvalue of the product of the marker variance (S_{11}), trait covariance matrix (S_{22}), and covariance matrices between the marker and the traits (S_{12}, S_{21}); expressed as notation: $S_{11}^{-1/2} \times S_{12} \times S_{22}^{-1} \times S_{11}^{-1/2}$ (Ferreira & Purcell, 2009). Similar to PCA, an asymptotic significance mv p-value is generated in the CCA output. This p-value was subsequently adjusted for population stratification and multiple testing on the genome and chromosome levels.

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4.6.9. Meta-analysis

Methodology development to increase the statistical power of GWAS is extremely important for study designs with heterogeneous traits and small sample sizes. Meta-analysis was carried out with the software TATES (Trait-based Association Test that uses Extended Simes procedure) (van der Sluis et al., 2013). TATES requires a phenotype correlation matrix of immune traits and a list of p-values in an ascending order of the phenotypes for a given SNP obtained in a corresponding uv linear regression analysis. During a meta-analysis uv GWAS was performed for each phenotype with PLINK (Shaun Purcell, 2010). Obtained p-values were adjusted to account for multiple testing and relationships between immune traits within the meta-analysis on the genome level. TATES combines the phenotype-specific p-values to obtain one overall trait-based p-value (P_T) as $P_T = Min\frac{m_e p_j}{m_{ej}}$, where m_e indicates the effective number of independent p-values of all phenotypes, and m_{ej} is the effective number of p-values among the top p-values, and p_j is the jth p-value (van der Sluis et al., 2013). Based on the procedure developed by Li et al (Li et al., 2011), the effective number of p-values ($m_{ej}$is estimated through a correction based on eigenvalue decomposition of the correlation matrix between the p-values associated with the phenotypes. Briefly, TATES transforms the trait correlation matrix into a corresponding SNP-p-value correlation matrix. The eigen-decomposition of this p-value

correlation matrix is used to weight uv p-values. Finally, the minimum of these weighted p-values is chosen as the corrected p-value for the joint association.

4.6.10. Bayesian multivariate regression

With the software mvBIMBAM (Stephens, 2013) a Bayesian mv regression test for association was conducted. Simultaneously the traits were subdivided according to their SNP effect and Bayes factors were used to access the association between the groups of phenotypes and a genetic variant. The analysis is based on the mv regression model like model (1), but with a Y(n x d) matrix of d phenotypes measured on each of n individuals. The mvBIMBAM approach attempts to partition the response variables Y into three groups according to their statistical association with a genetic variant: undirect (U), direct (D), and indirect (I). A set of models γ = (U, D, I) runs through partitions of the coordinates {1; …, d}. Under model γ an assumption is made that Y_U is independent of Z, and Y_I is conditionally independent of Z given Y_D. This gives

$$P_\gamma = P_\gamma(Y_U)P_\gamma(Y_D \vee Y_U, Z)P_\gamma(Y_I \vee Y_U, Y_D)$$

These scenarios were accessed with the option mph 2 within the mvBIMBAM software. The priors for the genetic effect were set at 0.1 and 0.2 according to the author's recommendation (Stephens, 2013). Bayes factor is computed as the support for partition γ compared with the global null hypothesis that all the phenotypes are unassociated with Z. It then summarizes the overall evidence against the null, as well as the posterior probability that each coordinate of Y is associated with Z:

$$BF_\gamma = \frac{P_\gamma(Y \vee Z)}{P_0(Y)}$$

Obtained $\log_{10}$ Bayes Factors for each genetic variant evaluated the association between the SNP and the traits averaging over all possible partitions. Log_{10} Bayes Factors value ≥3 was characterized as a spurious association while values ≥6 as a solid association between a marker and a trait on genome level.

4.6.11. Controlling population stratification and false-positive results

Genomic control (Devlin et al., 2001) was realized to correct for existing population stratification through adjustment of the significance of the test statistic in R (R Core Team, 2019). From GWAS obtained p-value was subsequently adjusted in the PCA and CCA. The inflation factor lambda was low to moderate in the LR (0.80-1.26) and LW (0.86-1.23) data sets. After stratification correction, the lambda values were acceptable in a range of < 1.05.

To control the number of false-positive results false discovery rate (FDR) was applied (Benjamini & Hochberg, 1995) on genome and chromosome level for uv linear regression method, PCA, and CCA. The significance level q (p-values adjusted with FDR) for FDR was

0.05 to detect associations between marker and trait on genome and chromosome level in R (R Core Team, 2019). Bayesian approaches express significance with a log10 Bayes factor threshold. Absolute values of three and six are considered as spurious and solid significance for an association (Scutari, 2010).

For uv and mv GWAS, QTL regions were defined considering significant SNPs that mapped at least ± 1 Mbp from another significant SNP and functional annotation was performed retrieving all annotated genes within a QTL region in *Sus scrofa*11.1 from Ensembl database (Hunt et al., 2018).

Chapter 5. General discussion

5.1. Multivariate association testing

One aim of this thesis was to study the genetic background among immune traits. Therefore, to investigate joint genetic foundation mv approaches were applied to immune traits in chapters 3 and 4. By theory, mv approaches should increase the power in QTL detection, but this superiority is markedly different across multiple effects. Multiple factors determine the true genotype-phenotype model, including the strength and sign of the correlation between the traits, the sign and generality of the SNP effect, and the presence of unaffected traits (Vroom et al., 2019a). The complexity of these factors makes it difficult to formulate globally applicable recommendations.

At first, detected SNPs and their implications were compared between different approaches and investigated pig breeds, LR and LW. As a first result, we found that all established SNPs with uvBIMBAM were completely overlapping the uvPLINK results. Hence, although very different in the underlying statistical background, SNP detection in our dataset is to a large extent independent of the uv method of choice.

Initially, a PCA was chosen to reduce the dimensions of information on phenotypic immune measurement levels. The majority of variation can be explained by analyzing only the first PC (Mähler et al., 2002). It has been shown by Aschard et al. (2014) that the second and following PCs may contain a considerable proportion of total genetic variation, which normally accounts for a tiny proportion of variance in phenotypic traits. Interestingly, when QTL effects oppose positively correlated traits, these PCs appear to be very powerful. When the correlation between the traits was taken into account, genetic variants with genotypic effects on phenotypes were more likely to be detected than those with negative pleiotropic genetic effects (Korte et al., 2012). In our study, the application of a PCA has led to a successful condensation of immune trait measurements. The first three PCs were significantly associated with 124 SNPs, which SNPs cover presumably a large proportion of the total genetic variation of the immune system. In addition, genetic analysis based on PCs instead of immune traits would consider the underlying strong biological trait relationships within the immune system. However, from a statistical point of view, the derivation of PC is solely based on the variance-covariance structure of the underlying data. Hence, despite higher statistical QTL detection power, the PC approach does not allow a clear genetic interpretation of the identified association. Even though PC loadings are sometimes useful for revealing the natural variables underlying biological processes, the loadings should be interpreted with greater caution (Crawley, 2007).

Besides the PC approach, various other mv methods are used to analyze complex data with a distinct correlation structure. Until now, no generally acceptable rule has been described in the

literature which of these methods is most effective regarding QTL detection. In our study (chapter 4), we utilized various mv (and uv) GWAS approaches and presented the theoretical background of these methods. We inspected Venn diagrams, which visualize overlapping SNP results of the different approaches. This comparison is not able to quantify the reliability, but a SNP which will be detected by the majority of the applied methods would have a higher expressiveness than those which has been found solely by one approach. This is in agreement with Aschard et al. (2014), who postulated that the application of various complementary methods allows for considering all the many different types of genetic effects in the most powerful manner.

A comparison of the uv and mv results revealed that a majority of markers (204) overlap across the methods, but only three common markers were identified with all applied mv approaches. On the other hand, taking into account an overlap of at least two or three methods (e.g. TATES, mvBIMBAM & CCA, or PCA & CCA) common QTL can be found, which can be linked to four interesting genetic variants as potential candidate genes (see chapter 4 for further details). Intuitively, when SNPs are detected with multiple approaches, they (should) provide more certainty for the GWAS results and contribute potential protein-coding candidate genes. However, a large amount of non-overlapping results shows, that QTL detection in our complex data depends on the statistical method of choice to a large extent.

Regarding this question, an inspection of the significance levels might be a useful complement to the assessment criteria “QTL overlap”. However, significance levels can only be estimated in an approximative manner. In addition, the possibility of chromosome-wide correction for multiple testing was not achievable for every mv approach.

Based on our result we conclude that the performance of different mv approaches is scenario-specific. This assessment complies with Galesloot et al. (2014) and Porter and O'Reilly (2017). Their simulation studies demonstrate the dependency of QTL detection power of different mv approaches and specific effects like allele frequency, number of investigated traits, and underlying correlation structures among the traits.

Until now, there is no single test that can detect all the variations of genetic effects that might occur within a GWAS setting (Zhou & Stephens, 2014b). Any given test can be manufactured to be as powerful as possible by manufacturing simulations. It is therefore important to view mv and uv tests as complementary instead of competing. Thus, it is necessary to identify the circumstances under which specific mv approaches perform well or poorly, as well as which (classes of) methods are most effective. Overall, mv approaches (mvPLINK, mvSNPTEST, MultiPhen, mvBIMBAM, PCHAT, TATES) outperform uv analyses in simulation scenarios

represented in simulations studies (Galesloot et al., 2014; Porter & O'Reilly, 2017; Vroom et al., 2019a). However, uv analysis performed well when all traits were associated with the genetic variant and the genetic correlation was positive. Even when the genetic correlation between traits is expected to be weak, mv GWAS can be recommended (Galesloot et al., 2014). Usually, the reviews (given in chapter 4) focus only on frequentist-based mv approaches that do not rely on permutation or bootstrapping. Methods based on mv Bayesian modeling e. g. SNPtest (Marchini et al., 2007) and mvBIMBAM (Stephens, 2013) or bootstrapping e. g. PCHAT (Klei et al., 2008) can be applied to detect pleiotropic SNPs as in the studies by Galesloot et al. (2014) and Porter and O'Reilly (2017).

The power in QTL detection of different mv methods depends on the size and sign of genetic and residual correlations of the traits (Galesloot et al. 2014). In their simulation study, the authors constructed 30 different scenarios for the number of traits associated with the QTL (one, two, or three out of three) and a combination of different parameter values like heritability, minor allele frequency, sign and size of residual and genetic correlation. They observed a higher power for mv methods than uv methods. Methods like CCA, MultiPhen, mvSNPTEST, and mvBIMBAM showed the best and similar performance with higher power with increasing residual correlation. This was most noticeable when the correlation induced by the QTL was negative for the scenarios when two out of three or all three traits were associated with the QTL. This superiority of mentioned four mv methods remained under simulation scenarios with negative genetic correlation. In this case, their power increased with increasing residual correlation. This effect has been also described in the literature (Ferreira & Purcell, 2009; J.-F. Liu et al., 2009; O'Reilly et al., 2012).

Usually, methods are compared based on empirically derived significance levels, adjusting each method to an exact 5% type I error rate. Simulations illustrated that for mvPLINK, mvSNPTEST, MultiPhen, mvBIMBAM, TATES, and PCA these empirical significance levels were all close to the nominal level of 0.05 for p-values or ≥ 3 for substantial Bayesian Factor values (Galesloot et al., 2014; Porter & O'Reilly, 2017).

In addition to power (and type I errors), other characteristics are considered when choosing the appropriate mv GWAS. The output from mv association results from mvPLINK contain trait loadings, which indicate how much each trait contributed (Ferreira & Purcell, 2009). Based on an overall association with at least one trait, mvBIMBAM calculates marginal posterior probabilities for each trait to be unaffected, directly affected, or indirectly affected by the QTL (Stephens, 2013). In addition to providing insight into the underlying biology, this additional

information can also facilitate the differentiation between pleiotropic and independent QTL effects.

Additionally, mvPLINK, MultiPhen, and TATES can be used to assess both quantitative and binary traits (case-control) (Ferreira & Purcell, 2009; O'Reilly et al., 2012; van der Sluis et al., 2013). It is possible to apply mvBIMBAM and TATES to GWAS result data without access to raw phenotype and genotype data which might be useful for meta-analyses (Stephens, 2013). The mvSNPTEST, MultiPhen, TATES, and PCA methods can also handle genotype probabilities that are obtained by imputation (Marchini et al., 2007; O'Reilly et al., 2012; van der Sluis et al., 2013). As a final point, simulation studies revealed that the methods take significantly different amounts of CPU time to run.

The study by Bray et al. (1995) showed that the power of MV approaches (e.g. MANOVA) can be improved by incorporating traits that are unaffected by the SNP if these traits are correlated with the affected traits. This knowledge can be applied to experimental studies if we possess prior or theoretical knowledge of which traits a given manipulation is expected to affect. GWAS, however, does not usually use such a theory to determine which traits to include or exclude.

Following Bray et al. (1995), adding further traits to the mv analysis is always beneficial:

- if the newly added indicators are not related to the SNP, then the power of mv methods generally increases because adding unrelated traits increases the power of mv methods
- if the newly added indicators are related to the SNP but in an opposite way to the relations that the already included indicators have to the SNP (opposite effects), then the power of mv methods to detect the SNP increases
- if the newly added indicators are also related to the SNP and in the same way (same direction of effect), then the power of mv methods will decrease, but generally no more than max. 15%.

It is often necessary to perform follow-up analyses after mv analyses to answer whether all or many traits are associated with the SNP. In preparation for the mv GWAS in chapter 4 we faced the same decision processes for the in- or exclusion of immune traits. Applying the Bayesian network approach, it was possible to set various combinations of immune traits for LR and LW regardless of the applied mv GWAS method.

In simulations, only additive codominant SNPs and normally distributed continuous traits are considered (Galesloot et al., 2014; Porter & O'Reilly, 2017; Vroom et al., 2019a). These choices fit the (distributional) assumptions underlying most mv analyses. It is important to note, that Type I error rates of various techniques (e.g., MANOVA, uv regression) may not be correct

when standard assumptions are violated in case of severely non-normal or non-continuous data (O'Reilly et al., 2012). However, Porter and O'Reilly (2017) have shown that for two of the most commonly used mv methods that may accommodate dichotomous data, the pattern of results is similar to that of continuous data.

Recently, multiple methods were developed that allow estimation of the genetic covariance between traits using GWAS e. g. GCTA (J. Yang et al., 2011), BOLT-REML (Loh et al., 2015), LD Score Regression (Bulik-Sullivan et al., 2015), MTAG (Turley et al., 2018) and genomic SEM (Grotzinger et al., 2019), which use this genetic covariance among traits to boost the statistical power to detect SNPs for sets of target traits. Applying these techniques was beyond the scope of our study and therefore, they were not included in the analyses described in chapter 4.

Mv methods can all be used to detect associations that may be due to pleiotropy. However, they do not answer the question of whether the detected association is truly pleiotropy, that is, whether the marker locus directly affects all mv components. A detectable association can affect some phenotypes and/or mediate the effects of these phenotypes on other phenotypes (C. Yang et al., 2015). It can be expected that underlying genes for immunocompetence may have pleiotropic effects which result in a close genetic correlation between several immune traits. Against this background, the utilization of mv methods is recommended to increase the statistical power to detect associations even if the rg between the traits is expected to be weak (Wimmers et al. 2009). Mv methods are often used to discover pleiotropic genetic variants, that is, SNPs that are statistically associated with more than one trait, possibly pointing toward a shared biological substrate (Solovieff et al., 2013). Simulations studies show that as the degree of the phenotypic correlation between traits increases, the power to detect global variants decreases (Minica et al., 2010; Neale et al., 2010; Vroom et al., 2019a); as one would expect with an increase in genetic relatedness; thus, mv approaches aren't optimized for identifying true pleiotropic genetic variants at the moment (Porter & O'Reilly, 2017). In our study in chapter 4, we focused on an empiric overlap between methods to identify pleiotropic QTL. However, it is only a rough method for the characterization of pleiotropy. Other methods, like Bayesian colocalization methods, are more suitable to detect pleiotropic SNPs and distinguish between different pleiotropic types as described by (Solovieff et al., 2013).

5.2. Genetic foundation of immune traits

In this thesis, the genetic foundation of porcine immune traits was studied with uv and mv approaches through immune profiling. The genetic potential for immunocompetence of the piglet and the dam was elaborated for two German maternal pig lines, LR and LW, in chapter

3. As a result, breed differences for immune traits phenotypic values, and genetic parameters were reported. Breed differences described also in previous studies are presumed to be related to various disease resistance traits (Henryon et al., 2001; Joling et al., 1993). Antibody response, lymphocyte proliferation, and delayed-type hypersensitivity (DTH) responsiveness were compared among purebred Dutch Landrace, Norwegian Landrace, Finnish Landrace, and Yorkshire (Joling et al., 1993). In this study, immunocompetence showed genetic involvement with h2 from 0.13 to 0.33 for antibody response and a h^2 from 0.41 to 0.44 for lymphocyte proliferation. The factors of breed, boar, and litter contributed significantly to the variation in immunocompetence. The Yorkshire breed showed a low-level response to all three immune parameters. The authors explain that within the genetic system the major histocompatibility complex (MHC), also called swine leucocytes antigen (SLA), genes are particularly important in terms of immune reactivity. The phenotype of the products of that gene complex has a considerable effect on the magnitude of the immunocompetence in the form of antibody response (Mallard et al., 1989). The distribution of SLA haplotypes is different between the breeds, which has been also investigated in specific pathogen-free Canadian Yorkshire and Landrace pigs (Gao et al., 2017). Furthermore, pigs from Duroc, LR, Hampshire, and Yorkshire breeds were shown to be genetically different in resistance to clinical and subclinical diseases (Henryon et al., 2001). However, other environmental and genetic factors may also influence the outcome of an immune response (Clapperton et al., 2009; Farmer, 2015). At the current state, a beneficial, stable, or advantageous immune system for different pig life stages and breeds is not characterized. Generally, the inclusion of immune traits in a selection program requires sufficient h^2 across generations. Results in chapter 3 suggest adequate genetic influence and therefore possible selective breeding for immune traits.

Besides additive genetic effects, maternal genes are presumed to influence the immunity of the piglet (Roehe et al., 2010). Previous studies on genetic indicators had not considered the dam as a source of variation for genetic variance component estimation. In the study from Rohrer et al. (2014) moderate m2 in genetic analysis of colostrum intake measured as γ-immunoglobulins complexes bound to ammonium sulfate (immunocrit) was estimated. Due to the epitheliochorial placentation of the sow, the passive transfer of antibodies from dams to piglets occurs during colostrum intake (Farmer, 2015). Therefore, several studies describe the importance of colostrum for the development of the piglet and a maternal impact on piglet's immunity in the form of antibody transfer, maturation of mucosal immunity, and colostrum intake (Bandrick et al., 2008; Hermesch et al., 2017; Rooke & Bland, 2002; Salmon et al., 2009). Considering the direct-maternal correlations between traits, the results of Knol et al. (2002) showed a positive

correlation between the direct component of piglet birth weight and the maternal component of stillbirth, indicating a negative influence on stillbirth if selection on the direct component of the individual birth weight occurs. In addition, Knol et al. (2001) reported decreased litter birth weight if selected directly for individual piglet survival. These findings show that direct-maternal correlations can be indicative when it comes to designing a model to breed for improved piglet survival. According to Bijma (2006), an estimation of (co)variances between direct and maternal effects is not feasible in populations with multiple litters and multiple offspring per litter. Heuß (2019), showed that direct-maternal correlations cause convergence problems, are not significant, and range massively between testing the models for traits like stillbirth, pre-weaning loss, and birth weight.

The impacts of maternal genetic and transferred immune factors on piglet's immunity are not completely clarified, yet. Consideration of maternal environmental effects and litter effects on piglet's immune traits in chapter 3 led to a decrease in h2 while at the same time causing an increase in m2 and rg indicating that it is possible to adjust piglet's immune measurements for maternal-derived immunity. Therefore, selection for immune traits in piglets can be accessed through the biological dam, which creates further opportunities to develop breeding strategies for immune-competent piglets.

Immune traits can send signals from one cell to another and communicate through direct cell-to-cell contacts (Zimmerman et al., 2012). In chapter 3 the relationships between immune cells, haptoglobin, and cytokines were investigated by estimation of rp and rg parameters. Moreover, a shared genetic foundation as common genetic markers between hematological immune traits were revealed in Chinese Sutai pigs (F. Zhang et al., 2014). Flori, Gao, Laloë, et al. (2011) estimated rg for components of innate and adaptive immunity and showed that components of the immune system are complementary. Detected correlations between immunocompetence parameters (IgG antibody response, lymphocyte proliferation, DTH) were moderate to highly positive (0.33-0.99) indicating strong connections within the immune system (Joling et al., 1993). This demonstrates associated relationships and highlights a strong network within the immune system where selection for specific immune traits would affect other immune components. Therefore, relationships between immune traits and other performance phenotypes should be examined in detail before including specific traits in any selection strategy.

5.3. Towards a breeding-based improvement of health traits

Currently, many animal breeding research institutions as well as commercial pig breeding are focused on the improving of health and robustness traits. In our and related studies (see chapter

3) moderate to high h2 for most of the immune traits were found. This implies that the incorporation of these traits into selection indexes, along with another economically relevant trait, is feasible.

Even though immune traits are heritable across generations and are promising to cover global immunocompetence in animals, amplification of breeding goals for such traits has not been done, yet. Possible reasons for retained schemes in breeding companies can be very diverse. It is difficult to determine correlative and causal relationships between immunity and other performance and animal welfare-related traits. Therefore, modification of the immune system could lead to unintentional or unfavorable relationships between performance and animal welfare. Directed modification to optimize immune traits is not possible due to missing reference values that would classify beneficial immunity for different animal life stages and environments. Nevertheless, the improvement of the animal immune system through breeding is influential to animal welfare and the economy. Evaluation of the economic value of different immune traits at the current stage is rather imprudent. Regardless of open research questions results within this thesis provide knowledge about immune traits as corresponding factors for immunocompetence. Underlying studies contribute to the development of breeding strategies for health-related traits.

Besides index selection novel biotechnological tools might help to improve health and robustness traits efficiently. As an example, in 2017 it was possible to generate pigs in which the porcine reproductive and respiratory syndrome virus (PRRSV) protein receptor on macrophages was modified with Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9 (CRISPR/Cas9) gene editing. These pigs showed a full resistance to infection with the PRRSV strain which can result in a general health benefit and a decreased need for antimicrobial use (Burkard et al., 2017). However, direct biotechnological or selection strategies that target specific pathogen resistance may result in increased susceptibility to other diseases which was already shown by Mallard et al. (1992) and Wilkie and Mallard (1999). Mallard et al. (1992) challenged pigs with Hen Egg White Lysozyme (HEWL), synthetic peptide TGAL, and sheep erythrocytes, and selected according to the antibody and cell-mediated response (adaptive immunity), and monocyte function (innate immunity) of Yorkshire pigs. The h2 of these immunological traits ranged from 0 for monocyte function to 0.25 for secondary antibody response (HEWL). After eight years of selection, two distinct lines were formed: a high immune response (HIR) and a low immune response (LIR). HIR line had a higher incidence of arthritis after the Mycoplasma hyorhinis challenge (Wilkie & Mallard, 1999). This selection experiment demonstrates that selection for response against a

specific pathogen may have unpredictable consequences for other traits and unfavorable effects on the response against other pathogens. So far, most extensively studied immune response traits in pigs are those reflecting the antibody cell-mediated immunity such as antibody response to various antigens (Edfors-Lilja et al., 1994; Groves et al., 1993; Kadowaki et al., 2012; Mallard et al., 1992; Nguyen et al., 1998; Wilkie & Mallard, 1999).

In their review, Pluske et al. (2018) suggested that there are negative outcomes for animal health and productivity through both under- and over-responsiveness of the immune system. Pigs reared in conventional housing systems with high microbial loads grow 10-20% more slowly than pigs kept in 'clean' environments or pigs reared in isolation or pigs receiving antibiotics. An animal should have the capacity to mount a substantial immune response against invading pathogenic organisms, but the negative effects of pro-inflammatory cytokines should be minimized. Selecting pigs, particularly in a non-challenging environment, without including immune traits in the index is likely to lead to progeny that is less capable of dealing with demanding environments. Best results are likely to occur when pigs are selected in the same environment where the progeny will be reared and immune traits are included in the selection index. For this purpose, previous research has focused on breeding pigs for high robustness for a various range of environments (Hermesch et al., 2015; Knap, 2005; Pluske et al., 2018).

An indirect breeding approach focuses on immune traits providing a measure of immunocompetence and can predict the responses to pathogens in general (Flori, Gao, Oswald, et al., 2011). Genetic differences in the total and differential number of circulating leukocytes and the ability of mononuclear cells to produce IL-2 have earlier been indicated in swine (Edfors-Lilja et al., 1994). In addition, QTL for a cellular and humoral immune response (leucocyte counts, phagocytosis, mitogen-induced proliferation, IL-2 production, interferon-alpha production antibody response) were identified by Edfors-Lilja et al. (1998) and Wimmers et al. (2009). An indirect indicator for disease incidence or animal health status of immune responsiveness. Moreover, immunological traits are associated with performance (Clapperton et al., 2009; Clapperton et al., 2008). These traits have also been found to display genetic variation within, and between breeds (Clapperton et al., 2009; Flori, Gao, Oswald, et al., 2011; Henryon et al., 2001), demonstrating the possibility of breeding for resistance, tolerance, or both, through selection for breed-specific immunocompetence. Currently, the implementation of the relationships among immune traits, as it has been detected here (chapter 4), cannot be realized. Besides missing biological causes for these relationships among the immune traits, it is necessary to determine the optimal range of these traits before breeding progress can be achieved.

Chapter 6. Conclusion of the thesis

Examined immune traits demonstrate genetic potential for immunocompetence of LR and LW piglets and their corresponding dams. Examined immune traits show moderate to high, breed-specific genetic parameters including h2, m2, and rg. With the help of mv approaches condensed immune phenotypes for example PCs can be considered to establish breeding strategies that take into account highly correlated relationships among different traits. In further, the joint genetic background of immune traits in LR and LW piglets through the application of various uv and mv GWAS approaches was determined. GWAS uv and mv methodology revealed several overlapping associations and immune-relevant potential candidate genes. The possibility of chromosome- or a genome-wide correction for multiple testing was only conducted in two approaches. In this thesis, the observation that one single test is not able to detect all the many different types of genetic effects in the most powerful manner was confirmed.

Modification of the immune system could lead to unintentional or unfavorable relationships to performance and animal welfare. Reference values are needed to evaluate and characterize the immune status. Currently, directed adjustment to optimize immune traits is not possible due to missing reference values that would classify beneficial immunity for different animal life stages and environments. A physiological reference value update is necessary due to accelerated genetic progress and changes in breeding objectives over the past few years.

Yet, it is unclear how the biological dam fully influences piglets' immune system. The results indicate consequences for immune traits in piglets depending on their biological dam's immune trait status. Nevertheless, a more defined correction for the dam's effect as a random parameter is needed.

According to our results, there is a clear difference between breeds. Furthermore, our results confirm that immunologically relevant traits and health indicators have a complex genetic background. Pleiotropic backgrounds are suggested by several genomic regions. There needs to be further investigation of the relationships between the immune system, survivability, performance characteristics, and other economically critical traits. Our results provide important insights into regions whose immune system is particularly crucial for piglets, as health and immune traits are expected to become more and more important in balanced pig breeding.

The improvement of the animal immune system through breeding is profitable and beneficial to consumers' concerns about animal welfare. Immune traits can be used to gain breeding-based health improvement. The analysis of immune traits has to be extended to characterize relationships between immunity and performance to gain an improved immune system without

accidental losses in productivity. In further research steps, the economic value of different immune traits should be classified.

Chapter 7. Summary

In pig breeding immune traits are considered to serve as potential biomarkers for pig's health-competence. A limited number of published studies indicate medium to high heritabilities (h^2) for several immune traits. Genetic variance and covariance components of immune traits were estimated in chapter 3 to examine the quantitative genetic background of these traits. For this purpose, blood samples were collected for Landrace (LR) (n=611) and Large White (LW) (n=544) piglets and their biological dams (n=298, 272, respectively) in a short period around birth. Immune profile was covered by 22 traits including immune cells, red blood cell characteristics, and cytokines. Maternal impacts on piglet's immune profile were investigated as well as close phenotypic and genetic-based relationships in a multivariate approach. Immune traits showed low to high breed-specific h^2. Strong positive genetic correlations (r_g) were estimated among red blood cell characteristics (0.77 to 0.99) as well as among cytokines (0.48 to 0.99). The litter impact on piglet's immunity was examined and strengthened already observed breed differences. In LR h^2 (0.22 to 0.15) and litter effect (c^2) (0.52 to 0.44) for IFN-γ decreased after statistical consideration of maternal impact. In LW a decrease in h^2 (0.32 to 0.18) for IFN-γ and an increase in c^2 (0.54 to 0.56) was observed.

The development of selection strategies requires deep investigations with appropriate statistical genome-wide association study approaches to explore the joint genetic foundation for health biomarkers. Consideration of previously established r_g between immune traits were used to identify pleiotropic genetic markers. For this reason, several univariate (uv) and multivariate (mv) genetic association testing methods were applied on immune traits in chapter 4. Mv GWAS approaches detected 647 associations for different mv immune trait combinations that were summarized to 133 quantitative trait loci (QTL). SNPs for different trait combinations (n=66) were detected with more than one mv method. Most of these SNPs are associated with red blood cell related immune trait combinations. With uv methods shared markers were not observed between the breeds, whereas mv approaches were able to detect two conjoint SNPs for LR and LW.

Most immune traits are heritable and are promising to cover global breed-specific immunocompetence in animals. With uv and mv approaches, the joint genetic background of immune traits was demonstrated by revealing immune relevant potential candidate genes. Investigated traits can be used to gain a breeding-based health improvement in piglets whereby special attention has to be laid on the relationship between immunocompetence and further performance characteristics.

Chapter 8. References

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Chapter 9. Appendix

Table S 1: ANOVA p-values for fixed effects in piglet data set

Trait	Landrace					Large White					Landrace and Large White				
	HYSS	Parity	Age	Weight	Age x weight	HYSS	Parity	Age	Weight	Age x weight	HYSS	Parity	(Age x breed)*	(Weight x breed)*	((Breed x age) x weight)*
RBC	0.000	0.277	0.204	0.047	0.196	0.000	0.900	0.190	0.467	0.004	0.000	0.695	0.237	0.098	0.005
Hemoglobin	0.000	0.727	0.675	0.000	0.102	0.000	0.748	0.005	0.126	0.004	0.000	0.808	0.014	0.000	0.003
Hematocrit	0.000	0.729	0.939	0.001	0.265	0.000	0.783	0.048	0.065	0.001	0.000	0.723	0.143	0.001	0.002
MCV	0.000	0.074	0.017	0.004	0.658	0.000	0.322	0.088	0.010	0.179	0.000	0.143	0.022	0.001	0.361
MCH	0.015	0.032	0.007	0.000	0.732	0.285	0.375	0.002	0.064	0.934	0.057	0.088	0.000	0.000	0.954
MCHC	0.000	0.477	0.351	0.014	0.432	0.000	0.534	0.011	0.338	0.044	0.000	0.275	0.062	0.012	0.177
Platelets	0.000	0.492	0.006	0.267	0.982	0.001	0.224	0.446	0.776	0.737	0.000	0.549	0.049	0.383	0.895
WBC	0.000	0.418	0.000	0.101	0.194	0.000	0.104	0.956	0.774	0.199	0.000	0.302	0.007	0.224	0.178
Neutrophils	0.001	0.537	0.971	0.001	0.350	0.002	0.848	0.797	0.000	0.364	0.000	0.575	0.930	0.000	0.449
Lymphocytes	0.000	0.459	0.898	0.022	0.410	0.000	0.640	0.906	0.000	0.510	0.000	0.306	0.959	0.000	0.591
Monocytes	0.000	0.018	0.090	0.000	0.304	0.000	0.465	0.599	0.001	0.536	0.000	0.031	0.201	0.000	0.534
Eosinophils	0.021	0.108	0.601	0.016	0.514	0.002	0.018	0.560	0.463	0.058	0.012	0.181	0.785	0.009	0.225
Basophils	0.027	0.475	0.076	0.838	0.197	0.011	0.006	0.303	0.985	0.673	0.024	0.421	0.040	0.743	0.354
Haptoglobin	0.000	0.795	0.000	0.941	0.000	0.000	0.747	0.061	0.177	0.765	0.000	0.723	0.000	0.355	0.000
IFN-γ	0.000	0.000	0.668	0.101	0.106	0.000	0.367	0.143	0.730	0.757	0.000	0.000	0.186	0.164	0.187
IL-10	0.000	0.001	0.385	0.150	0.143	0.000	0.000	0.653	0.294	0.267	0.000	0.000	0.754	0.158	0.147
IL-12	0.000	0.025	0.648	0.430	0.423	0.001	0.195	0.781	0.749	0.700	0.000	0.065	0.904	0.897	0.874
IL-1β	0.000	0.063	0.055	0.010	0.009	0.000	0.001	0.449	0.718	0.634	0.000	0.000	0.298	0.050	0.043
IL-4	0.000	0.002	0.163	0.046	0.045	0.000	0.000	0.401	0.675	0.544	0.000	0.000	0.426	0.151	0.131
IL-6	0.000	0.016	0.289	0.139	0.138	0.000	0.000	0.300	0.693	0.666	0.000	0.000	0.428	0.285	0.281
IL-8	0.057	0.103	0.801	0.288	0.232	0.046	0.178	0.529	0.084	0.101	0.005	0.075	0.939	0.237	0.239
TNF-α	0.000	0.036	0.896	0.171	0.184	0.000	0.046	0.581	0.768	0.688	0.000	0.023	0.828	0.316	0.326

HYSS=herd-year-season-sex, RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC= white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α, x=interaction, *=nested effect, cytokines and haptoglobin were log-transformed

Table S 2: Immune variables and their correspondent summary statistics for Landrace and Large White piglets and dams.

Trait	Unit	Piglet data set						Dam data set					
		Landrace			Large White			Landrace			Large White		
		N	Mean±SD	Min-Max	N	Mean±SD	Min-Max	N	Mean±SD	Min-Max	N	Mean±SD	Min-Max
Flow cytometry													
RBC	T/l	611	6.35±0.66[a]	3.50-8.51	533	6.07±0.75[b]	2.30-8.10	298	5.65±0.6	2.14-8.29	272	5.67±0.80	1.71-7.67
Hemoglobin	g/l	611	119.2±13.26[a]	67.00-158.00	533	108.86±14.31[b]	41.00-150.00	298	115.47±10.68	44.00-165.00	272	115.39±15.27	34.00-152.00
Hematocrit	l/l	611	0.40±0.04[a]	0.21-0.54	533	0.36±0.05[b]	0.13-0.47	298	0.36±0.03	0.12-0.52	272	0.36±0.05	0.10-0.48
MCV	fl	611	62.16±3.12[a]	53.60-71.00	533	58.56±3.13[b]	50.00-68.20	298	63.68±3.18	56.30-75.50	272	62.79±3.54	54.00-76.60
MCH	pg	611	18.8±1.16[a]	11.30-30.20	533	17.94±0.98[b]	15.20-22.80	298	20.51±1.05	18.00-23.90	272	20.40±1.08	17.20-23.60
MCHC	g/dl	611	30.26±1.6[a]	17.80-48.60	533	30.67±1.11[b]	27.10-36.00	298	32.22±0.94	28.70-35.40	272	32.51±0.85	30.00-35.30
Platelets	G/l	611	338.67±134.55[a]	24.00-783.00	533	346.88±146.18[a]	14.00-830.00	298	273.92±92.55	17.00-543.00	272	270.75±91.64	6.00-580.00
WBC	G/l	611	19.74±4.98[a]	5.70-49.00	533	19.13±5.78[a]	4.50-45.70	298	14.31±3.2	3.40-30.50	272	12.92±3.30	3.90-25.80
Neutrophils	%	611	47.64±9.98[a]	18.00-87.00	533	41.48±10.67[b]	3.00-74.00	298	58.58±8.06	33.00-86.00	272	53.85±10.15	8.00-86.00
Lymphocytes	%	611	45.84±9.98[a]	10.00-74.00	533	52.89±10.51[b]	22.00-93.00	298	31.43±6.96	10.00-55.00	272	37.46±8.72	12.00-67.00
Monocytes	%	611	3.53±1.65[a]	0.00-10.00	533	3.57±1.86[a]	0.00-14.00	298	3.64±1.44	1.00-9.00	272	3.98±3.17	0.00-50.00
Eosinophils	%	611	2.78±1.57[a]	0.00-13.00	533	1.88±1.12[a]	0.00-8.00	298	6.01±2.91	1.00-21.00	272	4.43±2.09	0.00-18.00
Basophils	%	611	0.15±0.37[a]	0.00-2.00	533	0.07±0.26[b]	0.00-2.00	298	0.21±0.43	0.00-2.00	272	0.11±0.31	0.00-1.00
Band cells	%	611	0.00±0.04[a]	0.00-1.00	533	0.01±0.17[b]	0.00-4.00	298	0.00±0.00	0.00-0.00	272	0.00±0.06	0.00-1.00
Other cells	%	611	0.01±0.12[a]	0.00-1.00	533	0.01±0.11[a]	0.00-1.00	298	0.02±0.16	0.00-1.00	272	0.00±0.06	0.00-1.00
Spectrophotometry													
Haptoglobin	mg/ml	610	0.62±0.52[a]	0.30-2.50	531	0.72±0.64[a]	0.30-7.20	298	1.81±0.5	0.31-2.50	272	1.92±0.53	0.30-2.50
Multiplex Magnetic Bead													
IFN-γ	ng/ml	522	10.89±20.12[a]	0.06-109.65	456	8.88±18.86[a]	0.06-129.14	261	31.8±36.72	0.06-182.76	231	22.94±26.64	0.06-111.07
IL-10	ng/ml	534	1.66±3.09[a]	0.01-15.61	461	1.32±2.73[b]	0.01-25.66	257	10.57±31.68	0.06-388.22	232	5.50±5.30	0.01-38.23
IL-12	ng/ml	534	0.66±0.47[a]	0.08-2.82	461	0.84±0.42[b]	0.13-3.13	259	1.32±1.45	0.08-14.07	234	1.06±0.74	0.10-3.97
IL-1β	ng/ml	534	1.04±1.6[a]	0.06-9.04	461	0.83±1.41[b]	0.06-9.56	256	4.15±5.21	0.06-55.87	231	2.93±2.30	0.06-10.28
IL-4	ng/ml	534	3.21±7.43[a]	0.03-39.94	461	2.46±6.6[a]	0.03-63.22	260	19.81±32.18	0.03-250.00	232	11.61±13.14	0.03-63.33
IL-6	ng/ml	534	0.56±1.14[a]	0.01-6.94	461	0.46±1.15[b]	0.01-11.94	261	4.98±13.67	0.02-103.66	235	2.02±2.38	0.01-16.39
IL-8	ng/ml	534	0.71±0.75[a]	0.01-8.28	461	0.60±0.71[b]	0.02-7.70	265	0.54±0.94	0.01-10.61	235	0.22±0.28	0.01-2.15
TNF-α	ng/ml	534	0.35±0.88[a]	0.01-5.40	461	0.20±0.58[a]	0.01-5.40	264	1.36±2.58	0.01-20.69	235	0.54±0.88	0.01-4.68

RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC= white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α, Means with different letters (a, b) differ significantly at the 5% level.

Table S 3: Pairwise genetic correlations for immune variables in Landrace piglets

	RBC	Hemo-globin	Hema-tocrit	MCV	MCH	MCHC	Platelets	WBC	Neutro-phils	Lympho-cytes	Mono-cytes	Eosino-phils	Baso-phils	Hapto-globin	IFN-γ	IL-10	IL-12	IL-1β	IL-4	IL-6	IL-8	TNF-α
RBC	**0.41 ±0.10**	0.81 ±0.06	0.82 ±0.05	-0.21 ±0.19	-0.38 ±0.20	-0.87 ±0.43	-0.18 ±0.30	0.51 ±0.28	-0.29 ±0.12	0.26 ±0.12	0.34 ±0.2	0.14 ±0.41	-0.16 ±0.54	-0.47 ±0.37	0.49 ±0.29	0.43 ±0.31	0.01 ±0.29	0.40 ±0.43	0.36 ±0.36	0.21 ±0.33	0.36 ±0.35	0.61 ±0.17
Hemo-globin	0.83	**0.41 ±0.11**	0.99 ±0.00	0.39 ±0.15	0.24 ±0.07	-0.86 ±0.46	-0.34 ±0.33	0.27 ±0.16	-0.15 ±0.17	0.08 ±0.16	0.50 ±0.21	0.13 ±0.27	0.04 ±0.30	-0.12 ±0.26	0.71 ±0.23	0.71 ±0.25	0.09 ±0.28	0.73 ±0.44	0.69 ±0.28	0.56 ±0.27	0.32 ±0.37	0.65 ±0.16
Hema-tocrit	1.00	1.00	**0.43 ±0.11**	0.37 ±0.14	0.24 ±0.14	-0.8 4±0.44	-0.39 ±0.35	0.26 ±0.14	-0.17 ±0.16	0.11 ±0.15	0.46 ±0.2	0.12 ±0.27	-0.09 ±0.22	-0.04 ±0.26	0.68 ±0.22	0.69 ±0.25	0.07 ±0.27	0.66 ±0.32	0.69 ±0.23	0.52 ±0.23	0.37 ±0.29	0.61 ±0.17
MCV	-0.16	0.24	0.35	**0.53 ±0.1**	0.99 ±0.02	0.02 ±0.72	-0.30 ±0.21	-0.30 ±0.16	0.18 ±0.19	-0.21 ±0.22	0.14 ±0.18	0.06 ±0.18	0.12 ±0.17	0.16 ±0.18	0.47 ±0.24	0.55 ±0.27	0.14 ±0.21	0.42 ±0.32	0.66 ±0.21	0.62 ±0.18	0.03 ±0.24	0.12 ±0.19
MCH	-0.29	0.29	0.06	0.67	**0.41 ±0.08**	0.09 ±0.57	-0.24 ±0.16	-0.26 ±0.20	0.29 ±0.20	-0.30 ±0.15	0.24 ±0.13	0.08 ±0.17	0.26 ±0.17	0.13 ±0.23	0.40 ±0.14	0.49 ±0.22	0.13 ±0.21	0.52 ±0.36	0.71 ±0.27	0.54 ±0.21	-0.07 ±0.26	0.12 ±0.2
MCHC	-0.15	0.12	-0.33	-0.26	0.57	**0.02 ±0.02**	0.35 ±0.40	0.61 ±0.38	0.41 ±0.54	-0.44 ±0.22	0.64 ±0.43	0.09 ±0.25	0.97 ±0.08	-0.11 ±0.31	0.31 ±0.32	0.21 ±0.27	0.17 ±0.42	0.43 ±1.12	0.20 ±1.04	-0.16 ±1.12	-0.54 ±0.4	0.10 ±0.28
Plate-lets	0.03	-0.04	-0.01	-0.05	-0.12	-0.1	**0.24 ±0.08**	-0.19 ±0.28	-0.40 ±0.27	0.35 ±0.18	-0.12 ±0.22	-0.26 ±0.19	0.05 ±0.19	-0.32 ±0.28	0.30 ±0.28	0.21 ±0.25	0.18 ±0.32	0.33 ±0.34	0.20 ±0.40	0.42 ±0.25	0.48 ±0.33	0.14 ±0.25
WBC	0.18	0.13	0.19	0.00	-0.06	-0.09	0.13	**0.18 ±0.06**	0.62 ±0.23	-0.71 ±0.25	-0.27 ±0.14	0.42 ±0.25	-0.25 ±0.17	0.14 ±0.22	0.43 ±0.26	-0.11 ±0.22	0.00 ±0.22	0.23 ±0.25	0.13 ±0.31	-0.11 ±0.23	0.18 ±0.28	-0.04 ±0.2
Neutro-phils	-0.14	-0.11	-0.14	0.03	0.06	0.05	-0.09	0.28	**0.25 ±0.08**	-0.98 ±0.01	-0.28 ±0.20	0.64 ±0.16	-0.48 ±0.17	-0.03 ±0.20	-0.03 ±0.25	-0.01 ±0.43	-0.10 ±0.36	0.10 ±0.60	0.00 ±0.52	-0.26 ±0.26	-0.57 ±0.27	-0.43 ±0.19
Lympho-cytes	0.14	0.10	0.13	-0.05	-0.08	-0.05	0.12	-0.23	-0.97	**0.30 ±0.08**	0.12 ±0.18	-0.82 ±0.17	0.36 ±0.17	0.18 ±0.29	-0.18 ±0.25	-0.05 ±0.31	0.20 ±0.20	-0.03 ±0.35	-0.08 ±0.32	0.10 ±0.16	0.28 ±0.25	0.18 ±0.17
Mono-cytes	0.00	0.03	0.04	0.04	0.06	0.01	0.02	-0.09	-0.17	0.01	**0.32 ±0.09**	-0.16 ±0.2	0.23 ±0.21	0.02 ±0.22	0.65 ±0.22	0.26 ±0.28	-0.28 ±0.19	0.42 ±0.30	0.56 ±0.25	0.44 ±0.24	0.83 ±0.17	0.53 ±0.15
Eosino-phils	0.00	0.02	0.00	0.02	0.01	0.01	-0.24	-0.22	0.05	-0.22	0.01	**0.22 ±0.08**	0.37 ±0.23	-0.5 6±0.25	0.47 ±0.27	0.29 ±0.29	-0.21 ±0.18	-0.08 ±0.32	0.04 ±0.31	0.19 ±0.24	0.05 ±0.30	0.40 ±0.20
Baso-phils	0.03	0.07	0.09	0.04	0.06	0.00	0.03	-0.02	-0.17	0.10	0.18	0.06	**0.22 ±0.08**	-0.14 ±0.21	0.7 3±0.18	0.48 ±0.28	0.47 ±0.26	0.49 ±0.40	0.63 ±0.36	0.53 ±0.29	0.71 ±0.29	0.30 ±0.23
Hapto-globin	0.00	-0.08	-0.12	-0.11	-0.12	-0.03	0.01	0.21	0.14	-0.14	0.06	0.00	0.01	**0.18 ±0.07**	-0.13 ±0.36	-0.86 ±0.16	-0.62 ±0.29	-0.89 ±0.13	-0.96 ±0.10	-0.73 ±0.18	0.12 ±0.33	-0.48 ±0.19
IFN-γ	0.09	0.12	0.13	0.08	0.04	-0.04	0.02	-0.01	-0.10	0.08	-0.03	0.05	0.11	-0.05	**0.22 ±0.08**	0.73 ±0.13	-0.37 ±0.22	0.61 ±0.65	0.63 ±0.42	0.88 ±0.16	0.87 ±0.23	0.78 ±0.11
IL-10	0.11	0.15	0.16	0.12	0.08	-0.03	0.03	0.00	-0.14	0.12	0.00	0.03	0.15	-0.08	0.64	**0.24 ±0.10**	0.23 ±0.34	0.95 ±0.06	1.00 ±0.01	0.99 ±0.02	0.72 ±0.17	0.91 ±0.07
IL-12	0.02	0.04	0.02	0.02	0.04	0.04	0.00	0.04	-0.03	0.03	-0.04	0.01	0.06	0.00	-0.17	0.18	**0.34 ±0.13**	0.35 ±0.37	0.38 ±0.32	0.34 ±0.28	-0.43 ±0.28	0.12 ±0.28
IL-1β	0.12	0.16	0.14	0.05	0.05	0.02	0.00	0.07	-0.04	0.02	-0.01	0.06	0.10	0.00	0.53	0.85	0.25	**0.17 ±0.09**	0.97 ±0.04	0.93 ±0.06	0.64 ±0.38	0.96 ±0.06
IL-4	0.07	0.11	0.11	0.09	0.06	-0.02	0.01	-0.02	-0.12	0.10	0.04	0.07	0.13	-0.13	0.59	0.89	0.23	0.82	**0.19 ±0.09**	0.98 ±0.03	0.70 ±0.28	0.89 ±0.09

IL-6	0.09	0.14	0.13	0.10	0.07	-0.02	0.03	0.03	-0.14	0.12	0.00	0.05	0.14	-0.08	0.62	0.92	0.16	0.81	0.84	**0.35 ±0.09**	0.73 ±0.22	0.80 ±0.09
IL-8	0.10	0.12	0.10	-0.01	0.02	0.05	-0.05	-0.18	-0.16	0.13	0.02	0.08	0.09	-0.12	0.15	0.12	0.02	0.14	0.11	0.10	**0.15 ±0.08**	0.65 ±0.23
TNF-α	0.10	0.12	0.12	0.05	0.03	-0.02	0.00	0.02	-0.08	0.06	0.07	0.02	0.04	-0.08	0.56	0.58	0.11	0.55	0.57	0.58	0.14	**0.61 ±0.09**

Bold font indicates heritabilities (h^2±SE) on the diagonal. Phenotypic correlations (r_p) under the diagonal and genetic correlations (r_g±SE) above the diagonal RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC= white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α, NA=not available.

Table S 4: Pairwise genetic correlations for immune variables in Large White piglets

	RBC	Hemo-globin	Hema-tocrit	MCV	MCH	MCHC	Platelets	WBC	Neutro-phils	Lympho-cytes	Mono-cytes	Eosino-phils	Baso-phils	Hapto-globin	IFN-γ	IL-10	IL-12	IL-1β	IL-4	IL-6	IL-8	TNF-α
RBC	0.36 ±0.08	0.77 ±0.10	0.90 ±0.09	-0.99 ±0.00	-0.64 ±0.24	0.43 ±0.26	0.23 ±0.88	0.33 ±0.36	-0.16 ±0.14	0.29 ±0.14	-0.35 ±0.17	-0.70 ±0.20	-0.24 ±0.74	0.17 ±0.59	0.56 ±0.24	0.46 ±0.35	0.77 ±0.33	0.75 ±0.36	0.50 ±0.38	0.74 ±0.28	0.00 ±0.17	0.96 ±0.10
Hemo-globin	0.88	0.18 ±0.08	0.97 ±0.04	-0.30 ±0.24	0.02 ±0.35	0.91 ±0.12	0.79 ±0.55	-0.11 ±0.36	0.07 ±0.13	-0.02 ±0.27	-0.04 ±0.30	-0.78 ±0.32	0.28 ±0.67	-0.09 ±0.62	0.43 ±0.32	-0.09 ±0.38	0.82 ±0.28	0.07 ±0.43	0.24 ±0.48	0.37 ±0.39	0.19 ±0.17	0.79 ±0.20
Hema-tocrit	1.00	1.00	0.09 ±0.06	-0.55 ±0.30	-0.34 ±0.35	0.87 ±0.21	0.65 ±0.70	0.04 ±0.42	-0.04 ±0.27	0.07 ±0.3	-0.25 ±0.35	-0.82 ±0.37	0.17 ±0.71	0.01 ±0.60	0.40 ±0.34	-0.02 ±0.47	0.78 ±0.32	0.10 ±0.42	0.03 ±0.32	0.69 ±0.81	0.22 ±0.25	0.88 ±0.16
MCV	-0.23	0.16	0.25	0.61 ±0.1	0.94 ±0.03	0.18 ±0.23	0.67 ±0.88	-0.46 ±0.36	0.19 ±0.26	-0.34 ±0.21	0.49 ±0.23	0.65 ±0.38	0.19 ±0.47	-0.27 ±0.4	-0.58 ±0.19	-0.69 ±0.21	-0.44 ±0.25	-0.90 ±0.16	-0. 79 ±0.15	-0.80 ±0.13	0.16 ±0.15	-0.87 ±0.17
MCH	-0.26	0.23	0.09	0.79	0.66 ±0.12	0.49 ±0.20	0.79 ±0.50	-0.60 ±0.30	0.20 ±0.22	-0.45 ±0.20	0.62 ±0.21	0.45 ±0.24	0.45 ±0.44	-0.38 ±0.42	-0.47 ±0.20	-0.71 ±0.24	-0.12 ±0.25	-0.84 ±0.17	-0.66 ±0.17	-0.73 ±0.20	0.19 ±0.17	-0.58 ±0.17
MCHC	-0.16	0.12	-0.20	-0.24	0.40	0.15 ±0.07	0.57 ±0.91	-0.28 ±0.43	-0.03 ±0.43	-0.11 ±0.30	0.93 ±0.24	-0.24 ±0.34	0.94 ±0.26	-0.31 ±0.63	0.17 ±0.32	0.07 ±0.41	0.72 ±0.27	-0.07 ±0.33	0.25 ±0.21	0.14 ±0.21	0.08 ±0.26	0.48 ±0.22
Plate-lets	0.19	0.14	0.17	-0.05	-0.12	-0.14	0.01 ±0.02	-0.54 ±0.65	0.18 ±1.03	-0.11 ±0.65	-0.10 ±0.54	0.97 ±0.18	-0.30 ±0.64	0.01 ±1.13	-0.81 ±0.43	-0.64 ±0.86	0.50 ±1.04	-0.54 ±0.97	-0.26 ±1.41	-0.58 ±0.63	0.64 ±0.43	0.16 ±0.76
WBC	0.25	0.21	0.26	-0.03	-0.10	-0.11	0.26	0.08 ±0.07	0.72 ±0.29	-0.58 ±0.38	-0.76 ±0.30	0.19 ±0.42	-0.93 ±0.18	-0.36 ±0.70	0.54 ±0.44	0.41 ±0.48	-0.68 ±0.37	0.63 ±0.66	0.58 ±0.67	0.43 ±0.59	-0.14 ±0.58	0.07 ±0.69
Neutro-phils	-0.11	-0.11	-0.15	-0.05	0.01	0.08	0.04	0.24	0.12 ±0.08	-0.96 ±0.03	0.15 ±0.29	-0.08 ±0.45	-0.61 ±0.48	-0.85 ±0.32	0.43 ±0.41	0.67 ±0.33	-0.14 ±0.32	0.84 ±0.16	0.67 ±0.24	0.71 ±0.29	-0.65 ±0.25	0.31 ±0.36
Lympho-cytes	0.13	0.11	0.15	0.01	-0.04	-0.07	-0.02	-0.21	-0.98	0.14 ±0.08	-0.46 ±0.28	0.15 ±0.48	0.00 ±0.78	0.88 ±0.29	-0.22 ±0.41	-0.62 ±0.32	0.03 ±0.41	-0.83 ±0.26	-0.70 ±0.31	-0.78 ±0.20	0.86 ±0.10	0.10 ±0.32
Mono-cytes	-0.02	0.01	0.04	0.14	0.08	-0.10	0.08	-0.10	-0.22	0.05	0.17 ±0.07	0.40 ±0.44	0.78 ±0.38	-0.51 ±0.39	-0.21 ±0.34	0.12 ±0.35	0.33 ±0.35	0.18 ±0.43	0.16 ±0.37	0.24 ±0.28	-0.30 ±0.19	-0.82 ±0.17
Eosino-phils	-0.13	-0.07	-0.09	0.12	0.14	0.04	-0.27	-0.17	0.07	-0.17	-0.06	0.06 ±0.05	0.08 ±0.63	-0.44 ±0.52	-0.92 ±0.16	-0.57 ±0.44	0.41 ±0.37	-0.57 ±0.39	-0.50 ±0.52	-0.54 ±0.51	0.15 ±0.43	-0.85 ±0.26
Baso-phils	0.06	0.07	0.05	-0.01	0.00	0.03	0.01	0.12	-0.15	0.12	0.10	-0.04	0.03 ±0.04	0.62 ±0.52	-0.24 ±0.60	-0.18 ±0.53	0.81 ±0.26	0.13 ±0.59	0.43 ±0.48	-0.16 ±0.64	0.64 ±0.30	-0.12 ±0.72
Hapto-globin	-0.01	-0.10	-0.08	-0.11	-0.09	-0.10	0.16	0.18	0.10	-0.10	-0.02	0.06	0.00	0.03 ±0.03	-0.15 ±0.70	-0.66 ±0.50	-0.48 ±0.56	-0.71 ±0.37	-0.47 ±0.44	-0.84 ±0.26	0.64 ±0.47	-0.65 ±0.54
IFN-γ	0.11	0.04	0.04	-0.16	-0.13	0.03	0.00	0.09	0.11	-0.09	-0.06	-0.13	-0.05	0.00	0.32 ±0.10	0.89 ±0.11	-0.27 ±0.30	0.92 ±0.11	0.73 ±0.17	0.99 ±0.08	-0.44 ±0.28	0.35 ±0.32
IL-10	0.04	0.01	-0.04	-0.14	-0.07	0.11	-0.01	0.11	0.05	-0.05	0.00	-0.12	0.02	0.06	0.60	0.25 ±0.10	0.22 ±0.31	0.97 ±0.06	0.95 ±0.05	0.98 ±0.04	-0.62 ±0.48	0.38 ±0.40
IL-12	0.02	0.06	0.02	0.06	0.06	0.00	-0.01	-0.03	-0.10	0.10	0.02	-0.03	0.03	-0.19	-0.14	0.14	0.18 ±0.09	0.28 ±0.35	0.52 ±0.28	0.10 ±0.44	-0.12 ±0.39	0.51 ±0.44
IL-1β	0.06	0.04	0.00	-0.12	-0.06	0.08	0.02	0.14	0.03	-0.03	0.05	-0.16	0.06	0.03	0.52	0.88	0.18	0.16 ±0.09	0.95 ±0.06	0.96 ±0.06	-0.67 ±0.33	0.48 ±0.34
IL-4	0.07	0.04	-0.01	-0.16	-0.10	0.10	0.05	0.10	0.00	0.00	0.02	-0.10	0.00	0.04	0.53	0.85	0.18	0.82	0.27 ±0.13	0.85 ±0.08	-0.45 ±0.30	0.58 ±0.38

IL-6	0.12	0.09	0.05	-0.18	-0.08	0.16	0.05	0.12	0.02	-0.01	0.01	-0.16	-0.02	0.05	0.59	0.90	0.12	0.85	0.86	0.31 ±0.10	-0.49 ±0.28	0.54 ±0.26
IL-8	0.12	0.18	0.25	0.14	0.14	0.00	-0.14	-0.31	-0.33	0.33	0.02	-0.04	0.00	-0.09	0.01	-0.04	0.10	-0.05	-0.03	-0.05	0.36 ±0.11	-0.06 ±0.33
TNF-α	0.11	0.08	0.12	-0.04	-0.06	-0.04	0.09	0.09	0.06	-0.06	0.02	-0.13	-0.01	0.06	0.56	0.52	0.11	0.52	0.51	0.53	0.05	0.13 ±0.08

Bold font indicates heritabilities (h^2±SE) on the diagonal. Phenotypic correlations (r_p) under the diagonal and genetic correlations (r_g±SE) above the diagonal. RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC= white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α, NA=not available.

Table S 5: Principal components and their composition based on loading values of Landrace and Large White dams.

	Landrace		Large White	
	PC1	**PC2**	**PC1**	**PC2**
Biological functional network: RBC				
RBC	31.48	0.03	31.50	1.24
Hemoglobin	23.32	9.99	29.61	1.85
Hematocrit	25.93	9.85	30.58	2.96
MCV	4.51	38.59	0.30	48.29
MCH	9.55	31.41	1.79	40.94
MCHC	3.82	0.49	2.53	4.07
Platelets	1.25	9.16	3.26	0.64
Haptoglobin	0.16	0.47	0.43	0.02
% of variance	38.83	23.95	37.81	25.25
Biological functional network: Cells				
WBC	14.10	12.47	14.48	3.55
Neutrophils	36.72	3.31	37.82	2.75
Lymphocytes	27.45	0.04	29.54	0.26
Monocytes	13.18	0.93	7.41	42.00
Eosinophils	6.17	37.05	6.34	35.30
Basophils	2.39	46.21	4.42	16.15
% of variance	41.43	18.72	40.37	17.48
Biological functional network: Cytokines				
IFN-γ	9.86		10.12	2.42
IL-10	14.90		15.35	4.17
IL-12	14.66		14.93	2.17
IL-1β	14.69		15.03	4.64
IL-4	14.97		15.53	3.77
IL-6	14.85		15.54	3.82
IL-8	5.88		5.89	43.89
TNF-α	10.20		7.62	35.12
% of variance	79.28		75.27	12.97

PC=Principal component, % of variance= percentage of explained variance by a PC, RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC= white blood cells,

IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α. PCs are estimated within three distinguished biological functional frameworks like cells (Cell), RBC and additional RBC characteristics including haptoglobin (RBC), and Cytokines.

Table S 6: Genetic effects for Landrace and Large White piglets after consideration for maternal environmental effects

Trait	Landrace			Large White		
	σ^2_p	h^2±SE	c^2±SE	σ^2_p	h^2±SE	c^2±SE
RBC	0.10	0.36±0.12	0.06±0.04	0.06	0.35±0.08	0.02±0.01
Hemoglobin	13462.96	**0.41±0.12**	0.08±0.05	17200.32	0.28±0.08	0.04±0.03
Hematocrit	0.001	**0.44±0.12**	0.05±0.04	0.001	0.14±0.06	0.06±0.04
MCV	0.001	**0.41±0.09**	0.10±0.05	67.73	**0.59±0.09**	0.10±0.04
MCH	0.83	0.29±0.07	0.03±0.03	0.71	**0.66±0.09**	0.05±0.03
MCHC	2.25	0.02±0.03	0.03±0.02	1.06	0.16±0.08	0.14±0.06
Platelets	263542756.00	0.22±0.08	0.21±0.05	419554927.64	0.01±0.02	0.27±0.05
WBC	567.87	0.17±0.06	0.08±0.04	929.03	0.09±0.07	0.16±0.06
Neutrophils	7508.22	0.22±0.08	0.11±0.04	10348.99	0.13±0.07	0.17±0.05
Lymphocytes	7873.01	0.30±0.08	0.11±0.05	9990.00	0.13±0.07	0.17±0.05
Monocytes	4.67	0.31±0.08	0.03±0.04	8.58	0.17±0.07	0.29±0.06
Eosinophils	5.29	0.21±0.07	0.08±0.04	1.28	0.05±0.05	0.04±0.03
Basophils	0.02	0.24±0.08	0.04±0.03	0.001	0.04±0.04	0.14±0.05
Haptoglobin	0.001	0.18±0.07	0.06±0.04	0.01	0.03±0.04	0.04±0.03
IFN-γ	0.18	0.15±0.08	**0.44±0.06**	0.29	0.18±0.09	**0.56±0.06**
IL-10	0.04	0.16±0.10	**0.53±0.06**	0.08	0.23±0.12	**0.44±0.07**
IL-12	0.001	0.31±0.12	0.36±0.07	0.001	0.20±0.10	0.35±0.07
IL-1β	0.03	0.09±0.08	**0.49±0.06**	0.05	0.10±0.07	**0.40±0.06**
IL-4	0.12	0.14±0.08	**0.47±0.06**	0.24	0.16±0.09	**0.42±0.07**
IL-6	0.05	0.19±0.09	**0.52±0.06**	0.11	0.28±0.11	**0.45±0.07**
IL-8	0.01	0.12±0.07	0.24±0.06	0.02	0.38±0.11	0.16±0.06
TNF-α	0.06	**0.41±0.11**	0.31±0.07	0.06	0.08±0.06	**0.42±0.06**

RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, WBC= white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α, h^2=heritability, c^2=litter effect, σ^2_p=phenotypic variance, cytokines are log-transformed, bold font indicates high h^2 or c^2 above 0.4

Table S 7: Principal components and their composition based on loading values of Landrace and Large White piglets

	Landrace			Large White			
	PC1	**PC2**	**PC3**	**PC1**	**PC2**	**PC3**	**PC4**
Biological functional network: RBC							
RBC	22.88	14.35	3.26	24.94	12.80	0.50	0.91
Hemoglobin	**31.55**	0.004	3.59	**32.39**	0.72	0.99	0.12
Hematocrit	**31.20**	2.86	1.02	**31.65**	1.34	1.35	0.60
MCV	6.76	14.78	**33.89**	4.67	**32.13**	**20.36**	0.12
MCH	5.24	**44.79**	0.37	5.99	**39.14**	0.74	9.30
MCHC	0.001	16.77	**50.04**	0.22	1.24	**61.08**	16.12
Platelets	2.36	3.28	0.06	0.02	7.96	6.60	29.27
Haptoglobin	0.02	3.17	7.76	0.11	4.68	8.37	**43.56**
% of variance	37.23	22.43	16.98	37.49	22.84	16.57	12.47
Biological functional network: Cells							
WBC	8.03	17.35	23.47	2.60	**45.02**	0.47	
Neutrophils	**44.04**	0.54	0.10	**45.08**	0.47	0.03	
Lymphocytes	**41.17**	6.50	0.87	**43.32**	0.30	0.50	
Monocytes	2.43	13.91	**34.34**	5.20	5.58	1.07	
Eosinophils	0.35	**46.82**	13.09	3.08	**38.32**	18.61	
Basophils	3.97	14.88	28.12	0.74	10.32	**79.31**	
% of variance	35.96	20.95	18.94	35.49	21.89	16.42	
Biological functional network: Cytokines							
IFN-γ	12.53			13.09	0.65		
IL-10	17.17			18.79	0.37		
IL-12	6.67			2.30	**33.72**		
IL-1β	15.68			17.58	0.33		
IL-4	16.58			17.48	0.28		
IL-6	16.50			18.40	0.85		
IL-8	1.97			0.31	**63.75**		
TNF-α	12.90			12.05	0.06		
% of variance	68.13			60.13	13.45		

PC=Principal component, % of variance= percentage of explained variance by a PC, RBC=red blood cells, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin,

MCHC=mean corpuscular hemoglobin concentration, WBC= white blood cells, IFN-γ=interferon-γ, IL=interleukin, TNF-α=tumor necrosis factor-α, bold font indicates contributing immune traits within the PC. PCs are estimated within three distinguished biological functional frameworks like cells (Cell), RBC and additional RBC characteristics including haptoglobin (RBC), and Cytokines.

Table S 8: Genetic parameters of principal components as new dependent immune variables for Landrace and Large White piglets

BFN	PC	Cell			RBC				Cyto		
		PC1	PC2	PC3	PC1	PC2	PC3	PC4	PC1	PC2	Breed
Cell	PC1	**0.31±0.08** **0.12±0.07**			0.16±0.16 0.00±0.39	-0.24±0.16 0.06±0.25	0.07±0.30 -0.02±0.29	NA -0.84±0.30	0.17±0.20 0.52±0.41	NA 0.78±0.26	LR LW
	PC2		**0.20±0.08** **0.05±0.04**		0.06±0.19 -0.27±0.63	0.54±0.20 0.19±0.39	-0.31±0.28 -0.64±0.28	NA 0.89±0.26	0.51±0.27 -0.93±0.19	NA -0.71±0.27	LR LW
	PC3			**0.18±0.07** **0.04±0.04**	0.46±0.20 0.38±0.79	0.00±0.25 -0.89±0.29	0.34±0.25 0.15±0.47	NA -0.84±0.45	0.68±0.25 0.36±0.44	NA 0.77±0.42	LR LW
RBC	PC1	0.07 -0.10	-0.02 -0.15	0.10 -0.02	**0.50±0.10** **0.08±0.08**				0.68±0.16 0.24±0.54	NA -0.70±0.34	LR LW
	PC2	-0.06 0.01	0.15 0.24	-0.06 -0.09		**0.35±0.08** **0.58±0.11**			0.34±0.25 -0.70±0.20	NA -0.02±0.15	LR LW
	PC3	-0.02 0.03	0.00 0.14	0.03 -0.04			**0.13±0.06** **0.17±0.06**		-0.30±0.26 0.86±0.19	NA -0.16±0.21	LR LW
	PC4	NA 0.13	NA -0.14	NA 0.03				**NA** **0.10±0.06**	NA -0.05±0.15	NA -0.54±0.25	LR LW
Cyto	PC1	0.11 0.03	0.04 -0.17	0.05 0.07	0.17 0.02	0.01 -0.13	-0.06 0.09	NA 0.06	**0.32±0.10** **0.27±0.09**		LR LW
	PC2	NA 0.35	NA -0.21	NA 0.43	NA -0.21	NA -0.14	NA -0.02	NA 0.14		**NA** **0.14±0.06**	LR LW

BFN=biological functional network, PC=principal component, PCs are estimated within three distinguished BFN like cells (Cell), RBC and additional RBC characteristics including haptoglobin (RBC), cytokines (Cyto), heritabilities (h^2±SE) are indicated in bold font on the diagonal, phenotypic correlations (r_p) under the diagonal and genetic correlations (r_g±SE) above the diagonal, LR=Landrace, LW=Large White, NA=not available

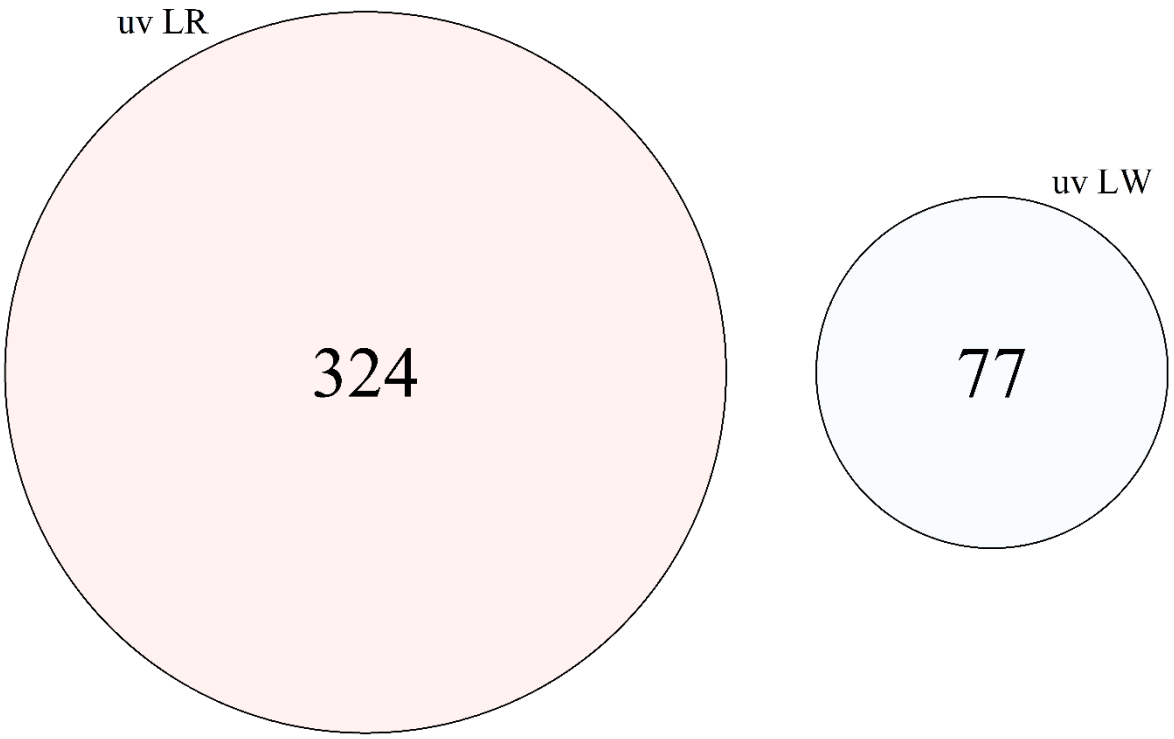

Figure S 1: Comparison of different methods used to detect significant univariate associations for Landrace and Large White

Multiple identical significant SNPs for different immune traits within a method are counted a single time. uv=univariate, LR=Landrace, LW=Large White

Table S 9: Significant associated genetic markers identified with univariate methods (continued)

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LW	MCH	1	ALGA0000795	8724875	A/G	74,10	0,03	CHR	PLINK	1	TULP4, GTF2H5, SERAC1, SYNJ2, SNX9, ZDHHC14, TMEM242
LW	MCH	1	ASGA0000892	8739103	T/C	25,90	0,03	CHR	PLINK	1	
LW	MCH	1	ALGA0000837	8810463	T/G	25,80	0,03	CHR	PLINK	1	
LW	MCH	1	ASGA0000925	8896901	T/C	25,90	0,03	CHR	PLINK	1	
LW	MCH	1	ALGA0106880	9725288	A/G	26,00	0,03	CHR	PLINK	1	
LW	MCH	1	ASGA0000922	10777632	C/T	74,00	0,04	CHR	PLINK	2	
LW	MCH	1	H3GA0000711	10830305	A/G	25,90	0,03	CHR	PLINK	2	
LW	HMG	2	DRGA0002793	21669969	A/G	87,10	0,03	CHR	PLINK	3	
LW	HMG	2	ASGA0101016	21751485	C/T	86,90	0,03	CHR	PLINK	3	
LW	HMG	2	ALGA0012559	22792581	G/A	86,40	0,03	CHR	PLINK	4	
LW	HMG	2	ALGA0012570	22989364	T/G	90,00	0,03	CHR	PLINK	4	
LR	HAP	2	MARC0055904	37117707	A/G	91,50	0,02	CHR	PLINK	5	SLC17A6, ANO5, U6, NELL1
LR	HAP	2	ALGA0013060	37186143	C/T	4,10	0.001/3.51	CHR	PLINK, BIMBAM	5	
LR	HAP	2	ALGA0013078	37762734	A/G	4,10	0.001/3.51	CHR	PLINK, BIMBAM	5	
LR	HAP	2	MARC0064216	37514046	A/G	90,00	0,04	CHR	PLINK	5	
LR	HAP	2	MARC0018628	37632205	T/C	89,60	0,04	CHR	PLINK	5	
LR	HAP	2	ALGA0013104	37945462	G/T	4,10	0.001/3.59	CHR	PLINK, BIMBAM	5	
LR	HAP	2	DRGA0002935	37202269	C/T	95,90	0.001/3.51	CHR	PLINK, BIMBAM	5	
LR	HAP	2	ALGA0013106	38128487	T/C	90,70	0,01	CHR	PLINK	6	NELL1
LR	BAS	3	MARC0006534	112713663	T/G	78,90	0,04	GEN	PLINK	7	HADHB
LW	MCH	4	MARC0084905	4298000	G/A	4,60	0,05	CHR	PLINK	8	COL22A1
LW	MCH	4	ASGA0017522	5419206	C/T	4,80	0,05	CHR	PLINK	9	
LR	MCV	4	ALGA0026246	82530260	T/G	48,80	0,02	CHR	PLINK	10	
LR	MCHC	5	ALGA0106408	17162699	C/T	68,80	0,00	CHR	PLINK	11	SCN8A
LR	MCHC	5	H3GA0016097	23400843	A/C	37,10	0,03	CHR	PLINK	12	LRIG3
LR	HMT	5	ASGA0025128	23778757	A/G	46,70	0,05	CHR	PLINK	12	
LR	HMT	5	ASGA0025132	23816873	G/A	42,50	0,05	CHR	PLINK	12	
LR	HMT	5	ASGA0025137	23933098	T/C	79,00	0,01	CHR	PLINK	12	
LR	HMT	5	ALGA0031314	24000573	G/T	21,00	0,01	CHR	PLINK	12	
LR	HMT	5	ASGA0025140	24069910	T/G	79,10	0,01	CHR	PLINK	12	
LR	HMT	5	ALGA0031321	24135911	A/C	79,30	0,01	CHR	PLINK	12	
LR	MCHC	5	DRGA0005609	29991703	T/G	84,10	0,02	CHR	PLINK	13	
LR	MCHC	5	DRGA0005613	30469491	T/G	84,10	0,02	CHR	PLINK	13	HMGA2

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	MCHC	5	ASGA0025326	31271737	A/C	22,10	0,02	CHR	PLINK	14	U6, ssc-mir-9808, CAND1
LR	MCHC	5	ALGA0034323	31867380	A/G	88,60	0,02	CHR	PLINK	14	
LR	MCHC	5	MARC0114715	32497165	A/C	0,00	0,04	CHR	PLINK	15	IL26, IL22
LR	MCHC	5	ALGA0031657	32603961	C/T	19,30	0,04	CHR	PLINK	15	
LR	MCHC	5	ALGA0031690	33946621	A/G	27,10	0,02	CHR	PLINK	16	CCT2, RAB3A, BEST3, MYRFL, CNOT2, KCNMB4, PTPRB
LR	HMT	5	H3GA0016244	34769398	A/G	70,20	0.01/3.17	CHR	PLINK, BIMBAM	16	
LR	MCHC	5	ALGA0031731	36197319	A/C	25,50	0,02	CHR	PLINK	17	TRHDE, U4
LR	HMT	5	ALGA0031736	36314172	A/C	27,90	0,05	CHR	PLINK	17	
LR	HMT	5	ASGA0025454	36903934	C/T	35,90	0,03	CHR	PLINK	17	
LR	HMT	5	ALGA0031749	37261727	T/C	32,50	0,02	CHR	PLINK	18	
LR	MCHC	5	INRA0019263	38864890	T/C	69,80	0,02	CHR	PLINK	19	
LR	MCHC	5	MARC0037200	38880761	T/C	69,80	0,02	CHR	PLINK	19	
LR	MCHC	5	rs334622443	42436328	A/T	NA	0,02	CHR	PLINK	20	AMN1, ETFBKMT, DENND5B, SINHCAF, CAPRIN2, IPO8
LR	MCHC	5	DRGA0005776	43220509	C/T	30,50	0,02	CHR	PLINK	20	
LR	MCHC	5	DRGA0005773	43252599	A/G	75,30	0,02	CHR	PLINK	20	
LR	MCHC	5	MARC0113545	43293810	A/G	0,00	0,02	CHR	PLINK	20	
LR	MCHC	5	ALGA0031826	43320525	C/A	30,50	0,02	CHR	PLINK	20	
LR	MCHC	5	ASGA0025493	43385239	G/A	30,50	0,02	CHR	PLINK	20	
LR	MCHC	5	H3GA0016271	43428743	C/A	30,50	0,02	CHR	PLINK	20	
LR	MCHC	5	ASGA0025490	43480338	T/C	71,40	0,02	CHR	PLINK	21	U6, TMTC1
LR	MCHC	5	DRGA0005767	43556787	C/T	30,50	0,02	CHR	PLINK	21	
LR	MCHC	5	MARC0003440	43664480	T/C	69,50	0,02	CHR	PLINK	21	
LR	MCHC	5	INRA0019288	43688401	T/C	73,50	0,02	CHR	PLINK	21	
LR	MCHC	5	MARC0030421	43750584	C/T	28,60	0,02	CHR	PLINK	21	
LR	MCHC	5	ALGA0031834	43879295	G/A	30,60	0,02	CHR	PLINK	21	
LR	MCHC	5	ALGA0031838	43979571	T/G	30,50	0,02	CHR	PLINK	21	
LR	MCHC	5	H3GA0016294	47424047	A/G	38,30	0,02	CHR	PLINK	22	ITPR2
LR	MCHC	5	ALGA0031924	48896828	T/G	57,00	0,01	GEN	PLINK	23	BCAT1
LR	MCHC	5	MARC0001027	50094492	G/A	23,70	0,01	CHR	PLINK	24	SOX5
LR	MCHC	5	DRGA0005841	50243918	A/G	76,30	0,01	CHR	PLINK	24	
LR	MCHC	5	ALGA0032074	58601394	A/G	76,00	0,01	GEN	PLINK	25	GRIN2B, EMP1
LR	MCHC	5	H3GA0016359	58625915	C/T	25,10	0,00	CHR	PLINK	25	
LR	MCHC	5	H3GA0016379	58840179	G/A	23,90	0,00	CHR	PLINK	25	
LR	MCHC	5	ALGA0032146	59340760	A/C	82,80	0,01	GEN	PLINK	25	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	MCV	5	ASGA0025778	61783155	A/G	23,10	0,02	CHR	PLINK	26	TMEM52B, OLR1, CLEC7A, CLEC1A, CLEC12B, CLEC1B, CLEC12A, CLEC12B, CLEC2B, CD69, LOC100520491, CLEC2D, KLRB1, LOC100524679, PZP, A2M, KLRG1, M6PR, PHC1, A2ML1, RIMKLB
LR	MCV	5	ASGA0025791	61931507	A/G	76,80	0,02	CHR	PLINK	26	
LR	MCV	5	DRGA0005951	61966384	G/A	76,80	0,02	CHR	PLINK	26	
LR	MCV	5	ASGA0025794	62115185	T/G	23,40	0,02	CHR	PLINK	26	
LR	MCV	5	DRGA0005956	62134657	T/G	80,00	0,02	CHR	PLINK	26	
LR	MCHC	5	MARC0100616	62372560	C/T	0,00	0,00	CHR	PLINK	26	
LR	MCV	5	ALGA0032322	62455175	G/A	65,60	0,02	CHR	PLINK	26	
LR	MCV	5	DIAS0000002	62481418	A/G	34,90	0,02	CHR	PLINK	26	
LR	MCV	5	ASGA0025802	62601778	T/C	77,10	0,02	CHR	PLINK	26	
LR	MCV	5	ALGA0032345	62737145	T/C/G	39,00	0,02	CHR	PLINK	26	
LR	MCHC	5	ASGA0025827	63827447	G/A	84,70	0,03	CHR	PLINK	27	ENO2
LW	RBC	5	ALGA0033064	77286779	T/C	98,20	0,02	CHR	PLINK	28	SLC38A4, AMIGO2, PCED1B, RPAP3
LW	RBC	5	ASGA0093314	77402409	A/G	8,50	0,02	CHR	PLINK	28	
LW	RBC	5	ALGA0104452	77541676	A/G	7,50	0,02	CHR	PLINK	28	
LW	RBC	5	MARC0090729	77680830	C/T	0,00	0,02	CHR	PLINK	28	
LW	RBC	5	MARC0098250	77948633	G/A	0,00	0,02	CHR	PLINK	28	
LW	RBC	5	ALGA0109048	77962305	T/C	6,20	0,02	CHR	PLINK	28	
LW	RBC	5	ALGA0101247	77990021	A/G	2,90	0,02	CHR	PLINK	28	
LW	RBC	5	ALGA0104065	77997876	C/T	97,10	0,02	CHR	PLINK	28	
LW	RBC	5	MARC0009241	78029583	G/A	97,10	0,02	CHR	PLINK	28	
LW	RBC	5	ALGA0104516	78032160	G/T	97,10	0,02	CHR	PLINK	28	
LW	RBC	5	ALGA0033127	79513170	A/G	87,80	0,02	CHR	PLINK	29	ALDH1L2, C12orf45, SLC41A2, U6, CHST11, TXNRD1
LW	RBC	5	H3GA0016899	80171271	C/T	90,30	0,02	CHR	PLINK	29	
LW	RBC	5	ALGA0115368	80487779	T/C	6,20	0,02	CHR	PLINK	29	
LW	RBC	5	ALGA0103880	80562374	T/C	94,10	0,02	CHR	PLINK	30	
LW	RBC	5	DRGA0006061	82345818	A/G	1,60	0,02	CHR	PLINK	31	
LR	IFN	5	MARC0080493	90118573	A/G	79,20	0,03	CHR	PLINK	32	
LR	MCHC	5	ASGA0101924	97259676	T/C	98,90	0,00	CHR	PLINK	33	
LR	MCHC	5	DRGA0006295	97412529	A/C	98,70	0,00	CHR	PLINK	33	
LR	MCHC	5	H3GA0017216	97477241	C/T	1,10	0,00	CHR	PLINK	33	
LR	MCHC	5	DRGA0006288	102305039	A/G	1,10	0,00	CHR	PLINK	34	
LR	MCHC	5	INRA0020540	102513112	A/G	98,90	0,00	CHR	PLINK	34	
LR	IL-6	6	MARC0041561	16171435	C/T	80,90	0,05	CHR	PLINK	35	
LR	IL-6	6	MARC0075761	16188799	G/A	80,90	0,05	CHR	PLINK	35	
LR	IL-4	6	H3GA0055874	47536918	C/T	16,30	0,04	CHR	PLINK	36	ACTN4, HNRNPL
LR	MCV	6	ASGA0094719	70404572	A/G	34,60	0,04	CHR	PLINK	37	UBE4B

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	MCV	6	ALGA0111762	70460911	C/T	67,30	0,04	CHR	PLINK	37	
LR	MCV	6	ALGA0105286	74623829	C/A	31,30	0,01	CHR	PLINK	38	FHAD1
LR	MCV	6	ALGA0105225	75820891	C/T	36,60	0,04	CHR	PLINK	39	PADI1-6, RCC2, ARHGEF10L
LR	MCV	6	MARC0076222	75960523	C/T	34,50	0,04	CHR	PLINK	39	
LR	MCV	6	ALGA0115349	75971546	C/T	32,60	0,04	CHR	PLINK	39	
LR	MCV	6	MARC0098064	76038583	C/T	0,00	0,05	CHR	PLINK	39	
LR	MCV	6	MARC0004865	76063337	G/A	34,60	0,04	CHR	PLINK	39	
LR	MCV	6	ASGA0090874	76089914	G/A	53,00	0,04	CHR	PLINK	39	
LR	MCV	6	ALGA0116768	76114734	A/G	65,40	0,04	CHR	PLINK	39	
LR	MCV	6	ASGA0101002	76151935	A/G	64,60	0,05	CHR	PLINK	39	
LR	MCV	6	MARC0098251	76210521	T/C	0,00	0,04	CHR	PLINK	39	
LR	MCV	6	ALGA0035695	80258992	G/A	62,40	0,04	CHR	PLINK	40	ZBTB40, EPHA8, C1QA, C1QC, C1QB
LR	MCV	6	MARC0026937	80582130	G/A	42,60	0,01	CHR	PLINK	40	
LR	MCV	6	DBWU0000032	80596783	T/C	31,30	0,01	CHR	PLINK	40	
LR	MCV	6	ALGA0114670	80603591	C/A	31,30	0,01	CHR	PLINK	40	
LR	MCV	6	H3GA0055046	80642168	C/T	31,30	0,01	CHR	PLINK	40	
LR	MCV	6	ASGA0099954	80643934	T/C	57,30	0,01	CHR	PLINK	40	
LR	MCV	6	ASGA0098887	84046293	A/G	31,80	0,01	CHR	PLINK	41	ARID1A, PIGV, ZDHHC18, GPATCH3, NR0B2, NUDC, KDF1, TRNP1, TENT5B, SLC9A1, WDTC1, TMEM222, SYTL1, MAP3K6, CD164L2, GPR3, WASF2, FGR, IFI6, FAM76A, STX12
LR	MCV	6	ALGA0105183	84069079	A/G	31,80	0,01	CHR	PLINK	41	
LR	MCV	6	ASGA0028717	84522894	G/A	47,30	0,04	CHR	PLINK	41	
LR	MCV	6	ASGA0028724	84705728	A/G	52,90	0,01	CHR	PLINK	41	
LR	MCV	6	ASGA0099240	84961781	C/T	65,90	0,02	CHR	PLINK	41	
LR	MCV	6	ALGA0121599	85086986	A/G	37,50	0,04	CHR	PLINK	42	XKR8, EYA3, PTAFR, U1, DNAJC8, ATP5IF1, SESN2, MED18, PHACTR4, SNORA73, RCC1, TRNAU1AP, SNORD99, SNORA61, SNORA44, SNORA16B, RAB42, TAF12, GMEB1, YTHDF2, OPRD1, EPB41, SRSF4
LR	MCV	6	MARC0018089	85997279	C/T	49,40	0,05	CHR	PLINK	42	
LR	MCV	6	ALGA0103867	86036915	T/C	45,40	0,04	CHR	PLINK	42	
LR	MCV	6	ALGA0035788	86282384	A/G	47,00	0,04	CHR	PLINK	43	
LR	MCV	6	ASGA0028727	86333941	A/G	41,00	0,04	CHR	PLINK	43	
LR	MCV	6	ALGA0114520	86401903	A/G	40,10	0,04	CHR	PLINK	43	
LR	IL-10, IL-4	6	ASGA0083561	87364936	T/C	67,90	0,04	CHR	PLINK	44	LAPTM5
LR	MCV	6	ASGA0028790	88118337	C/A	39,10	0,04	CHR	PLINK	45	HCRTR1, PEF1, COL16A1, ADGRB2
LR	IL-10, IL-6, IL-4	6	ASGA0028956	88264983	T/C	59,30	0,04	CHR	PLINK	45	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	IL-10, IL-6	6	H3GA0053380	93420594	G/T	47,80	0,02	CHR	PLINK	46	ZC3H12A, MEAF6, SNIP1, DNALI1, GNL2, RSPO1, C1orf109, CDCA8, EPHA10, MANEAL, YRDC, C1orf122, MTF1, INPP5B, SF3A3, FHL3, UTP11, POU3F1
LR	IL-10, IL-6	6	MARC0082470	93442952	T/C	47,90	0,04	CHR	PLINK	46	
LR	IL-10, IL-4, IL-6	6	ALGA0117017	93498560	A/G	92,70	0,02	CHR	PLINK	46	
LR	IL-10, IL-6	6	ASGA0028870	93958186	A/G	55,50	0,03	CHR	PLINK	46	
LR	IL-10, IL-4, IL-6	6	DIAS0000434	93982653	G/A	22,70	0,02	CHR	PLINK	46	
LR	IL-10, IL-6	6	ALGA0035971	94051380	C/T	62,30	0,03	CHR	PLINK	46	
LR	IL-10, IL-4, IL-6	6	MARC0019060	94096694	T/C	72,40	0,01	CHR	PLINK	46	
LR	IL-10, IL-6	6	MARC0114889	94223271	C/T	0,00	0,04	CHR	PLINK	46	
LR	IL-10	6	ASGA0028900	94309034	A/G	91,50	0,04	CHR	PLINK	46	
LR	IL-10, IL-4, IL-6	6	M1GA0008815	94712287	C/T	33,60	0,01	CHR	PLINK	47	RRAGC, RRAGC, GJA9, RHBDL2, AKIRIN1, NDUFS5, U6, MACF1, KIAA0754, BMP8A, PABPC4, SNORA55, HEYL, NT5C1A, HPCAL4, PPIE, BMP8B, TRIT1
LR	IL-10	6	ASGA0028941	94769975	C/T	29,90	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	DIAS0002803	94919296	A/G	59,30	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	SIRI0000176	95054229	C/T	0,00	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	ALGA0036052	95081294	G/T	59,30	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	ALGA0036056	95114962	T/C	40,70	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	MARC0008963	95161607	T/C	59,30	0,04	CHR	PLINK	47	
LR	IL-10, IL-6, IL-4	6	ASGA0028958	95203496	T/G	40,70	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	ALGA0036062	95230387	T/C	59,30	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	ALGA0036064	95251820	T/C	59,30	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	MARC0076965	95275331	A/G	59,40	0,04	CHR	PLINK	47	
LR	IL-10, IL-6, IL-4	6	ASGA0028971	95359973	G/T	40,70	0,04	CHR	PLINK	47	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	IL-10, IL-4, IL-6	6	ALGA0036086	95397864	A/G	40,70	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	H3GA0018528	95498545	A/G	59,20	0,02	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	ALGA0036101	95512565	A/C/G	59,20	0,02	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	ALGA0036104	95528500	A/G	59,20	0,02	CHR	PLINK	47	
LR	IL-4, IL-6	6	ALGA0036113	95648826	C/T	58,50	0,04	CHR	PLINK	47	
LR	IL-10, IL-4, IL-6	6	MARC0033580	95566980	G/A	45,50	0.001/3.58	CHR	PLINK, BIMBAM	47	
LR	IL-10, IL-6, IL-4	6	ASGA0029025	95751711	C/T	40,80	0,02	CHR	PLINK	48	MFSD2A, CAP1, PPT1, RLF, TMCO2, MPSTE24, COL9A2, MC5R, RNMT, LDLRAD4, CEP192
LR	IL-4, IL-6	6	MARC0097281	95772705	G/A	0,00	0,03	CHR	PLINK	48	
LR	IL-6	6	MARC0074457	96121023	T/C	41,10	0,03	CHR	PLINK	48	
LR	IL-6	6	MARC0054619	96196142	G/A	41,20	0,03	CHR	PLINK	48	
LR	IL-6	6	MARC0015713	96240060	T/C	58,80	0,03	CHR	PLINK	48	
LR	IL-6	6	ASGA0097503	96306952	C/T	41,10	0,03	CHR	PLINK	48	
LR	IL-6	6	ASGA0106427	96344704	A/G	58,90	0,03	CHR	PLINK	48	
LR	IL-6	6	DIAS0001681	96352093	G/A	41,20	0,03	CHR	PLINK	48	
LR	IL-10, IL-4, IL-6	6	MARC0022542	96650040	T/G	59,80	0,02	CHR	PLINK	48	
LR	IL-6	6	MARC0074986	96678769	A/G	31,90	0,03	CHR	PLINK	48	
LR	IL-10, IL-1b, IL-4, IL-6	6	ALGA0036131	97620286	T/C	32,20	0.001/3.37	CHR	PLINK, BIMBAM	49	
LR	IL-10, IL-4, IL-6	6	M1GA0026030	96767590	A/G	59,80	0,02	CHR	PLINK	49	PTPN2, PSMG2, CEP76, SPIRE1, PRELID3A, AFG3L2, TUBB6, CIDEC, IMPA2, MPPE1, GNAL
LR	IL-6	6	DIAS0004325	96880806	C/T	30,40	0,03	CHR	PLINK	49	
LR	IL-10, IL-4, IL-6	6	CASI0006620	96926928	G/A	31,00	0,03	CHR	PLINK	49	
LR	IL-10, IL-4, IL-6	6	ASGA0091444	97104675	T/G	8,80	0,01	CHR	PLINK	49	
LR	IL-10, IL-4, IL-6	6	MARC0032131	97343439	T/C	23,50	0,01	CHR	PLINK	49	
LR	IL-10, IL-4, IL-6	6	ALGA0036189	99931515	G/A	72,60	0,01	CHR	PLINK	50	PTPRM
LR	IL-10, IL-4, IL-6	6	ALGA0036191	99956687	T/C	94,30	0,02	CHR	PLINK	50	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	IL-10, IL-4, IL-6	6	CASI0005798	100018316	T/C	94,30	0,02	CHR	PLINK	51	PTPRM, LRRC30, LAMA1, ARHGAP28
LR	IL-10, IL-4, IL-6	6	MARC0003203	100175109	G/A	27,90	0,01	CHR	PLINK	51	
LR	IL-10, IL-4, IL-6	6	ALGA0115176	100207770	C/T	1,40	0,02	CHR	PLINK	51	
LR	IL-10, IL-4, IL-6	6	MARC0021350	100311040	C/T	5,70	0,02	CHR	PLINK	51	
LR	IL-10, IL-4, IL-6	6	H3GA0054139	100709160	T/C	87,00	0,01	CHR	PLINK	51	
LR	IL-10, IL-6, IL-4	6	ASGA0029105	102340927	G/A	9,80	0,01	CHR	PLINK	52	DLGAP1
LR	IL-10, IL-4, IL-6	6	ALGA0036219	102362625	G/A	9,40	0,01	CHR	PLINK	52	
LR	IL-10, IL-4, IL-6	6	ALGA0036233	102464736	T/C	98,60	0,01	CHR	PLINK	52	
LR	IL-10, IL-4, IL-6	6	ALGA0036235	102495561	A/G	98,40	0,01	CHR	PLINK	52	
LR	IL-10, IL-4, IL-6	6	H3GA0018606	102641493	C/T	10,10	0,01	CHR	PLINK	52	
LR	IL-10, IL-4, IL-6	6	DRGA0006658	102664930	T/G	89,90	0,01	CHR	PLINK	52	
LR	IL-10, IL-4, IL-6	6	H3GA0018609	102696604	G/A	10,10	0,01	CHR	PLINK	52	
LR	IL-10, IL-6, IL-4	6	ASGA0029117	102709352	T/G	89,90	0,01	CHR	PLINK	52	
LR	IL-10, IL-4, IL-6	6	ALGA0036251	102732393	A/G	10,10	0,01	CHR	PLINK	52	
LR	IL-10, IL-4, IL-6	6	ASGA0097110	108033469	C/T	5,90	0,01	CHR	PLINK	53	
LR	MCV	6	ALGA0107074	119087839	C/T	62,60	0,04	CHR	PLINK	54	ZSCAN30, ZNF397, ZNF24, ZNF396, INO80C, GALNT1, C18orf21, RPRD1A, U6, SLC39A6, ELP2, MOCOS, FHOD3
LR	MCV	6	MARC0042822	120066519	A/G	60,10	0,05	CHR	PLINK	54	
LR	MCV	6	ALGA0036538	120233587	C/T	18,90	0,04	CHR	PLINK	55	FHOD3
LR	MCV	6	MARC0087327	120497118	G/A	39,50	0,04	CHR	PLINK	55	
LR	MCV	6	ASGA0104109	152485189	C/T	19,60	0,01	CHR	PLINK	56	CYP2J34
LR	MCV	6	H3GA0019217	164044870	A/C/G	44,90	0,04	CHR	PLINK	57	FOXD2, FOXE3, CMPK1, STIL
LR	MCV	6	DIAS0002089	164172188	G/A	58,70	0,04	CHR	PLINK	57	
LR	MCV	6	ALGA0037661	164267809	A/G	41,30	0,04	CHR	PLINK	57	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	MCV	6	DIAS0000412	165061162	A/G	52,60	0,04	CHR	PLINK	58	FAAH, NSUN4, LOC100524873, LRRC41, RAD54L, LURAP1, POMGNT1, TSPAN1, P3R3URF, LOC100511937, MAST2
LR	MCV	6	ALGA0037681	165115253	A/C	41,70	0,01	CHR	PLINK	58	
LR	MCV	6	ALGA0037677	165136688	G/A	47,50	0,01	CHR	PLINK	58	
LR	MCV	6	CASI0007691	165252413	G/A	73,90	0,01	CHR	PLINK	58	
LR	MCV	6	ASGA0030214	165295895	A/G	23,80	0,04	CHR	PLINK	58	
LR	MCV	6	ALGA0037700	165361501	C/T	73,90	0,01	CHR	PLINK	58	
LR	MCV	6	ASGA0030228	165464833	T/C	73,50	0,01	CHR	PLINK	58	
LR	MCV	6	ALGA0037714	165590160	A/G	80,10	0,01	CHR	PLINK	58	
LR	MCV	6	ASGA0030235	165616490	C/T	61,20	0,01	CHR	PLINK	58	
LR	MCV	6	ALGA0037706	165657661	G/A	70,30	0,01	CHR	PLINK	58	
LR	IL-10	6	CASI0008589	169767808	C/T	60,10	0,03	CHR	PLINK	59	
LW	BAS	7	H3GA0019427	2568232	C/T	3,40	0,04	CHR	PLINK	60	
LR	IFN	7	H3GA0019660	5050865	C/T	67,60	0,04	CHR	PLINK	61	BMP6
LR	IFN	7	H3GA0019664	5067246	T/C	42,00	0,04	CHR	PLINK	61	
LW	IL-6	7	ALGA0038559	10527098	C/T	15,10	0,03	CHR	PLINK	62	
LR	MCH	7	ALGA0039086	17730613	T/C	78,50	0,03	CHR	PLINK	63	
LR	IFN	7	DRGA0007705	61127162	G/A	17,50	0,05	CHR	PLINK	64	SEC23A
LR	IFN	7	MARC0055700	64966359	G/A	69,00	0,01	CHR	PLINK	65	BAZ1A
LR	IFN	7	DRGA0007743	66272613	C/T	72,00	0,05	CHR	PLINK	66	NPAS3
LR	IFN	7	ALGA0042479	67635211	C/T	21,00	0,01	CHR	PLINK	67	NUBPL, GPR33, DTD2, HECTD1
LR	IFN	7	ALGA0042490	67678462	T/C	58,80	0,02	CHR	PLINK	67	
LR	IFN	7	ASGA0034445	68130280	G/A	23,50	0,01	CHR	PLINK	67	
LR	IFN	7	ASGA0034452	68167119	A/G	76,50	0,01	CHR	PLINK	67	
LR	IFN	7	H3GA0022038	68213063	T/C	23,50	0,01	CHR	PLINK	67	
LR	IFN	7	ASGA0034456	68344394	G/A	72,70	0,01	CHR	PLINK	67	
LR	IFN	7	ASGA0034457	68408727	A/G	76,50	0,01	CHR	PLINK	67	
LR	IFN	7	INRA0026398	72991035	A/G	76,50	0,01	CHR	PLINK	68	
LR	IFN	7	ALGA0042582	74264086	C/T	28,30	0,02	CHR	PLINK	69	STXBP6
LR	IFN	7	ALGA0042584	74302403	A/G	72,90	0,02	CHR	PLINK	69	
LR	IFN	7	ALGA0042597	74546893	T/C	43,60	0,02	CHR	PLINK	69	
LR	IFN	7	ALGA0042601	74580371	A/G	43,60	0,02	CHR	PLINK	69	
LW	IL-8	7	M1GA0010866	115793412	C/T	15,50	0,02	CHR	PLINK	70	
LW	IL-8	7	rs338367467	122915952	G/A	NA	0,02	CHR	PLINK	71	
LW	IL-4	8	MARC0111479	4598871	T/G	0,00	0,03	CHR	PLINK	72	JAKMIP1, C8H4orf50
LW	IL-4	8	ALGA0107038	4605432	T/C	36,80	0,02	CHR	PLINK	72	
LW	IL-4	8	ASGA0092577	4674424	G/A	76,30	0,02	CHR	PLINK	72	
LR	TNF	8	ALGA0046861	20647847	C/T	1,30	0.02/3.23	GEN	PLINK, BIMBAM	73	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	IL-1b, IL-6	8	ALGA0046899	20831553	G/A	26,30	0.03/3.16	CHR	PLINK, BIMBAM	73	
LR	MCH	8	ASGA0038765	39341631	T/C	84,40	0.02/3.09	CHR	PLINK, BIMBAM	74	
LW	TNF	9	ALGA0056053	138782132	T/C	36,50	0.001/3.43	CHR	PLINK, BIMBAM	75	
LW	TNF	9	ASGA0097568	138517855	T/C	79,30	0.001/4.14	CHR	PLINK, BIMBAM	75	
LW	BAS	10	ALGA0057018	10046457	A/C	79,60	0,05	CHR	PLINK	76	MARK1, C1orf115, MARC2, HLX
LW	BAS	10	ASGA0046469	10399957	A/C	6,60	0,05	CHR	PLINK	76	
LR	PLT	10	ALGA0057208	13092434	C/G	32,40	0,03	CHR	PLINK	77	
LW	IFN	10	ALGA0057334	14504374	G/A	52,90	0,03	CHR	PLINK	78	
LW	IL-10, IL-1b	10	ASGA0085873	14348970	T/C	34,20	0.02/3.02	CHR	PLINK, BIMBAM	78	
LW	PLT	10	MARC0008318	16846881	C/T	46,30	0,04	CHR	PLINK	79	ZBTB18, ADSS, CATSPERE, DESI2, COX20, HNRNPU, EFCAB2, KIF26B
LW	IFN	10	ALGA0057529	17731595	T/C	40,50	0,04	CHR	PLINK	79	
LR	BAS	10	ASGA0046986	19572163	C/A	22,70	0,03	GEN	PLINK	80	CCDC185, CAPN8, CAPN2, TP53BP2, FBXO28, ASPM, ZBTB41, CRB1, DENND1B
LR	BAS	10	ALGA0057739	20062069	G/A	16,30	0,03	GEN	PLINK	80	
LR	BAS	10	ASGA0047018	20134916	G/A	63,30	0,01	CHR	PLINK	80	
LR	BAS	10	MARC0058358	20157046	C/T	13,70	0,01	CHR	PLINK	80	
LR	BAS	10	MARC0050841	20188434	G/A	63,40	0,01	CHR	PLINK	80	
LR	BAS	10	ALGA0106008	20444762	A/C	75,40	0,01	CHR	PLINK	80	
LR	BAS	10	H3GA0053667	20584936	C/T	73,00	0,04	GEN	PLINK	81	DENND1B, C1orf53, LHX9, NEK7
LR	BAS	10	H3GA0052936	20795956	T/C	69,90	0,02	GEN	PLINK	81	
LR	BAS	10	ASGA0098001	20805520	C/T	30,10	0,02	GEN	PLINK	81	
LR	BAS	10	MARC0108793	21031390	T/C	0,00	0,04	GEN	PLINK	81	
LR	BAS	10	MARC0018828	21054756	G/A	6,20	0,04	GEN	PLINK	81	
LR	BAS	10	DRGA0010387	21726062	T/G	63,40	0,01	CHR	PLINK	82	PTPRC
LR	BAS	10	ALGA0057837	22018259	T/C	98,60	0,01	CHR	PLINK	82	
LR	BAS	10	ASGA0047084	22210885	G/A	1,40	0,01	CHR	PLINK	82	
LR	PLT	10	H3GA0029613	22302588	G/T	45,80	0,03	CHR	PLINK	82	
LR	BAS	10	ASGA0083356	22817715	A/C	91,70	0,02	GEN	PLINK	83	NR5A2
LR	IFN	10	ALGA0059049	47339095	G/A	13,80	0,02	CHR	PLINK	84	FRMD4A, PRPF18
LR	WBC	10	H3GA0030245	47362497	C/A	67,40	0,03	CHR	PLINK	84	
LR	IFN	10	ALGA0059118	47607670	C/T	36,00	0,02	CHR	PLINK	84	
LR	IFN	10	H3GA0030271	47676308	G/T	36,00	0,02	CHR	PLINK	84	
LR	IFN	10	ALGA0103761	47805800	G/A	40,50	0,02	CHR	PLINK	84	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	IFN	10	MARC0063711	47808917	G/A	77,50	0,02	CHR	PLINK	84	
LR	IFN	10	MARC0018399	47902144	T/C	63,70	0,02	CHR	PLINK	84	
LR	IFN	10	ALGA0106385	48144674	A/G	69,80	0,05	CHR	PLINK	84	
LR	PLT	11	DRGA0011044	29520725	G/A	24,60	0,04	CHR	PLINK	85	
LR	PLT	11	ALGA0061774	31018065	A/G	24,60	0,04	CHR	PLINK	86	
LR	PLT	11	ALGA0061941	37838969	C/A	56,20	0,03	CHR	PLINK	87	
LR	PLT	11	MARC0063044	38170099	G/A	57,60	0,03	CHR	PLINK	87	
LW	IL-4, IL-6	12	MARC0051288	11986602	T/C	19,40	0,05	CHR	PLINK	88	RGS9
LW	IL-4, IL-6	12	ALGA0113815	12017916	G/A	11,60	0,05	CHR	PLINK	88	
LW	PLT	12	ASGA0105124	43334485	A/G	48,70	0,05	CHR	PLINK	89	
LW	RBC	12	ALGA0066876	50111768	T/C	79,00	0,05	CHR	PLINK	90	ZZEF1
LW	RBC	12	ALGA0066881	50146135	A/G	79,00	0,05	CHR	PLINK	90	
LR	MCH	12	H3GA0035045	59136124	T/G	63,20	0,04	CHR	PLINK	91	TRPV2
LR	PLT	13	CASI0007872	80594858	G/A	13,20	0,04	CHR	PLINK	92	
LR	IL-4	13	MARC0096953	159404532	C/T	0,00	0,06	CHR	PLINK	92	
LR	BAS	13	ALGA0073579	192910051	T/C	10,50	0,02	GEN	PLINK	93	GRIK1
LW	IL-6	13	MARC0058120	199890469	T/C	92,10	0,04	CHR	PLINK	94	DOP1B
LR	HMT	14	ASGA0063672	57514155	T/C	89,30	0,04	CHR	PLINK	95	
LR	HMG, HMT	14	H3GA0040407	57739629	C/T	26,80	0,02	CHR	PLINK	96	
LR	HMG, HMT	14	ALGA0077929	57765084	A/G	26,60	0,02	CHR	PLINK	96	
LR	HMT	14	ALGA0078039	59298541	C/T	51,40	0,05	CHR	PLINK	97	
LR	HMG, HMT	14	ALGA0078088	59646142	C/T	30,80	0,01	CHR	PLINK	97	
LR	HMG, HMT	14	ALGA0078075	59656180	A/C	30,90	0,01	CHR	PLINK	97	
LR	HMG, HMT	14	ALGA0106769	59712299	A/G	11,30	0,04	CHR	PLINK	97	
LR	HMG, HMT	14	MARC0004519	59803997	G/A	65,30	0,01	CHR	PLINK	97	
LR	HMG, HMT	14	ALGA0078091	59831072	T/C	71,40	0,01	CHR	PLINK	97	
LR	HMG, HMT	14	ASGA0063815	59277912	C/T	30,40	0.01/3.07	CHR	PLINK, BIMBAM	97	
LR	HMG, HMT	14	MARC0013023	59263540	C/T	12,60	0.01/3.07	CHR	PLINK, BIMBAM	97	TRIM67, FAM89A, ARV1, TTC13, C1orf198, CAPN9, AGT, COG2
LR	IL-4, IL-10	14	ASGA0066844	126901849	T/C	35,70	0.04/3.49	CHR	PLINK, BIMBAM	98	HSPA12A
LR	IL-4	14	M1GA0019225	126921868	C/T	33,70	0.04/3.09	CHR	PLINK, BIMBAM	98	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LW	RBC	15	ALGA0085557	55981133	G/A	94,30	0,03	CHR	PLINK	99	
LR	IL-8	15	INRA0049820	84421614	T/C	95,80	0,02	CHR	PLINK	100	
LR	IL-8	15	INRA0049822	93936954	A/G	4,30	0,02	CHR	PLINK	101	COL5A2
LR	IL-8	15	DRGA0017581	102403412	T/C	63,20	0,03	CHR	PLINK	102	U6
LR	IL-8	15	INRA0049968	102936048	G/A	12,70	0,03	CHR	PLINK	102	
LR	IL-8	15	ALGA0086618	107604568	T/C	14,50	0,01	CHR	PLINK	103	PARD3B
LR	IL-8	15	DRGA0015341	107753847	G/A	83,50	0,02	CHR	PLINK	103	
LR	IL-8	15	MARC0089453	107887493	C/A	34,30	0,02	CHR	PLINK	103	
LR	IL-8	15	ALGA0086631	108024616	T/C	46,70	0.001/3.13	CHR	PLINK, BIMBAM	104	PARD3B, U6
LR	IL-8	15	ALGA0108737	108335353	G/A	48,80	0.01/3.39	CHR	PLINK, BIMBAM	104	
LR	IL-8	15	ALGA0086637	108446984	G/A	57,80	0,04	CHR	PLINK	104	
LR	IL-8	15	DRGA0015357	108505209	A/G	53,00	0,02	CHR	PLINK	104	
LR	IL-8	15	MARC0089139	108677884	A/C	65,30	0,01	CHR	PLINK	104	
LR	IL-8	15	ASGA0070317	108794926	A/G	32,30	0,01	CHR	PLINK	104	
LR	IL-8	15	H3GA0044820	108848114	G/C	39,60	0,02	CHR	PLINK	104	
LR	IL-8	15	ASGA0102483	108311749	C/T	48,80	0.001/3.39	CHR	PLINK, BIMBAM	104	
LR	IL-8	15	ALGA0086678	109394965	G/A	50,70	0.001/3.28	CHR	PLINK, BIMBAM	105	
LR	IL-8	15	ALGA0086703	109971469	G/A	60,00	0.001/3.09	CHR	PLINK, BIMBAM	105	
LR	IL-8	15	ASGA0093834	109215027	G/A	14,30	0,02	CHR	PLINK	105	INO80D, NDUFS1, EEF1B2, SNORD51, SNORA41, GPR1, ZDBF2, ADAM23, FAM237A, DYTN
LR	IL-8	15	INRA0050045	112324352	C/A	45,60	0,04	CHR	PLINK	106	MAP2, UNC80
LR	MON	15	ALGA0086800	112624977	G/A	90,10	0,02	CHR	PLINK	106	
LR	IL-8	15	ALGA0086892	116134508	A/C	68,80	0.001/3.85	CHR	PLINK, BIMBAM	107	
LR	IL-8	15	ASGA0097364	115687234	T/C	78,60	0,02	CHR	PLINK	107	SPAG16
LR	IL-8	15	ASGA0070437	115906733	C/T	28,50	0,02	CHR	PLINK	107	
LR	IL-8	15	ASGA0070443	115987500	T/C	33,40	0,03	CHR	PLINK	107	
LR	IL-8	15	MARC0034868	116018447	T/C	66,60	0,03	CHR	PLINK	107	
LR	IL-8	15	ALGA0086890	116078414	T/C	78,60	0,02	CHR	PLINK	107	
LR	IL-8	15	H3GA0044887	116385362	T/C	23,90	0,02	CHR	PLINK	107	
LR	IL-8	15	MARC0109222	116779658	C/A	0,00	0,02	CHR	PLINK	108	VWC2L
LR	IL-8	15	ASGA0100540	116787417	T/C	22,00	0,02	CHR	PLINK	108	
LR	IL-8	15	ALGA0086910	116823946	G/A	78,00	0,02	CHR	PLINK	108	
LR	IL-8	15	ALGA0087116	120286163	A/G	31,90	0.001/4.47	CHR	PLINK, BIMBAM	109	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LR	IL-8	15	ASGA0070586	120106066	T/C	68,20	0.001/5.84	CHR	PLINK, BIMBAM	109	
LR	IL-8	15	ASGA0070620	120351434	T/C	41,60	0.001/4.22	CHR	PLINK, BIMBAM	109	
LR	IL-8	15	H3GA0044814	119982356	A/G	53,70	0,02	CHR	PLINK	109	TNS1, RUFY4, CXCR2, ARPC2, GPBAR1, AAMP, PNKD, TMBIM1
LR	IL-8	15	H3GA0044951	119984036	T/C	59,10	0,02	CHR	PLINK	109	
LR	IL-8	15	ASGA0070560	119995203	T/C	40,00	0,02	CHR	PLINK	109	
LR	IL-8	15	ASGA0070582	120083397	G/A	59,80	0,02	CHR	PLINK	109	
LR	IL-8	15	ALGA0087090	120139024	T/C	87,80	0,01	CHR	PLINK	109	
LR	IL-8	15	M1GA0020457	121398466	C/A	30,00	0,02	CHR	PLINK	110	DNPEP, ssc-mir-4334, DES, SPEGNB, GMPPA, ASIC4, CHPF, TMEM198, OBSL1
LR	IL-8	15	ASGA0083683	121570012	G/A	56,30	0,02	CHR	PLINK	110	
LR	IL-8	15	ALGA0110389	121570230	A/G	43,60	0,02	CHR	PLINK	110	
LR	IL-8	15	ASGA0070855	122524508	T/C	57,50	0,03	CHR	PLINK	111	EPHA4
LR	IL-8	15	ALGA0087356	122895848	C/A	43,80	0,01	CHR	PLINK	111	
LR	IL-8	15	ALGA0087350	122979514	C/T	15,40	0,04	CHR	PLINK	111	
LR	IL-8	15	MARC0114457	123052286	T/C	0,00	0,02	CHR	PLINK	111	
LR	IL-8	15	DRGA0015530	123132577	T/C	60,00	0,03	CHR	PLINK	111	
LR	IL-8	15	ALGA0087340	123144118	C/T	23,10	0,03	CHR	PLINK	111	
LR	IL-8	15	ASGA0070822	123171616	C/T	10,90	0,02	CHR	PLINK	111	
LR	IL-8	15	ALGA0087328	123241971	A/G	68,10	0,02	CHR	PLINK	111	
LR	IL-8	15	MARC0070811	123293141	T/C	68,10	0,02	CHR	PLINK	111	
LR	IL-8	15	MARC0028230	123311817	C/T	10,80	0,02	CHR	PLINK	111	
LR	IL-8	15	ALGA0087324	123363010	G/A	21,40	0,02	CHR	PLINK	111	
LR	IL-8	15	ALGA0087321	123392506	T/C	59,10	0,02	CHR	PLINK	111	
LR	IL-8	15	ALGA0100462	123671193	C/T	32,30	0,02	CHR	PLINK	112	PAX3, SGPP2
LR	IL-8	15	ALGA0087297	123851318	T/G	40,20	0,02	CHR	PLINK	112	
LR	IL-8	15	ASGA0070779	124103554	C/T	55,70	0,03	CHR	PLINK	112	
LR	IL-8	15	ASGA0070769	124118055	C/T	40,80	0,04	CHR	PLINK	112	
LR	IL-8	15	M1GA0020474	124151048	T/C	59,30	0,04	CHR	PLINK	112	
LR	IL-8	15	H3GA0045081	124207280	G/A	40,80	0,04	CHR	PLINK	112	
LR	IL-8	15	ALGA0087267	124331577	T/C	63,10	0,02	CHR	PLINK	112	
LR	IL-8	15	H3GA0045073	124347713	G/T	35,60	0,02	CHR	PLINK	112	
LR	IL-8	15	ASGA0071003	126072246	T/C	37,00	0.001/3.57	CHR	PLINK, BIMBAM	113	
LR	IL-8	15	H3GA0045046	124686575	A/G	61,30	0,03	CHR	PLINK	113	ACSL3, KCNE4, SCG2, AP1S3, WDFY1, MRPL44, SERPINE2
LR	IL-8	15	ASGA0101298	126013489	C/T	55,60	0,02	CHR	PLINK	113	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LW	RBC	16	ALGA0089752	23580846	T/G	74,10	0,01	CHR	PLINK	114	EGFLAM, LIFR, OSMR, RICTOR, U6, U4, FYB1
LW	RBC	16	DRGA0015975	24344082	T/C	53,10	0,00	CHR	PLINK	114	
LW	RBC	16	ALGA0089777	24362179	T/C	39,40	0,01	CHR	PLINK	114	
LW	RBC	16	ASGA0072751	25032947	C/T	82,10	0,00	CHR	PLINK	115	
LW	MCH	16	ALGA0090595	45164366	C/A	22,60	0,04	CHR	PLINK	116	MAST4
LW	MCH	16	ALGA0090596	45178452	T/C	55,30	0,04	CHR	PLINK	116	
LW	MCH	16	DRGA0016198	45430274	T/C	30,30	0,04	CHR	PLINK	116	
LW	MCH	16	ALGA0090558	48020257	T/G	43,30	0,04	CHR	PLINK	117	
LW	MCH	16	ALGA0091962	73764474	A/C	42,10	0.001/3.08	CHR	PLINK, BIMBAM	118	
LW	MCH	16	MARC0075417	73485704	A/C	44,40	0,04	CHR	PLINK	118	U6
LW	MCH	16	ALGA0091954	73703925	G/A	61,40	0,04	CHR	PLINK	118	
LW	RBC, HMG, HMT	16	ASGA0074790	78019054	C/T	99,10	0,03	GEN	PLINK	119	
LW	RBC, HMG, HMT	16	M1GA0021462	78037702	T/C	7,90	0,00	CHR	PLINK	119	
LW	BAS	17	ALGA0112929	106110	G/A	55,50	0,01	GEN	PLINK	120	
LW	IL-10, TNF	17	DRGA0016627	20677871	T/G	8,40	0,03	CHR	PLINK	121	
LW	IL-10, TNF	17	MARC0055684	20763022	A/C	89,70	0,03	CHR	PLINK	121	
LW	IL-10	17	ASGA0075780	22286059	C/T	37,00	0,01	CHR	PLINK	122	TASP1
LW	IL-10, IL-1b, TNF	17	ASGA0075903	26077336	C/T	81,10	0.01/3.23	CHR	PLINK, BIMBAM	123	
LW	IL-10	17	MARC0069703	25378015	C/T	74,30	0,01	CHR	PLINK	123	PCSK2, BFSP1, DSTN, RRBP1
LW	IL-10	17	ASGA0075884	25454088	C/A	4,40	0,04	CHR	PLINK	123	
LW	IL-10	17	ASGA0075887	25830486	A/G	69,60	0,03	CHR	PLINK	123	
LR	PLT	17	ASGA0076045	28192131	C/T	8,80	0.001/3.11	CHR	PLINK, BIMBAM	124	CFAP61
LR	PLT	17	MARC0093077	28351838	G/A	0,00	0.001/3.16	CHR	PLINK, BIMBAM	124	
LR	PLT	17	ASGA0076328	30803219	A/C	78,90	0,04	CHR	PLINK	125	ACSS1
LR	PLT	17	ASGA0076514	33282761	C/T	95,70	0.001/3.32	CHR	PLINK, BIMBAM	126	
LW	TNF	17	M1GA0021900	32932811	A/G	51,60	0,03	CHR	PLINK	126	EBF4, IDH3B, NOP56, SNORD57, SNORD56, SNORD86, SNORD110, TMC2, SNRPB, TGM6, STK35, PDYN
LW	TNF	17	H3GA0048609	33080621	T/C	43,70	0,03	CHR	PLINK	126	
LW	TNF	17	MARC0018597	33099516	A/G	54,90	0,03	CHR	PLINK	126	
LR	PLT	17	M1GA0021930	33651909	A/C	72,60	0,01	CHR	PLINK	126	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/BF	Type of significance	Method	QTL	Nearest gene within QTL
LW	BAS	18	DRGA0016945	25162286	G/A	16,60	0,02	CHR	PLINK	127	PTPRZ1
LW	BAS	18	ALGA0097582	25200554	C/T	83,40	0,02	CHR	PLINK	127	
LW	BAS	18	ASGA0079343	25373224	C/T	17,00	0,02	CHR	PLINK	127	
LR	IL-8	18	H3GA0051155	50710948	T/C	7,20	0,01	CHR	PLINK	128	DDX56, NPC1L1, NUDCD3, GCK, CAMK2B
LR	IL-8	18	M1GA0023403	50826524	G/A	95,50	0,06	CHR	PLINK	128	
LR	IL-8	18	ALGA0098768	50874905	A/C	16,00	0,06	CHR	PLINK	128	

SSC=Sus scrofa chromosome, SNP=single nucleotide polymorphism, m/M allele=minor/major allele, MAF=minor allele frequency, QTL nr.=quantitative trait loci progressive number based on ±1Mbp distance from a significant SNP, LR=Landrace, LW=Large White, RBC=red blood cells, HMG=hemoglobin, HMT=hematocrit, MCV= mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, PLT=platelets, WBC=white blood cells, NEU=neutrophils, LYM=lymphocytes, MON=monocytes, EOS=eosinophils, BAS=basophils, HAP=haptoglobin, IFN-γ= interferon-γ, IL=interleukin, TNF-α= tumor necrosis factor-α.

Table S 10: Significant associated genetic markers identified with multivariate methods (continued)

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	IL4 IL10 IL1b IL6, L6 IFN IL10 IL1b	1	MARC0070292	2139822	C/A	43,70	3,17	GEN	mvBIMBAM	1	
LR	HMT HMG MCHC	1	MARC0008402	3478464	G/T	17,00	0,01	CHR	CCA	2	
LR	HMT HMG MCHC	1	ALGA0000682	7402285	A/G	87,30	0,01	CHR	CCA	3	IGF2R, MAS1, PNLDC, MRPL18, TCP1, SNORA29, ACAT2, SNORA20, SOD2, FNDC1, TAGAP, RSPH3
LW	RBC HMG HMT MCV MCH MCHC	1	ALGA0000778	8362294	G/A	23,10	0,05	CHR	CCA	3	
LW	RBC HMG HMT MCV MCH MCHC	1	ALGA0000795	8724875	A/G	74,10	0,05	CHR	CCA	4	TULP4
LW	RBC HMG HMT MCV MCH MCHC	1	ASGA0000892	8739103	T/C	25,90	0,05	CHR	CCA	4	
LW	RBC HMG HMT MCV MCH MCHC	1	ALGA0000837	8810463	T/G	25,80	0,05	CHR	CCA	5	TULP4 , SERAC1, SYNJ2, SNX9, ZDHHC14, TMEM242
LW	RBC HMG HMT MCV MCH MCHC	1	ASGA0000925	8896901	T/C	25,90	0,05	CHR	CCA	5	
LW	RBC HMG HMT MCV MCH MCHC, HMG MCHC	1	ALGA0106880	9725288	A/G	26,00	0.023/3.27	GEN	CCA, mvBIMBAM	5	
LW	IFN IL12 IL8 TNF	1	ASGA0001122	12337822	A/G	46,30	0,01	CHR	PCA	6	CNKSR3
LW	IL4 IL10 IL1b IL6	1	H3GA0002135	78746469	G/A	12,30	3,16	GEN	mvBIMBAM	7	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	WBC NEU LYM MON	1	ASGA0004864	148013788	G/A	70,70	0,05	CHR	PCA	8	ZNF516
LR	WBC NEU LYM MON	1	H3GA0003011	148452203	A/G	87,30	0,05	CHR	PCA	8	
LR	WBC NEU LYM MON	1	ALGA0006425	149261646	A/G	90,20	0,05	CHR	PCA	9	ZNF407, CNDP1, CNDP2
LR	WBC NEU LYM MON	1	ALGA0006427	149286248	A/G	90,20	0,05	CHR	PCA	9	
LR	WBC NEU LYM MON	1	ASGA0004896	149573916	T/C	90,20	0,05	CHR	PCA	9	
LR	WBC NEU LYM MON	1	ALGA0006599	159660303	G/A	45,70	0,05	CHR	PCA	10	CDH20
LR	WBC NEU LYM MON	1	ALGA0006623	160347188	T/C	37,60	0,05	CHR	PCA	10	
LW	RBC HMG HMT MCV MCH MCHC	1	ASGA0006456	243182935	T/C	6,60	0,01	GEN	CCA	11	TMEM246
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC, PLT RBC WBC	1	ASGA0006490	245186944	G/A	71,20	0,05	CHR	CCA	12	SMC2, OR13C8, NIPSNAP3A, ABCA1
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC, PLT RBC WBC	1	DRGA0002258	245243350	T/C	28,80	0,05	CHR	CCA	12	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC, PLT RBC WBC	1	ASGA0006492	245332724	G/A	71,20	0,05	CHR	CCA	12	
LW	HMT HMG MCHC	1	DIAS0000064	245564988	T/C	26,20	0,02	CHR	CCA	12	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	RBC HMG HMT MCV MCH MCHC	1	DIAS0000004	246185461	T/C	8,40	0,03	GEN	CCA	12	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC, PLT RBC WBC	1	ALGA0008960	247051725	T/C	27,20	0,03	GEN	CCA	13	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC, PLT RBC WBC	1	MARC0053473	247630798	G/A	20,30	0,05	CHR	CCA	14	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC, PLT RBC WBC	1	ALGA0008971	247688139	G/A	14,40	0,05	CHR	CCA	14	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC, PLT RBC WBC	1	ALGA0008972	247721382	T/C	84,40	0,05	CHR	CCA	14	
LW	RBC HMG HMT	1	ASGA0008077	270968825	G/A	1,20	0,05	CHR	PCA	15	LAMC3, AIF1L, NUP214, PLPP7, FAM78A
LW	RBC HMG HMT	1	H3GA0056709	271239665	T/C	95,30	0,05	CHR	PCA	15	
LW	RBC HMG HMT	1	MARC0039390	271251440	G/A	13,30	0,05	CHR	PCA	15	
LW	RBC HMG HMT MCV MCH MCHC	2	H3GA0053137	9252507	C/T	39,70	0,02	CHR	CCA	16	
LW	IL4 IL10 IL1b IL6	2	H3GA0006173	17462745	T/C	98,00	4,06	GEN	mvBIMBAM	17	TP53I11, TSPAN18
LR	HMT HMG MCHC	2	ALGA0122588	17672685	G/A	11,70	0,00	GEN	CCA	17	
LR	HMT HMG MCHC	2	H3GA0006190	17683291	A/G	88,20	0,00	GEN	CCA	17	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	2	DRGA0002793	21669969	A/G	87,10	0,04	GEN	CCA	18	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	2	ASGA0101016	21751485	C/T	86,90	0,01	CHR	CCA	18	
LW	RBC HMG HMT MCV MCH MCHC, HMG MCH	2	ALGA0012559	22792581	G/A	86,40	0,01	CHR	CCA	19	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0012570	22989364	T/G	90,00	0,01	CHR	CCA	19	
LW	RBC HMG HMT MCV MCH MCHC	2	H3GA0006308	23073900	G/A	7,40	0,02	CHR	CCA	19	
LR	WBC HMT EOS HAP IL8	2	ALGA0013060	37186143	C/T	4,10	0,03	CHR	CCA, TATES	20	ANO5, U6, NELL1
LR	WBC HMT EOS HAP IL8	2	DRGA0002935	37202269	A/G	95,90	0,03	CHR	CCA, TATES	20	
LR	WBC HMT EOS HAP IL8	2	ALGA0013078	37762734	G/T	4,10	0,03	CHR	CCA, TATES	20	
LR	WBC HMT EOS HAP IL8	2	ALGA0013104	37945462	C/T	4,10	0,03	CHR	CCA, TATES	20	
LW	RBC HMG HMT MCV MCH MCHC	2	MARC0025931	82861588	G/A	28,50	0,02	CHR	CCA	21	ARHGEF28
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010629	84881427	T/C	64,10	0,02	CHR	CCA	22	SV2C, IQGAP2, F2RL2, F2R, F2RL1, S100Z
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010636	84975794	G/A	47,30	0,05	CHR	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC	2	H3GA0006974	85003252	T/G	68,20	0,05	CHR	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014115	85026066	T/C	52,70	0,05	CHR	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010644	85053423	G/A	32,30	0,04	GEN	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014120	85137614	G/A	33,40	0.001/3.24	GEN	CCA, mvBIMBAM	22	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	RBC HMG HMT MCV MCH MCHC	2	H3GA0006975	85151135	T/C	57,70	0,01	GEN	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC	2	MARC0064603	85463127	C/T	39,90	0,03	GEN	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	2	ASGA0105637	85559227	A/G	66,20	0,00	GEN	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010665	85664532	A/G	52,00	0,03	GEN	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC	2	H3GA0006999	85759107	A/G	44,30	0,03	CHR	CCA	22	
LW	RBC HMG HMT MCV MCH MCHC	2	DRGA0003080	85772887	C/T	41,30	0.001/3.16	GEN	CCA, mvBIMBAM	22	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0104997	86320678	T/C	54,80	0,03	GEN	CCA	23	WDR41, OTP, TBCA, AP3B1, SCAMP1, LHFPL2, ssc-mir-10384-2
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014192	86505377	T/C	41,90	0,03	CHR	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014189	86542827	A/G	42,70	0,03	CHR	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010704	86556317	C/T	48,40	0,03	GEN	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	2	ASGA0101845	86593472	G/A	38,20	0.001/3.27	GEN	CCA, mvBIMBAM	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010722	86799398	G/A	32,30	0,05	GEN	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014199	86842615	A/C	56,20	0,03	GEN	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014200	86869012	T/C	55,80	0,03	GEN	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	2	ALGA0014210	86926962	C/T	24,80	0.001/3.39	GEN	CCA, mvBIMBAM	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014211	86998119	G/T	56,00	0,03	GEN	CCA	23	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014214	87021610	G/A	40,40	0.001/3.16	GEN	CCA, mvBIMBAM	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010734	87247735	T/C	54,70	0,05	GEN	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014235	87337977	A/G	65,10	0,02	GEN	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014249	87434796	T/C	59,90	0,01	CHR	CCA	23	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	2	ASGA0010750	87530974	C/T	24,90	0.001/3.39	GEN	CCA, mvBIMBAM	24	ARSB, DMGDH, BHMT
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010766	87596607	T/C	51,80	0,05	CHR	CCA	24	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010767	87610569	G/A	48,10	0,05	CHR	CCA	24	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014269	87662401	C/T	41,70	0,05	GEN	CCA	24	
LW	RBC HMG HMT MCV MCH MCHC	2	MARC0085122	87708844	A/G	62,90	0,03	GEN	CCA	24	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010772	87745745	T/C	50,50	0,02	GEN	CCA	24	
LW	RBC HMG HMT MCV MCH MCHC	2	MARC0055537	87768647	C/T	47,60	0,02	GEN	CCA	24	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0010776	87798540	G/T	39,90	0,01	CHR	CCA	24	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0014272	87888457	A/G	44,10	0,05	GEN	CCA	24	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0097255	119098798	G/A	48,60	0,05	CHR	CCA	25	
LR	BAS MON	2	ALGA0102645	120728602	G/T	38,40	0,03	GEN	CCA	26	
LW	RBC HMG HMT MCV MCH MCHC	2	MARC0085402	129684982	G/A	9,40	0,03	CHR	CCA	27	ALDH7A1, PHAX, TEX43, LMNB1, MARCH3, PRRC1
LR	HMG MCHC IL10, HMT HMG MCHC	2	DIAS0002725	129695476	G/A	80,50	0,04	GEN	CCA	27	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	HMG MCHC IL10, HMT HMG MCHC	2	DIAS0003483	129723516	T/C	10,30	0,02	GEN	CCA	27	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0015941	130460915	T/C	25,80	0,01	CHR	CCA	27	
LW	IFN IL8 TNF	2	ALGA0016514	138589831	A/G	5,80	0,02	CHR	PCA	28	
LW	RBC HMG HMT MCV MCH MCHC	2	MARC0002516	148357959	A/G	70,50	0,05	CHR	CCA	29	PPP2R2B, STK32A, DPYSL3, JAKMIP2
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0106143	148447412	G/A	51,30	0,05	CHR	CCA	29	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0106373	148499924	G/A	48,70	0,05	CHR	CCA	29	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0115025	148536882	T/C	48,60	0,05	CHR	CCA	29	
LW	RBC HMG HMT MCV MCH MCHC	2	H3GA0052415	148550613	T/C	51,30	0,05	CHR	CCA	29	
LW	RBC HMG HMT MCV MCH MCHC	2	ALGA0116650	148616044	A/G	20,80	0,05	CHR	CCA	29	
LW	RBC HMG HMT MCV MCH MCHC	2	ASGA0104922	148631405	C/T	49,60	0,05	CHR	CCA	29	
LW	RBC HMG HMT MCV MCH MCHC	2	MARC0011897	148905198	T/C	59,00	0,03	CHR	CCA	29	
LR	WBC NEU MON EOS BAS TNF	3	ASGA0093070	18058797	C/T	29,00	0,05	CHR	CCA	30	MVP
LR	WBC NEU MON EOS BAS TNF	3	ASGA0084261	18059444	G/A	29,00	0,05	CHR	CCA	30	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	WBC NEU MON EOS BAS TNF	3	MARC0081878	22791691	A/G	43,10	0,05	GEN	CCA	31	COG7, SCNN1B, SCNN1G, USP31, HS3ST2, OTOA, METTL9, IGSF6
LR	WBC NEU MON EOS BAS TNF	3	ASGA0099130	23688143	A/G	33,90	0,03	CHR	CCA	31	
LR	WBC NEU MON EOS BAS TNF	3	ASGA0094403	23968274	T/C	88,00	0,05	CHR	CCA	32	SDR42E2, VWA3A, MOSMO, PDZD9, UQCRC2, CRYM, ANKS4B, ZP2, TMEM159
LR	WBC NEU MON EOS BAS TNF	3	ASGA0013894	24070234	C/A	51,10	0,05	CHR	CCA	32	
LR	WBC NEU MON EOS BAS TNF	3	M1GA0004187	24176936	T/G	87,30	0,04	CHR	CCA	32	
LR	WBC NEU MON EOS BAS TNF	3	ALGA0123859	24582079	C/T	14,50	0,05	CHR	CCA	32	
LR	WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	3	ASGA0094325	24963920	C/T	16,40	0,03	GEN	CCA	32	
LR	WBC NEU MON EOS BAS TNF	3	ASGA0013904	25072734	A/G	70,60	0,05	CHR	CCA	33	LYRM1, DCUN1D3, REXO5, ERI2, ACSM3, THUMPD1, ACSM4, ACSM5, PDILT, UMOD, GP2, GPR139

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	3	ASGA0013908	25111534	C/A	20,00	0.001/3.1	GEN	CCA, mvBIMBAM	33	
LR	WBC NEU MON EOS BAS TNF	3	ALGA0102450	25723257	C/A	62,30	0,04	GEN	CCA	33	
LW	BAS WBC NEU, LYM NEU MON EOS BAS	3	ASGA0014250	35404289	G/T	76,50	4,51	GEN	mvBIMBAM	34	RBFOX1
LR	WBC HMT EOS HAP IL8	3	ALGA0019692	70967762	G/A	4,90	0,03	CHR	CCA	35	
LR	WBC HMT EOS HAP IL8	3	ALGA0123028	71124411	C/T	4,90	0,03	CHR	CCA	35	
LR	WBC HMT EOS HAP IL8	3	MARC0055616	71462992	G/A	4,90	0,03	CHR	CCA	35	
LR	WBC HMT EOS HAP IL8	3	ASGA0015118	72651493	C/T	90,60	0,02	CHR	CCA	36	ANXA4, AAK1, NFU1, GFPT1, U6, ANTXR1
LR	WBC HMT EOS HAP IL8	3	MARC0001946	72973452	A/G	95,30	0,02	CHR	CCA	36	
LR	WBC HMT EOS HAP IL8	3	MARC0021343	73260048	T/C	95,20	0,02	CHR	CCA	36	
LR	BAS MON	3	MARC0006534	112713663	T/G	78,90	0,05	CHR	CCA	37	HADHB
LR	EOS PLT, WBC HMT EOS HAP IL8, WBC NEU MON EOS BAS TNF	3	ASGA0016494	121139181	G/A	30,70	4,63	GEN	mvBIMBAM	38	
LR	RBC HMG HMT MCV MCH	4	ALGA0023253	12432764	G/A	91,60	0,04	CHR	CCA	39	
LR	IFN IL12 IL8	4	ALGA0023430	14382005	A/G	65,60	0,06	CHR	PCA	40	NSMCE2, WASHC5
LR	IFN IL12 IL8	4	ASGA0018536	14601654	G/A	64,20	0,03	CHR	PCA	40	
LW	NEU LYM	4	DBWU0000703	36228000	C/T	55,70	0,02	CHR	PCA	41	
LR	IL6 IL10 IL1b	4	H3GA0012747	56888492	C/T	23,50	0,05	CHR	CCA	42	
LR	IL6 IL10 IL1b	4	MARC0096487	60396561	G/A	0,00	0,01	CHR	CCA	43	
LR	IL6 IL10 IL1b	4	ALGA0025441	63422287	G/T	38,60	0,01	CHR	CCA	44	TRPA1
LR	IL6 IL10 IL1b	4	H3GA0012835	63533485	G/A/T	36,10	0,01	CHR	CCA	44	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL6 IL10 IL1b	4	MARC0063844	63563088	G/T	36,30	0,01	CHR	CCA	44	
LR	RBC HMG HMT MCV MCH	4	INRA0015168	79694780	T/C	8,60	0,06	GEN	CCA	45	PRKDC
LR	RBC HMG HMT MCV MCH	4	H3GA0013209	81279399	A/G	67,90	0,01	CHR	CCA	46	SELL
LR	RBC HMG HMT MCV MCH	4	ASGA0020483	81301454	A/C	62,90	0,01	CHR	CCA	46	
LR	RBC HMG HMT MCV MCH	4	ASGA0020484	81321340	T/C	62,90	0,01	CHR	CCA	46	
LR	RBC HMG HMT MCV MCH	4	ALGA0026246	82530260	T/G	48,80	0,01	CHR	CCA	47	
LR	RBC HMG HMT MCV MCH	4	ALGA0026434	86347263	G/A	97,10	0,06	GEN	CCA	48	
LR	RBC HMG HMT MCV MCH	4	ALGA0026437	86379017	G/A	1,60	0,06	GEN	CCA	48	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	4	ALGA0026453	87048942	A/C	71,00	0,00	GEN	CCA	48	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	4	ALGA0027586	103876353	A/G	72,50	0,05	CHR	CCA	49	CD2, IGSF3, CD58, ATP1A1
LW	RBC HMG HMT MCV MCH MCHC, HMG MCHC, WBC RBC HAP IL1b, PLT RBC WBC	4	ASGA0021646	104373115	C/T	79,20	3,38	GEN	mvBIMBAM	49	
LR	NEU RBC WBC MON BAS	4	H3GA0014300	112534903	G/A	35,50	0,04	CHR	CCA	50	NTNG1, PRMT6
LR	NEU RBC WBC MON BAS	4	ASGA0022296	112635430	C/T	40,40	0,04	CHR	CCA	50	
LR	NEU RBC WBC MON BAS	4	ASGA0022298	112667121	C/T	25,80	0,04	CHR	CCA	50	
LR	NEU RBC WBC MON BAS	4	DRGA0005123	112686245	G/A	20,90	0,05	GEN	CCA	50	
LR	NEU RBC WBC MON BAS	4	DRGA0005125	112708191	C/T	43,60	0,04	CHR	CCA	50	
LR	WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	4	H3GA0014305	112850117	A/G	34,30	0,05	GEN	CCA	50	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	NEU RBC WBC MON BAS	4	ASGA0022330	113006080	C/T	51,30	0,04	CHR	CCA	50	
LR	NEU RBC WBC MON BAS	4	ALGA0028362	113024620	T/C	48,70	0,04	CHR	CCA	50	
LR	NEU RBC WBC MON BAS	4	DRGA0005145	113052359	G/A	48,60	0,04	CHR	CCA	50	
LR	NEU RBC WBC MON BAS	4	ASGA0087092	113071236	A/G	52,00	0,04	CHR	CCA	50	
LR	RBC HMG HMT MCV MCH	4	ALGA0028434	114016613	T/C	40,80	0,03	CHR	CCA	51	
LR	HMT HMG MCHC	4	M1GA0006536	122037141	A/C	38,90	0,02	CHR	CCA	52	
LR	HMT HMG MCHC	4	ASGA0090553	122828997	T/G	17,00	0,04	CHR	CCA	53	F3
LR	RBC HMG HMT MCV MCH	5	H3GA0015293	6978152	C/T	1,50	0,04	CHR	CCA	54	CSDC2
LW	HMG MCH	5	ALGA0030157	8854690	A/G	74,90	0,04	CHR	CCA	55	
LR	RBC HMG HMT MCV MCH	5	ASGA0024572	13266811	T/C	45,90	0,04	CHR	CCA	56	CRY1, MTERF2, TMEM263, RIC8B, POLR3B, POLR3B
LR	RBC HMG HMT MCV MCH	5	H3GA0015743	13586949	T/C	77,50	0,04	CHR	CCA	56	
LR	RBC HMG HMT MCV MCH	5	MARC0091257	13633289	T/C	0,00	0,04	CHR	CCA	56	
LR	RBC HMG HMT MCV MCH	5	ASGA0024585	13654097	C/T	45,70	0,04	CHR	CCA	56	
LR	RBC HMG HMT MCV MCH	5	ALGA0030680	13697150	C/T	48,30	0,06	CHR	CCA	56	
LR	RBC HMG HMT MCV MCH	5	ALGA0030691	13798075	T/C	48,30	0,06	CHR	CCA	56	
LR	HMT HMG MCHC	5	ALGA0030761	14608518	T/G	35,10	0,04	CHR	CCA	57	CCNT1, C5H12orf75
LR	HMT HMG MCHC	5	ALGA0030794	14788695	C/A	31,10	0,03	CHR	CCA	57	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	ALGA0106408	17162699	C/T	68,80	0,04	CHR	CCA, TATES	58	SCN8A, ACVRL1, ACVR1B, GRASP, NR4A1, ATG101, KRT80, KRT7
LR	HMT HMG MCHC	5	MARC0095571	17585540	G/A	0,00	0,06	CHR	CCA	58	
LR	HMT HMG MCHC	5	H3GA0016097	23400843	A/C	37,10	0,02	CHR	CCA	59	LRIG3
LR	HMT HMG MCHC	5	ASGA0025128	23778757	A/G	46,70	0,02	CHR	CCA	59	
LR	HMT HMG MCHC	5	ASGA0025132	23816873	G/A	42,50	0,02	CHR	CCA	59	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ASGA0025137	23933098	T/C	79,00	0,03	CHR	CCA	59	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ALGA0031314	24000573	G/T	21,00	0,03	CHR	CCA	59	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ASGA0025140	24069910	T/G	79,10	0,03	CHR	CCA	59	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ALGA0031321	24135911	A/C	79,30	0,02	CHR	CCA	59	
LR	HMT HMG MCHC	5	INRA0018998	24393356	A/G	55,80	0,02	CHR	CCA	59	
LR	HMT HMG MCHC	5	INRA0019001	24702306	T/C	55,00	0,01	CHR	CCA	60	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	DRGA0005609	29991703	T/G	84,10	0,06	CHR	CCA	61	HMGA2
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	DRGA0005613	30469491	T/G	84,10	0,06	CHR	CCA	61	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ASGA0025326	31271737	A/C	22,10	0,06	CHR	CCA	62	U6, ssc-mir-9808, CAND1
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ALGA0034323	31867380	A/G	88,60	0,06	CHR	CCA	62	
LR	HMT HMG MCHC	5	MARC0114715	32497165	A/C	0,00	0,01	CHR	CCA	63	IL26, IL22

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	HMT HMG MCHC	5	ALGA0031657	32603961	C/T	19,30	0,01	CHR	CCA	63	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ALGA0031690	33946621	A/G	27,10	0,04	CHR	CCA	64	CCT2, BEST3, MYRFL, CNOT2, KCNMB4, PTPRB
LR	HMT HMG MCHC	5	ASGA0025416	34747588	T/C	80,60	0,04	CHR	CCA	64	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC, NEU RBC WBC MON BAS	5	H3GA0016244	34769398	A/G	70,20	0,01	CHR	CCA	64	
LR	LYM MON BAS	5	ALGA0031717	35361757	C/T	3,20	0,05	CHR	PCA	64	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	MARC0021861	35776165	T/C	37,10	0,04	CHR	CCA	65	TMEM19, TBC1D15, TPH2, TRHDE
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ALGA0031731	36197319	A/C	25,50	0,04	CHR	CCA	65	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ALGA0031736	36314172	A/C	27,90	0,05	CHR	CCA	65	
LR	HMT HMG MCHC	5	CASI0009605	36346640	A/G	27,40	0,03	CHR	CCA	65	
LR	NEU RBC WBC MON BAS	5	ALGA0031740	36426114	C/A	15,70	0,06	CHR	CCA	65	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ASGA0025454	36903934	C/T	35,90	0,02	CHR	CCA	66	
LR	RBC HMG HMT MCV MCH	5	DRGA0005711	37397149	T/C	29,80	0,04	CHR	CCA	66	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	INRA0019263	38864890	T/C	69,80	0,04	CHR	CCA	67	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	rs334622443	38872955	A/T	NA	0,04	CHR	CCA	67	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	MARC0037200	38880761	T/C	69,80	0,04	CHR	CCA	67	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	DRGA0005776	43220509	C/T	30,50	0,04	CHR	CCA	68	U6
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	DRGA0005773	43252599	A/G	75,30	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	MARC0113545	43293810	A/G	0,00	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ALGA0031826	43320525	C/A	30,50	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ASGA0025493	43385239	G/A	30,50	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	H3GA0016271	43428743	C/A	30,50	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ASGA0025490	43480338	T/C	71,40	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	DRGA0005767	43556787	C/T	30,50	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	MARC0003440	43664480	T/C	69,50	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	INRA0019288	43688401	T/C	73,50	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	MARC0030421	43750584	C/T	28,60	0,04	CHR	CCA	68	
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	ALGA0031834	43879295	G/A	30,60	0,04	CHR	CCA	68	
LR	HMT HMG MCHC	5	INRA0019312	47324666	T/C	71,80	0,06	CHR	CCA	69	ITPR2

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	5	H3GA0016294	47424047	A/G	38,30	0,04	CHR	CCA	69	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	ALGA0031924	48896828	T/G	57,00	0,02	CHR	CCA, TATES	70	BCAT1
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	MARC0001027	50094492	G/A	23,70	0,02	CHR	CCA, TATES	71	SOX5
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	DRGA0005841	50243918	A/G	76,30	0,02	CHR	CCA, TATES	71	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	ALGA0032074	58601394	A/G	76,00	0,03	CHR	CCA, TATES	72	GRIN2B, EMP1
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	H3GA0016359	58625915	C/T	25,10	0,03	CHR	CCA, TATES	72	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	H3GA0016379	58840179	G/A	23,90	0,03	CHR	CCA, TATES	72	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	ALGA0032146	59340760	A/C	82,80	0,03	CHR	CCA, TATES	72	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	RBC HMG HMT MCV MCH	5	ASGA0025778	61783155	A/G	23,10	0,04	CHR	CCA	73	TMEM52B, OLR1, CLEC7A, CLEC1A, CLEC12B, CLEC1B, CLEC12A, CLEC2B, CD69, KLRB1, A2M, KLRG1, M6PR, PHC1, A2ML1, RIMKLB
LR	RBC HMG HMT MCV MCH	5	ASGA0025791	61931507	A/G	76,80	0,04	CHR	CCA	73	
LR	RBC HMG HMT MCV MCH	5	DRGA0005951	61966384	G/A	76,80	0,04	CHR	CCA	73	
LR	RBC HMG HMT MCV MCH	5	ASGA0025794	62115185	T/G	23,40	0,04	CHR	CCA	73	
LR	RBC HMG HMT MCV MCH	5	DRGA0005956	62134657	T/G	80,00	0,04	CHR	CCA	73	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	MARC0100616	62372560	C/T	0,00	0,04	CHR	CCA, TATES	73	
LR	RBC HMG HMT MCV MCH	5	ALGA0032322	62455175	G/A	65,60	0,04	CHR	CCA	73	
LR	RBC HMG HMT MCV MCH	5	DIAS0000002	62481418	A/G	34,90	0,04	CHR	CCA	73	
LR	RBC HMG HMT MCV MCH	5	ASGA0025802	62601778	T/C	77,10	0,04	CHR	CCA	73	
LR	RBC HMG HMT MCV MCH	5	ALGA0032345	62737145	T/C/G	39,00	0,03	CHR	CCA	73	
LR	HMT HMG MCHC	5	ASGA0025827	63827447	G/A	84,70	0,02	CHR	CCA	74	ENO2
LR	HMT HMG MCHC	5	ASGA0100486	66362258	T/G	71,70	0,05	CHR	CCA	75	
LR	NEU RBC WBC MON BAS	5	H3GA0055380	75848496	A/G	94,10	0,03	CHR	CCA	76	NELL2, DBX2, ANO6
LR	LYM MON BAS	5	M1GA0008026	76155408	C/T	85,20	0,02	CHR	PCA	76	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	NEU RBC WBC MON BAS, LYM MON BAS	5	MARC0004505	76180231	G/A	94,30	0,05	CHR	CCA, PCA	76	
LR	NEU RBC WBC MON BAS	5	H3GA0016883	76215960	G/A	94,90	0,05	GEN	CCA	76	
LR	NEU RBC WBC MON BAS	5	MARC0002321	76276553	G/A	4,90	0,05	GEN	CCA	76	
LW	HMG MCH, PLT RBC WBC	5	ALGA0033064	77286779	T/C	98,20	0,04	CHR	CCA	77	SLC38A4, AMIGO2, PCED1B, RPAP3
LW	HMG MCH, PLT RBC WBC	5	ASGA0093314	77402409	A/G	8,50	0,04	CHR	CCA	77	
LW	HMG MCH, PLT RBC WBC	5	ALGA0104452	77541676	A/G	7,50	0,04	CHR	CCA	77	
LW	HMG MCH, PLT RBC WBC	5	MARC0090729	77680830	C/T	0,00	0,04	CHR	CCA	77	
LR	HMT HMG MCHC	5	MARC0012702	77884515	C/A	35,90	0,01	CHR	CCA	77	
LR	IL4 EOS IL10 IL1b TNF	5	ALGA0105937	77892336	A/G	89,40	0,01	GEN	CCA	77	
LW	HMG MCH, PLT RBC WBC	5	MARC0098250	77948633	G/A	0,00	0,04	CHR	CCA	77	
LW	HMG MCH, PLT RBC WBC	5	ALGA0109048	77962305	T/C	6,20	0,04	CHR	CCA	77	
LW	HMG MCH, PLT RBC WBC	5	ALGA0101247	77990021	A/G	2,90	0,04	CHR	CCA	77	
LW	HMG MCH, PLT RBC WBC	5	ALGA0104065	77997876	C/T	97,10	0,04	CHR	CCA	77	
LW	HMG MCH, PLT RBC WBC	5	MARC0009241	78029583	G/A	97,10	0,04	CHR	CCA	77	
LW	HMG MCH, PLT RBC WBC	5	ALGA0104516	78032160	G/T	97,10	0,04	CHR	CCA	77	
LW	RBC HMG HMT MCV MCH MCHC, HMG MCHC, WBC RBC HAP IL1b, PLT RBC WBC	5	MARC0013873	79815601	T/C	79,10	3,47	GEN	mvBIMBAM	78	CHST11
LR	NEU RBC WBC MON BAS	5	ALGA0033413	88424483	T/C	91,90	0,02	CHR	CCA	79	
LR	IL12 IL8	5	MARC0080493	90118573	A/G	79,20	0,04	CHR	PCA	80	
LW	HMG MCH	5	ALGA0105659	92864624	T/C	40,70	0,05	CHR	CCA	81	
LR	RBC HMG HMT MCV MCH	5	ASGA0100714	94149478	C/T	17,40	0,04	CHR	CCA	82	TMTC3, CEP290, C12orf29, C12orf50
LR	RBC HMG HMT MCV MCH	5	ASGA0026904	94238901	A/C	82,60	0,04	CHR	CCA	82	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	RBC HMG HMT MCV MCH	5	ALGA0033767	94367121	C/T	8,50	0,05	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	ALGA0033764	94457579	T/C	83,20	0,04	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	M1GA0008129	94490945	A/G	91,40	0,03	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	ALGA0033759	94518601	T/G	91,40	0,03	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	ALGA0033757	94541296	T/C	62,60	0,04	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	H3GA0017183	94558952	C/T	51,30	0,05	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	ALGA0033735	94705788	G/A	36,90	0,04	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	ASGA0026872	94785843	G/T	41,10	0,04	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	INRA0020482	94801310	C/T	41,70	0,05	CHR	CCA	82	
LR	WBC BAS	5	MARC0101043	94860354	A/G	0,00	0,05	GEN	PCA	82	
LR	RBC HMG HMT MCV MCH	5	ASGA0091315	95014018	A/C	81,70	0,04	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	ASGA0026863	95042109	T/C	81,00	0,04	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	DRGA0006240	95278246	A/G	81,00	0,04	CHR	CCA	82	
LR	RBC HMG HMT MCV MCH	5	H3GA0017164	95377091	G/A	20,10	0,04	CHR	CCA	83	
LR	RBC HMG HMT MCV MCH	5	ALGA0033673	95558910	A/C	54,40	0,04	CHR	CCA	83	
LR	RBC HMG HMT MCV MCH	5	ALGA0033670	95591504	T/G	54,30	0,04	CHR	CCA	83	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	ASGA0101924	97259676	T/C	98,90	0,00	GEN	CCA, TATES	84	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	DRGA0006295	97412529	A/C	98,70	0,00	GEN	CCA, TATES	84	
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	5	H3GA0017216	97477241	C/T	1,10	0,00	GEN	CCA, TATES	84	
LR	RBC HMG HMT MCV MCH	5	MARC0030237	99102014	T/G	23,10	0,06	CHR	CCA	85	TMTC2

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	HMT HMG MCHC	5	ALGA0034135	101846412	A/G	15,00	0,05	CHR	CCA	86	
LR	IL6 IL10 IL1b	6	MARC0041561	16171435	C/T	80,90	0,03	CHR	CCA	87	
LR	IL6 IL10 IL1b	6	MARC0075761	16188799	G/A	80,90	0,03	CHR	CCA	87	
LR	IL4 EOS IL10 IL1b TNF	6	ASGA0104222	39838897	C/A	26,10	0,05	CHR	CCA	88	URI1, ZNF536
LR	IL4 EOS IL10 IL1b TNF	6	MARC0005196	39859759	C/T	39,30	0,05	CHR	CCA	88	
LR	IL4 EOS IL10 IL1b TNF	6	MARC0113191	39937433	T/C	0,00	0,05	CHR	CCA	88	
LR	IL4 EOS IL10 IL1b TNF	6	ASGA0028105	40240336	C/A	43,50	0,05	CHR	CCA	88	
LR	IL4 EOS IL10 IL1b TNF	6	ASGA0097134	41279833	T/C	37,50	0,06	CHR	CCA	88	
LR	IL1b WBC EOS IL10 IL12	6	ALGA0100920	50604798	G/A	54,00	0,04	CHR	CCA	89	LYPD5, ZNF283, ZNF404, ZNF45, LOC110260999
LR	IL1b WBC EOS IL10 IL12	6	MARC0033200	50804198	C/T	61,90	0,04	CHR	CCA	89	
LR	IL6 IL10 IL1b	6	ASGA0085935	74701117	C/T	14,70	0,03	CHR	CCA	90	CTRC, CELA2A
LR	IL6 IL10 IL1b	6	ASGA0100599	74701809	C/T	14,70	0,03	CHR	CCA	90	
LR	IL6 IL10 IL1b	6	M1GA0025029	78113081	T/C	11,40	0,03	CHR	CCA	91	TMCO4
LR	IL6 IL10 IL1b	6	H3GA0053380	93420594	G/T	47,80	0,03	CHR	CCA	92	ZC3H12A, MEAF6, SNIP1, DNALI1, GNL2, RSPO1, C1orf109, CDCA8, EPHA10, MANEAL, YRDC, C1orf122, MTF1, INPP5B, SF3A3, FHL3, UTP11, POU3F1

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL6 IL10 IL1b	6	MARC0082470	93442952	T/C	47,90	0,06	CHR	CCA	92	
LR	IL6 IL10 IL1b	6	ASGA0028870	93958186	A/G	55,50	0,06	CHR	CCA	92	
LR	IL6 IL10 IL1b	6	ALGA0035971	94051380	C/T	62,30	0,06	CHR	CCA	92	
LR	IL6 IL10 IL1b	6	MARC0019060	94096694	T/C	72,40	0,03	CHR	CCA	92	
LR	IL6 IL10 IL1b	6	M1GA0008815	94712287	C/T	33,60	0,03	CHR	CCA	93	RRAGC, GJA9, RHBDL2, AKIRIN1, NDUFS5, U6, MACF1, PABPC4, SNORA55, HEYL, NT5C1A, HPCAL4
LR	HMG MCHC IL10, IL1b WBC EOS IL10 IL12, IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b	6	MARC0033580	95566980	C/T	45,50	0,02	GEN	CCA	93	
LR	IL6 IL10 IL1b	6	MARC0022542	96650040	T/G	59,80	0,03	CHR	CCA	94	CEP192, PTPN2, PSMG2, CEP76, SPIRE1, PRELID3A, AFG3L2, TUBB6, CIDEA, IMPA2, MPPE1, GNAL
LR	IL6 IL10 IL1b	6	M1GA0026030	96767590	T/C	59,80	0,03	CHR	CCA	94	
LR	IL6 IL10 IL1b	6	CASI0006620	96926928	C/T	31,00	0,06	CHR	CCA	94	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL1b WBC EOS IL10 IL12, IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b	6	ASGA0091444	97104675	G/A	8,80	0,03	CHR	CCA	94	
LR	IL1b WBC EOS IL10 IL12, IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b	6	MARC0032131	97343439	T/G	23,50	0,03	CHR	CCA	94	
LR	HMG MCHC IL10, IL1b WBC EOS IL10 IL12, IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b	6	ALGA0036131	97620286	T/C	32,20	0,02	GEN	CCA	94	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	ALGA0036189	99931515	G/A	72,60	0,03	CHR	CCA	95	PTPRM, U6, LRRC30, LAMA1, ARHGAP28
LR	IL1b WBC EOS IL10 IL12	6	ALGA0036191	99956687	T/C	94,30	0,02	CHR	CCA	95	
LR	IL1b WBC EOS IL10 IL12	6	CASI0005798	100018316	T/C	94,30	0,02	CHR	CCA	95	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b,	6	MARC0003203	100175109	G/A	27,90	0,03	CHR	CCA	95	
LR	IL1b WBC EOS IL10 IL12	6	ALGA0115176	100207770	C/T	1,40	0,02	CHR	CCA	95	
LR	IL1b WBC EOS IL10 IL12	6	ALGA0117017	100292060	A/G	92,70	0,02	CHR	CCA	95	
LR	IL1b WBC EOS IL10 IL12	6	MARC0021350	100311040	C/T	5,70	0,02	CHR	CCA	95	
LR	HMG MCHC IL10, IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	H3GA0054139	100709160	T/C	87,00	0,05	GEN	CCA	95	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	ASGA0029105	102340927	G/A	9,80	0,03	CHR	CCA	96	DLGAP1, TGIF1
LR	IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b	6	ALGA0036219	102362625	G/A	9,40	0,05	CHR	CCA	96	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	ALGA0036233	102464736	T/C	98,60	0,03	CHR	CCA	96	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	ALGA0036235	102495561	A/G	98,40	0,03	CHR	CCA	96	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	H3GA0018606	102641493	C/T	10,10	0,03	CHR	CCA	96	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	DRGA0006658	102664930	T/G	89,90	0,03	CHR	CCA	96	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	ASGA0029117	102709352	T/G	89,90	0,03	CHR	CCA	96	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	6	ALGA0036251	102732393	A/G	10,10	0,03	CHR	CCA	96	
LR	WBC BAS	6	ALGA0115459	103339184	A/G	99,00	0,00	GEN	PCA	96	
LR	IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b	6	ASGA0097110	108033469	C/T	5,90	0,05	CHR	CCA	97	
LR	IL1b WBC EOS IL10 IL12	6	H3GA0018950	147205921	G/A	25,10	0,04	CHR	CCA	98	AK4
LR	IL1b WBC EOS IL10 IL12	6	MARC0091155	149889171	C/T	0,00	0,03	CHR	CCA	99	DOCK7

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL4 EOS IL10 IL1b TNF	6	ALGA0115609	152846677	T/C	38,20	0,05	CHR	CCA	100	FGGY
LR	IL1b WBC EOS IL10 IL12, IL4 EOS IL10 IL1b TNF	6	ALGA0114316	152944549	C/T	41,10	0,04	CHR	CCA	100	
LR	HMT HMG MCHC	7	H3GA0020313	21444076	C/T	35,30	0,03	CHR	CCA	101	ssc-mir-7857, LOC110261671, LOC110261673, LOC100154071, LOC100621915
LR	HMT HMG MCHC	7	MARC0114063	21610238	G/A	0,00	0,03	CHR	CCA	101	
LR	HMT HMG MCHC	7	MARC0055565	22727959	G/A	41,40	0,05	CHR	CCA	102	TRIM10
LR	IL1b WBC EOS IL10 IL12	7	DRGA0008079	105341213	T/C	15,30	0,06	CHR	CCA	103	
LR	IL1b WBC EOS IL10 IL12	7	ASGA0035841	105393504	C/T	15,70	0,06	CHR	CCA	103	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	7	MARC0001297	108996302	T/C	76,60	0,06	CHR	CCA	104	
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	7	MARC0057446	109047374	A/C	76,00	0,06	CHR	CCA	104	
LR	IL6 IL10 IL1b	7	ALGA0044543	109067921	T/C	70,40	0,01	CHR	CCA	104	
LR	IL6 IL10 IL1b	7	CASI0006750	109101108	T/C	82,20	0,01	CHR	CCA	104	
LR	IL6 IL10 IL1b	7	ALGA0044610	109733901	C/T	9,30	0,03	CHR	CCA	105	GALC
LR	IL1b WBC EOS IL10 IL12, IL6 IL10 IL1b	7	MARC0067107	110057727	A/G	75,80	0,06	CHR	CCA	105	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL6 IL10 IL1b	7	ALGA0044644	110113876	C/T	9,70	0,01	CHR	CCA	105	
LR	HMT HMG MCHC	7	rs706107533	115179207	C/T	NA	0,03	CHR	CCA	106	
LR	IL4 EOS IL10 IL1b TNF	8	ALGA0046044	1186987	C/T	5,70	0,05	CHR	CCA	107	POLN, HAUS3
LW	IL4 IL10 IL1b IL6	8	MARC0111479	4598871	T/G	0,00	0,03	CHR	CCA	108	JAKMIP1
LW	IL4 IL10 IL1b IL6	8	ALGA0107038	4605432	T/C	36,80	0,02	CHR	CCA	108	
LW	IL4 IL10 IL1b IL6	8	ASGA0092577	4674424	G/A	76,30	0,02	CHR	CCA	108	
LR	TNF IFN IL10	8	M1GA0011804	11782932	A/G	55,00	0,03	CHR	CCA	109	LDB2
LR	IL4 EOS IL10 IL1b TNF	8	CASI0003674	13589586	C/A	7,00	0,02	CHR	CCA	110	
LR	IL4 EOS IL10 IL1b TNF	8	MARC0036889	13972046	A/G	75,50	0,02	CHR	CCA	110	
LR	IL4 EOS IL10 IL1b TNF	8	MARC0054361	14596289	T/C	74,10	0,02	CHR	CCA	110	
LR	IL4 EOS IL10 IL1b TNF, IL8 TNF, WBC NEU MON EOS BAS TNF, TNF IFN IL10	8	ALGA0046861	20647847	C/T	1,30	0,01	GEN	CCA	111	
LW	LYM NEU MON EOS BAS	8	ALGA0046885	20770188	G/T	59,00	0,03	GEN	CCA	111	
LR	IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b, IL8 TNF, WBC NEU MON EOS BAS TNF, TNF IFN IL10	8	ALGA0046899	20831553	G/A	26,30	0,02	CHR	CCA, TATES	111	
LR	WBC NEU MON EOS BAS TNF	8	ASGA0101895	30740074	T/C	94,50	0,05	CHR	CCA	112	UGDH
LW	RBC HMG HMT MCV MCH MCHC	8	ASGA0088957	35953783	A/G	17,70	0,03	CHR	CCA	113	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	RBC HMG HMT MCV MCH MCHC	8	ALGA0105374	37495537	G/A	16,50	0,03	CHR	CCA	114	ATP10D, CORIN, U6, NFXL1, CNGA1, NIPAL1, TXK, TEC, SLAIN2, SLC10A4, ZAR1, FRYL
LW	RBC HMG HMT MCV MCH MCHC	8	MARC0045311	37967413	T/C	15,70	0,03	CHR	CCA	114	
LW	RBC HMG HMT MCV MCH MCHC	8	M1GA0011926	38425208	T/G	74,30	0,03	CHR	CCA	114	
LW	RBC HMG HMT MCV MCH MCHC	8	MARC0056555	39391675	C/T	5,00	0,03	CHR	CCA	115	
LW	RBC HMG HMT MCV MCH MCHC	8	ALGA0047813	43027473	A/C	99,20	0,03	CHR	CCA	116	TLL1
LW	RBC HMG HMT MCV MCH MCHC	8	MARC0039159	44439766	C/T	79,00	0,03	CHR	CCA	117	
LW	LYM NEU MON EOS BAS	8	ASGA0040364	134911925	C/T	17,70	0,02	CHR	CCA	118	GPAT3, ABRAXAS1, MRPS18C, HELQ, HPSE, COQ2, LOC100524999, PLAC8, COPS4, LIN54, THAP9, SEC31A, SCD5, ssc-mir-9846, TMEM150C
LW	LYM NEU MON EOS BAS	8	ASGA0040417	135242215	G/A	23,10	0,04	CHR	CCA	118	
LW	LYM NEU MON EOS BAS	8	ASGA0040427	135274760	C/T	20,60	0,02	CHR	CCA	118	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	LYM NEU MON EOS BAS	8	ALGA0050145	135285532	G/A	17,80	0,02	CHR	CCA	118	
LW	LYM NEU MON EOS BAS	8	ALGA0115578	135550523	A/C	79,40	0,02	CHR	CCA	118	
LW	LYM NEU MON EOS BAS	8	H3GA0054370	135604963	T/C	77,60	0,02	CHR	CCA	118	
LW	LYM NEU MON EOS BAS	8	DRGA0017418	135607348	G/A	22,40	0,02	CHR	CCA	118	
LW	LYM NEU MON EOS BAS	8	ALGA0109193	135629399	A/G	75,00	0,03	CHR	CCA	118	
LW	LYM NEU MON EOS BAS	8	ASGA0082238	135665981	A/C	79,30	0,02	CHR	CCA	118	
LW	LYM NEU MON EOS BAS	8	ASGA0105760	135668712	C/T	26,10	0,02	CHR	CCA	118	
LW	LYM NEU MON EOS BAS	8	MARC0065298	135689152	A/G	72,20	0,02	CHR	CCA	118	
LW	RBC HMG HMT MCV MCH MCHC	9	MARC0008298	71070843	G/A	14,10	0,05	GEN	CCA	119	CDK14
LW	MON BAS	9	H3GA0027937	100939592	C/T	81,70	0,03	CHR	PCA	120	MAGI2
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	ASGA0046986	19572163	G/A	22,70	0,01	GEN	CCA	126	
LR	IL8 TNF	15	ALGA0087090	120139024	T/C	87,80	0,05	CHR	CCA	120	
LR	IL8 TNF, WBC HMT EOS HAP IL8	15	ALGA0087116	120286163	T/C	31,90	0,01	GEN	CCA, TATES	120	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	ALGA0057739	20062069	A/C	16,30	0,01	GEN	CCA	127	
LW	MON BAS	9	DRGA0009651	102878227	A/C	15,90	0,03	CHR	PCA	121	CCDC146
LR	IL8 TNF	15	ALGA0087356	122895848	C/A	43,80	0,05	CHR	CCA	121	
LR	IL8 TNF	15	MARC0114457	123052286	G/A	0,00	0,06	CHR	CCA	121	
LR	IL8 TNF	15	ALGA0087328	123241971	T/C	68,10	0,06	CHR	CCA	121	
LR	IL8 TNF	15	MARC0070811	123293141	T/C	68,10	0,06	CHR	CCA	121	
LW	TNF MON IFN IL12 IL6	9	ASGA0097568	138517855	C/A	79,30	0,01	GEN	TATES	122	
LR	IL12 IL8	15	ASGA0070763	124276187	G/A	67,70	0,04	CHR	PCA	122	
LW	BAS WBC NEU	10	M1GA0013576	3267437	G/A	78,00	0,05	CHR	CCA	123	BRINP3
LR	WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	ASGA0047018	20134916	C/T	63,30	0,02	GEN	CCA	127	ZBTB41, CRB1, DENND1B, C1orf53, LHX9, NEK7
LW	BAS WBC NEU	10	ALGA0057018	10046457	G/A	79,60	0,05	CHR	CCA	124	MARK1, C1orf115, MARC2, HLX
LW	BAS WBC NEU	10	ASGA0046469	10399957	A/C	6,60	0,05	CHR	CCA	124	
LW	BAS WBC NEU	10	H3GA0029248	10680375	C/T	15,40	0,05	CHR	CCA	124	
LW	BAS WBC NEU	10	ALGA0057079	10721280	T/C	15,60	0,05	CHR	CCA	124	

LW	BAS WBC NEU	10	MARC0010213	10784930	C/T	94,60	0,05	CHR	CCA	124	
LR	IL8 TNF	15	ALGA0088017	131325557	T/C	81,50	0,06	CHR	CCA	124	
LW	BAS WBC NEU	10	MARC0055782	13280955	G/A	94,50	0,05	CHR	CCA	125	
LR	HMT HMG MCHC	15	ASGA0084070	137221136	T/G	23,80	0,06	CHR	CCA	125	
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	MARC0058358	20157046	T/C	13,70	0,00	CHR	CCA	127	
LW	HMG MCH	16	ALGA0089752	23580846	G/A	74,10	0,04	CHR	CCA	126	EGFLAM, LIFR, OSMR, RICTOR, U6, U4, FYB1
LR	WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	MARC0050841	20188434	A/C	63,40	0,02	GEN	CCA	127	
LW	HMG MCH, PLT RBC WBC	16	ALGA0089777	24362179	T/C	39,40	0,04	CHR	CCA	126	
LR	WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	ALGA0106008	20444762	A/C	75,40	0,03	GEN	CCA	127	
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	H3GA0053667	20584936	C/A	73,00	0,03	GEN	CCA	127	
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	H3GA0052936	20795956	A/G	69,90	0,01	GEN	CCA, TATES	127	
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	ASGA0098001	20805520	A/G	30,10	0,01	GEN	CCA, TATES	127	
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	MARC0108793	21031390	C/T	0,00	0,05	GEN	CCA	127	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	MARC0018828	21054756	A/G	6,20	0,05	GEN	CCA	127	
LR	BAS MON, WBC NEU MON EOS BAS TNF, NEU RBC WBC MON BAS	10	ASGA0083356	22817715	G/A	91,70	0,01	GEN	CCA, TATES	129	NR5A2
LW	IL4 IL10 IL1b IL6, IL6 IFN IL10 IL1b	11	ALGA0062985	63626204	C/T	95,70	4,07	GEN	mvBIMBAM	143	DCT
LW	EOS MCV PLT WBC IL8, LYM NEU MON EOS BAS	11	ALGA0108815	70247157	T/C	7,30	4,35	GEN	mvBIMBAM	146	ITGBL1, FGF14, TPP2, METTL21C, TEX30, POGLUT2
LR	IL4 EOS IL10 IL1b TNF, IFN IL12 IL8	12	ALGA0113815	12017916	T/C	11,60	0,01	CHR	CCA, PCA	152	RGS9
LR	IL4 EOS IL10 IL1b TNF, IFN IL12 IL8	12	H3GA0033531	12973397	C/T	96,60	0,01	CHR	CCA, PCA	153	PRKCA, CACNG5, CACNG4, CACNG1, HELZ, U6, PSMD12, NOL11
LR	WBC NEU MON EOS BAS TNF	10	DRGA0010387	21726062	A/G	63,40	0,02	CHR	CCA	128	PTPRC
LR	WBC NEU MON EOS BAS TNF	10	ALGA0057837	22018259	G/A	98,60	0,02	CHR	CCA	128	
LR	WBC NEU MON EOS BAS TNF	10	ASGA0047084	22210885	T/C	1,40	0,02	CHR	CCA	128	
LR	IL4 EOS IL10 IL1b TNF	16	ASGA0073693	60020102	T/G	2,40	0,01	GEN	CCA	128	
LR	IL4 EOS IL10 IL1b TNF, IFN IL12 IL8	12	H3GA0055422	13531783	G/T	4,10	0,01	CHR	CCA, PCA	153	
LR	IL4 EOS IL10 IL1b TNF	16	ALGA0091375	66889281	C/T	24,20	0,01	GEN	CCA	129	
LR	WBC BAS	10	ASGA0095530	33811026	G/A	79,50	0,05	GEN	PCA	130	NDUFB6
LR	IL4 EOS IL10 IL1b TNF	16	MARC0081095	68806638	G/A	2,60	0,01	GEN	CCA	130	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	WBC BAS	10	MARC0001381	36349905	A/G	68,50	0,05	GEN	PCA	131	
LR	IL4 EOS IL10 IL1b TNF, PC3Cyto	12	MARC0113018	13642774	T/C	0,00	0,01	CHR	CCA	153	
LW	RBC HMG HMT MCV MCH MCHC	16	ALGA0091954	73703925	A/C	61,40	0,04	CHR	CCA	131	
LR	IL4 EOS IL10 IL1b TNF, IFN IL12 IL8	12	ALGA0105006	13982775	C/T	3,20	0,01	CHR	CCA, PCA	153	
LR	NEU RBC WBC MON BAS	10	H3GA0030245	47362497	C/T	67,40	0,04	CHR	CCA	132	
LR	IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b, IL8 TNF	12	ALGA0066702	45863925	A/G	94,90	0,04	CHR	CCA	163	EFCAB5, NSRP1, ssc-mir-423, SLC6A4, BLMH, TMIGD1, CPD, GOSR1
LR	IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b, IL8 TNF	12	DRGA0011783	45955884	T/C	5,10	0,04	CHR	CCA	163	
LR	IL6 IL10 IL1b	11	MARC0043055	2474595	A/G	90,80	0,02	CHR	CCA	133	
LR	IL4 EOS IL10 IL1b TNF, IL6 IL10 IL1b, IL8 TNF	12	ALGA0114806	46640334	T/G	9,50	0,04	CHR	CCA	163	
LR	IL6 IL10 IL1b	11	ALGA0060404	4665665	G/A	6,90	0,03	CHR	CCA	134	USP12
LR	EOS PLT	17	ASGA0076045	28192131	A/G	8,80	0,02	CHR	CCA	134	CFAP61
LR	EOS PLT	17	MARC0093077	28351838	G/A	0,00	0,02	CHR	CCA	134	
LR	IL6 IL10 IL1b	11	ALGA0060455	5431878	A/G	11,50	0,02	CHR	CCA	135	FLT3, PAN3, FLT1
LR	IL6 IL10 IL1b	11	ASGA0049456	5563855	C/T	88,50	0,02	CHR	CCA	135	
LR	IL6 IL10 IL1b	11	ALGA0060475	5591824	A/G	8,10	0,02	CHR	CCA	135	
LR	IL6 IL10 IL1b	11	ALGA0060479	5673798	C/T	8,10	0,02	CHR	CCA	135	
LR	EOS PLT, WBC HMT EOS HAP IL8, WBC NEU MON EOS BAS TNF	13	ALGA0072231	141247842	A/G	29,90	4,32	GEN	mvBIMBAM	166	IGSF11
LR	IL6 IL10 IL1b	11	ALGA0060600	7781214	T/C	62,90	0,02	CHR	CCA	136	B3GLCT, RXFP2, FRY

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL6 IL10 IL1b	11	DRGA0010773	7803554	G/A	62,90	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	DRGA0017521	7841215	T/C	37,10	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	ALGA0060603	7917555	A/G	62,90	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	DRGA0010774	7946341	G/A	37,10	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	H3GA0031207	7959313	A/G	71,90	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	INRA0034855	7970578	G/A	71,90	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	H3GA0031210	8015295	C/T	37,10	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	ALGA0060606	8067254	A/G	37,10	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	ALGA0060607	8101824	G/A	37,10	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	ALGA0060610	8130087	A/C	37,10	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	MARC0033486	8150468	T/C	62,90	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	H3GA0031211	8164005	G/A	67,50	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	DRGA0010776	8254699	G/A	71,90	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	MARC0032659	8298480	A/C	28,10	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	MARC0058476	8322594	T/C	37,10	0,02	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	ASGA0049620	8612176	G/A	26,70	0,02	CHR	CCA	136	
LR	EOS PLT	17	ASGA0076514	33282761	G/A	95,70	0,02	CHR	CCA	136	STK35, PDYN
LR	EOS PLT	17	M1GA0021930	33651909	A/C	72,60	0,04	CHR	CCA	136	
LR	IL6 IL10 IL1b	11	H3GA0031293	10367680	T/C	69,80	0,02	CHR	CCA	137	RFC3
LR	IL6 IL10 IL1b	11	MARC0011099	10387046	A/G	32,30	0,02	CHR	CCA	137	
LR	IL6 IL10 IL1b	11	ASGA0049736	10399072	G/A	73,70	0,02	CHR	CCA	137	
LR	IL6 IL10 IL1b	11	MARC0089033	10420321	C/A	87,90	0,02	CHR	CCA	137	
LR	IL6 IL10 IL1b	11	MARC0007430	10615611	T/A	19,20	0,02	CHR	CCA	137	
LR	HMG MCHC IL10, HMT HMG MCHC	14	ALGA0075572	13776542	C/T	42,10	3,69	GEN	mvBIMBAM	171	PRSS55
LR	IL6 IL10 IL1b	11	INRA0035360	13579315	G/A	26,30	0,02	CHR	CCA	138	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	EOS PLT, WBC HMT EOS HAP IL8, WBC NEU MON EOS BAS TNF	15	ASGA0070226	100590733	T/C	30,80	5,87	GEN	mvBIMBAM	183	CCDC150
LR	IL8 TNF, IL12 IL8	15	MARC0089139	108677884	T/A	65,30	0,05	CHR	CCA, PCA	185	PARD3B, NRP2, INO80D
LR	IL8 TNF, WBC HMT EOS HAP IL8, IL12 IL8	15	ALGA0086892	116134508	C/T	68,80	0.04/3.53	GEN	CCA, TATES, mvBIMBAM, PCA	188	SPAG16
LR	IL6 IL10 IL1b	11	ALGA0061341	21733098	G/A	42,60	0,05	CHR	CCA	139	
LR	IL6 IL10 IL1b	11	ALGA0061477	23986814	A/C	16,30	0,02	CHR	CCA	140	
LR	IL8 TNF, WBC HMT EOS HAP IL8, IL12 IL8	15	ASGA0070586	120106066	G/A	68,20	0.001/4.77	GEN	CCA, TATES, mvBIMBAM, PCA	120	TNS1, RUFY4, CXCR2, ARPC2, GPBAR1, AAMP, PNKD, TMBIM6
LW	IFN IL10 IL12 IL1b IL4 IL6	11	DRGA0011317	52909023	A/G	63,20	0,00	CHR	PCA	141	
LW	IFN IL10 IL12 IL1b IL4 IL6	11	INRA0036664	53861212	C/A	2,00	0,02	GEN	PCA	141	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	MCV MCHC HAP	18	MARC0016014	6814899	G/A	50,80	0,03	CHR	PCA	141	EPHA1, ZYX, FAM131B, CLCN1, TMEM139, GSTK1, TAS2R40, KEL, TRPV5, TRPV5, TAS2R39, PIP, OR6V1, LLCFC1, EPHB6, PRSS2, TRBV27, U6, TRBV25-1, TRBV19, LOC106508706, LOC100302368, TRBV3-1, PRSS58, LOC100511166, MGAM2
LR	IL8 TNF, WBC HMT EOS HAP IL8, IL12 IL8	15	ASGA0070620	120351434	C/T	41,60	0.03/4.04	GEN	CCA, TATES, mvBIMBAM, PCA	120	
LR	MCV MCHC HAP	18	ASGA0097545	7361550	T/C	24,30	0,05	CHR	PCA	141	
LR	IL8 TNF, WBC HMT EOS HAP IL8	15	ASGA0071003	126072246	C/T	37,00	0,06	GEN	CCA, TATES	123	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	RBC HMG HMT MCV MCH MCHC, HMG MCH, PLT RBC WBC	16	DRGA0015975	24344082	C/T	53,10	0,03	GEN	CCA	126	
LW	RBC HMG HMT MCV MCH MCHC, HMG MCH, PLT RBC WBC	16	ASGA0072751	25032947	C/T	82,10	0,03	GEN	CCA	127	
LW	HMG MCHC, WBC RBC HAP IL1b, PLT RBC WBC	16	MARC0030066	72841711	C/T	38,20	3,35	GEN	mvBIMBAM	131	SEMA5A, U6
LW	RBC HMG HMT MCV MCH MCHC, HMG MCH, HMG MCHC	16	ALGA0091962	73764474	G/A	42,10	0.05/3.05	GEN	CCA, mvBIMBAM	131	
LR	MCV MCHC HAP	18	ASGA0105592	7734440	C/A	24,30	0,06	CHR	PCA	141	
LW	RBC HMG HMT MCV MCH MCHC, HMG MCH, IL8 HMT WBC, WBC RBC HAP IL1b, PLT RBC WBC	16	ASGA0074790	78019054	G/A	99,10	0,01	GEN	CCA, TATES	132	
LW	RBC HMG HMT MCV MCH MCHC, HMG MCH, HMT HMG MCHC, IL8 HMT WBC, WBC RBC HAP IL1b, PLT RBC WBC	16	M1GA0021462	78037702	A/G	7,90	0,04	GEN	CCA	132	
LW	IFN IL10 IL12 IL1b IL4 IL6	11	ALGA0062457	53977790	A/G	98,00	0,02	GEN	PCA	142	
LW	IFN IL10 IL12 IL1b IL4 IL6	11	SIRI0000315	54315287	G/T	0,00	0,02	GEN	PCA	142	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	MCV MCHC HAP	18	MARC0112998	8006092	T/C	0,00	0,06	CHR	PCA	142	CLEC5A, PRSS37, TAS2R4, TAS2R3, SSBP1, WEE2, DENND11, AGK, MEM178B
LW	BAS WBC NEU, LYM NEU EOS BAS	17	ALGA0112929	106110	A/G	55,50	0,04	GEN	CCA, TATES	133	
LR	WBC NEU MON EOS BAS TNF, WBC BAS	17	ALGA0094419	31515709	T/C	4,80	0,01	GEN	CCA, PCA	135	
LR	MCV MCHC HAP	18	ASGA0078747	8204406	C/T	24,10	0,06	CHR	PCA	142	
LW	IL1b IL10 IL12, IL4 IL10 IL1b IL6, IL6 IFN IL10 IL1b	17	MARC0045544	38811036	A/C	19,30	4,48	GEN	mvBIMBAM	137	CEP250
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	17	ASGA0077178	45775572	G/A	59,50	0,05	CHR	CCA	138	PTPRT, U6
LR	MCV MCHC HAP	18	ALGA0096880	8321190	T/G	72,50	0,02	CHR	PCA	142	
LR	MCV MCHC HAP	18	ASGA0078758	8380065	G/A	24,10	0,06	CHR	PCA	142	
LR	MCV MCHC HAP	18	ASGA0078760	8442517	T/C	75,90	0,06	CHR	PCA	142	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	17	ALGA0123186	45833341	A/C	44,70	0,05	CHR	CCA	138	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC	17	ALGA0109744	45890603	C/A	53,70	0,05	GEN	CCA	138	
LW	RBC HMG HMT MCV MCH MCHC, HMT HMG MCHC, MCV MCHC HAP	18	H3GA0050210	2540065	G/A	76,30	0.02/9.44	GEN	CCA, mvBIMBAM, PCA	140	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	MCV MCHC HAP	18	H3GA0050329	9041613	G/A	76,90	0,06	CHR	PCA	143	BRAF, NDUFB2, ADCK2, U6, DENND2A, MKRN1, RAB19, SLC37A3, KDM7A, PARP12, TBXAS1, HIPK2
LR	MCV MCHC HAP	18	ALGA0096968	9386834	C/T	61,30	0,02	CHR	PCA	143	
LR	MCV MCHC HAP	18	H3GA0056352	9871442	A/C	54,30	0,01	CHR	PCA	143	
LW	EOS BAS	11	ASGA0051613	67683899	G/A	88,40	0,02	CHR	PCA	144	SLC15A1
LW	EOS BAS	11	rs342919012	67687842	G/A	NA	0,02	CHR	PCA	144	
LW	EOS BAS	11	rs326593788	67687850	T/C	NA	0,02	CHR	PCA	144	
LW	EOS BAS	11	ALGA0063379	67697289	G/A	11,60	0,02	CHR	PCA	144	
LW	EOS BAS	11	ASGA0051621	67714628	T/C	11,60	0,02	CHR	PCA	144	
LR	MCV MCHC HAP	18	ASGA0078874	10641854	T/C	60,00	0,01	CHR	PCA	144	ZC3HAV1L, KIAA1549, TMEM213, ATP6V0A4, U6, Y RNA, SVOPL, TRIM24
LR	MCV MCHC HAP	18	ALGA0097012	11264864	C/T	89,10	0,02	CHR	PCA	144	
LW	EOS BAS	11	ASGA0051648	68510765	C/T	19,90	0,02	CHR	PCA	145	CLYBL, ZIC5, ZIC2, PCCA, U6, GGACT
LR	IL6 IL10 IL1b	11	ALGA0063462	69323838	G/A	98,10	0,02	CHR	CCA	145	
LR	MCV MCHC HAP	18	INRA0055202	12429018	C/T	82,60	0,04	CHR	PCA	145	CHRM2, ssc-mir-490-1

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	MCV MCHC HAP	18	MARC0030508	13279854	T/G	67,70	0,02	CHR	PCA	145	
LR	RBC HMG HMT MCV MCH, PC3RBCs	18	MARC0072034	6968918	A/G	41,00	0,04	CHR	CCA	141	
LR	IL6 IL10 IL1b	11	M1GA0015299	70370312	C/T	98,50	0,06	CHR	CCA	146	
LR	IL6 IL10 IL1b	11	ALGA0063574	70392258	A/G	97,20	0,06	CHR	CCA	146	
LR	IL6 IL10 IL1b	11	ALGA0063603	70518157	C/T	3,20	0,06	CHR	CCA	146	
LR	IL6 IL10 IL1b	11	H3GA0032472	70572911	G/A	3,70	0,02	CHR	CCA	146	
LR	IL6 IL10 IL1b	11	MARC0051848	71048614	C/T	92,30	0,02	CHR	CCA	146	
LR	IL6 IL10 IL1b	11	MARC0085875	71100401	A/G	92,30	0,02	CHR	CCA	146	
LR	IL6 IL10 IL1b	11	DIAS0003373	71110085	C/T	6,20	0,02	CHR	CCA	146	
LR	MCV MCHC HAP	18	H3GA0050418	14855749	C/T	18,60	0,05	CHR	PCA	146	
LR	MCV MCHC HAP	18	INRA0055273	15706111	A/G	18,00	0,03	CHR	PCA	146	
LR	IL6 IL10 IL1b	11	ALGA0102712	71257051	G/A	3,80	0,02	CHR	CCA	147	
LR	IL6 IL10 IL1b	11	ALGA0102815	71280437	T/C	92,20	0,02	CHR	CCA	147	
LR	RBC HMG HMT MCV MCH	18	MARC0063061	24962723	C/T	37,60	0,03	CHR	CCA	147	AASS, PTPRZ1
LR	RBC HMG HMT MCV MCH	18	ASGA0092854	24990743	C/T	26,80	0,03	CHR	CCA	147	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	MARC0068323	7391549	G/A	69,20	0,03	CHR	CCA, PCA	141	
LW	BAS WBC NEU, LYM NEU MON EOS BAS	18	ALGA0097582	25200554	C/T	83,40	0,03	CHR	CCA	147	
LW	BAS WBC NEU, LYM NEU MON EOS BAS	18	ASGA0079343	25373224	C/T	17,00	0,05	CHR	CCA	147	
LR	IL6 IL10 IL1b	11	ASGA0051917	73150897	G/A/T	93,70	0,06	CHR	CCA	148	
LR	MCV MCHC HAP	18	H3GA0051025	46713612	A/G	22,00	0,06	CHR	PCA	148	
LR	IL6 IL10 IL1b	11	INRA0037562	76483089	A/G	98,10	0,02	CHR	CCA	149	
LR	RBC HMG HMT MCV MCH	18	MARC0025541	50663391	A/G	44,90	0,03	CHR	CCA	149	POLM
LR	WBC HMT EOS HAP IL8	18	H3GA0051155	50710948	T/C	7,20	0,02	GEN	CCA	149	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	NEU RBC WBC MON BAS	18	ASGA0080341	51353492	G/A	9,50	0,04	CHR	CCA	149	
LW	LYM NEU MON EOS BAS	12	M1GA0026919	7396035	C/A	18,80	4,80	GEN	mvBIMBAM	150	
LR	IFN IL12 IL8	12	ALGA0064792	9141861	T/C	8,60	0,05	CHR	PCA	151	
LW	IL4 IL10 IL1b IL6	12	ASGA0105686	9540202	G/A	39,30	3,07	GEN	mvBIMBAM	151	
LR	IL4 EOS IL10 IL1b TNF	12	M1GA0027137	11878926	A/G	4,70	0,04	CHR	CCA	152	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	ASGA0092914	7397094	A/C	30,80	0,03	CHR	CCA, PCA	141	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	ASGA0078726	7404576	A/G	69,20	0,03	CHR	CCA, PCA	141	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	ALGA0096832	7541311	G/C	26,40	0,03	CHR	CCA, PCA	141	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	ALGA0105511	7717391	C/T	55,70	0,06	GEN	CCA, PCA	141	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	ALGA0121880	7775625	G/A	73,20	0,04	CHR	CCA, PCA	141	
LR	IL4 EOS IL10 IL1b TNF, PC3Cyto	12	MARC0070276	14204868	G/A	92,10	0,01	CHR	CCA	154	BPTF
LR	IL4 EOS IL10 IL1b TNF	12	ALGA0065378	17196251	G/A	2,60	0,01	CHR	CCA	155	MAPT
LR	NEU RBC WBC MON BAS	12	DIAS0003753	21492055	G/A	77,80	0,06	CHR	CCA	156	
LW	IL4 IL10 IL1b IL6	12	ALGA0065672	24650734	T/C	0,60	4,71	GEN	mvBIMBAM	157	SKAP1
LW	IFN IL10 IL12 IL1b IL4 IL6	12	ASGA0082570	38304022	G/T	3,00	0,01	CHR	PCA	158	
LW	IFN IL10 IL12 IL1b IL4 IL6	12	MARC0092718	40705609	T/C	0,00	0,06	CHR	PCA	159	
LW	IFN IL8 TNF	12	MARC0087562	42225466	T/C	80,60	0,02	CHR	PCA	160	MYO1D
LW	IFN IL10 IL12 IL1b IL4 IL6	12	ALGA0108238	42366158	T/C	13,30	0,01	CHR	PCA	161	MYO1D
LW	IFN IL8 TNF	12	ALGA0066551	42419728	T/C	30,60	0,02	CHR	PCA	161	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW	IFN IL8 TNF	12	MARC0072172	43987384	G/A	80,60	0,02	CHR	PCA	162	KSR1, NOS2, NLK, TMEM97, IFT20, TNFAIP1, VTN, POLDIP2, TMEM199, SEBOX, SARM1, SLC46A1, SLC13A2, FOXN1, UNC119, PIGS, ALDOC, SPAG5, KIAA0100, KIAA0100, SDF2, SUPT6H, PROCA1, RAB34, RPL23A, SNORD42, TLCD1, SNORD4A, SNORD4B, NEK8, TRAF4, U6, FAM222B, ERAL1, ssc-mir-451, ssc-mir-144, FLOT2, DHRS13, PHF12, SEZ6, PIPOX, CRYBA1

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL6 IL10 IL1b	12	ALGA0066685	45415984	T/C	77,80	0,06	CHR	CCA	162	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	ALGA0118449	7777685	C/A	35,50	0,04	CHR	CCA, PCA	141	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	DIAS0001617	8165185	T/C	57,50	0,03	CHR	CCA, PCA	142	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	ALGA0096869	8190336	A/G	57,50	0,03	CHR	CCA, PCA	142	
LR	NEU RBC WBC MON BAS	12	ASGA0101646	60019204	T/C	46,00	0,06	CHR	CCA	164	
LR	NEU RBC WBC MON BAS	12	ALGA0107813	62837875	A/G/T	66,50	0,03	CHR	CCA	165	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	M1GA0023025	8250254	C/T	73,90	0,03	CHR	CCA, PCA	142	
LR	HMT HMG MCHC	13	MARC0065723	167096459	T/C	19,80	0,05	CHR	CCA	167	
LR	HMT HMG MCHC	13	ALGA0072888	174636996	C/T	6,40	0,05	CHR	CCA	168	
LR	HMT HMG MCHC	13	DRGA0013179	177439207	T/G	1,70	0,05	CHR	CCA	169	ROBO2
LR	WBC NEU MON EOS BAS TNF	13	ASGA0059913	198394220	T/C	91,00	0,04	GEN	CCA	170	RUNX1
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	rs339209283	8264050	T/C	NA	0,03	CHR	CCA, PCA	142	
LR	LYM MON BAS	14	ASGA0063055	42631536	C/T	39,70	0,03	CHR	PCA	172	SGSM1, PIWIL3, TMEM211, KIAA1671, CRYBB3, CRYBB2, GRK3, U6

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	LYM MON BAS	14	DIAS0001091	42951477	C/T	72,10	0,03	CHR	PCA	172	
LR	LYM MON BAS	14	H3GA0040005	43387115	G/A	72,30	0,03	CHR	PCA	172	
LR	LYM MON BAS	14	ALGA0077324	44752740	C/T	75,00	0,05	CHR	PCA	173	MN1, PITPNB, TTC28
LR	LYM MON BAS	14	ALGA0077342	45036066	T/C	75,60	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ASGA0063176	45080096	A/C	76,10	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	MARC0061666	45126379	G/A	22,30	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ALGA0077352	45167309	C/T	22,30	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ASGA0063186	45182965	T/C	77,70	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ASGA0063188	45211762	A/C	77,80	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ALGA0077360	45237972	C/T	77,70	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	MARC0021603	45277886	G/A	22,30	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ASGA0063192	45329416	T/C	22,30	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ASGA0063198	45347247	A/G	76,70	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ASGA0063199	45359541	A/C	23,90	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	MARC0006658	45412495	G/T	76,70	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	MARC0081626	45577136	T/G	18,60	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ASGA0063205	45602780	C/T	75,40	0,03	CHR	PCA	173	
LR	LYM MON BAS	14	ALGA0077379	45795115	G/A	23,30	0,03	CHR	PCA	174	TTC28

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	LYM MON BAS	14	MARC0047822	45827810	T/C	23,30	0,03	CHR	PCA	175	TTC28, U1, CHEK2, HSCB, CCDC117, XBP1, ZNRF3, C22orf31, KREMEN1, EMID1, RHBDD3, EWSR1, GAS2L1, RASL10A, AP1B1, SNORD125
LR	LYM MON BAS	14	ALGA0077382	46031357	A/C	76,70	0,03	CHR	PCA	175	
LR	LYM MON BAS	14	INRA0043964	46418356	G/A	23,30	0,03	CHR	PCA	175	
LR	LYM MON BAS	14	DBNP0002145	46436960	C/T	76,70	0,03	CHR	PCA	175	
LR	LYM MON BAS	14	ALGA0077394	46473900	G/A	76,70	0,03	CHR	PCA	175	
LR	LYM MON BAS	14	MARC0048650	46520497	A/G	40,40	0,03	CHR	PCA	175	
LR	LYM MON BAS	14	ASGA0063175	47751439	G/A	24,90	0,04	CHR	PCA	176	
LR	HMT HMG MCHC	14	H3GA0040407	57739629	C/T	26,80	0,02	CHR	CCA	177	
LR	HMT HMG MCHC	14	ALGA0077929	57765084	C/T	26,60	0,02	CHR	CCA	177	
LR	HMT HMG MCHC	14	MARC0013023	59263540	C/A	12,60	0,01	GEN	CCA	178	TRIM67, FAM89A, ARV1, TTC13, C1orf198, CAPN9, AGT, COG2
LR	HMT HMG MCHC	14	ASGA0063815	59277912	T/C	30,40	0,01	GEN	CCA	178	
LR	HMT HMG MCHC	14	ALGA0078088	59646142	C/T	30,80	0,00	CHR	CCA	178	
LR	HMT HMG MCHC	14	ALGA0078075	59656180	T/C	30,90	0,00	CHR	CCA	178	
LR	HMT HMG MCHC	14	ALGA0106769	59712299	T/C	11,30	0,02	CHR	CCA	178	
LR	HMT HMG MCHC	14	MARC0004519	59803997	A/C	65,30	0,00	CHR	CCA	179	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	HMT HMG MCHC	14	ALGA0078091	59831072	G/A	71,40	0,00	CHR	CCA	179	
LR	HMT HMG MCHC	14	ALGA0079175	79949671	G/A/T	9,50	0,03	CHR	CCA	180	KCNMA1
LR	HMT HMG MCHC	14	ALGA0079177	79982953	C/T	9,50	0,03	CHR	CCA	180	
LR	LYM MON BAS	14	ALGA0083196	137654632	C/T	89,30	0,04	CHR	PCA	181	
LR	HMT HMG MCHC	15	MARC0113166	22554502	G/T	0,00	0,06	CHR	CCA	182	
LR	HMT HMG MCHC	15	ASGA0068971	22571234	A/C	30,00	0,06	CHR	CCA	182	
LR	HMT HMG MCHC	15	ALGA0102752	23400874	G/A	75,60	0,06	CHR	CCA	182	
LR	RBC HMG HMT MCV MCH, PC3RBCs	18	MARC0007516	8567714	A/G	34,40	0,04	CHR	CCA	142	
LR	IL8 TNF	15	ALGA0086618	107604568	A/G	14,50	0,05	CHR	CCA	184	PARD3B, U6
LR	IL8 TNF	15	DRGA0015341	107753847	C/A	83,50	0,05	CHR	CCA	184	
LR	IL8 TNF	15	MARC0089453	107887493	T/G	34,30	0,06	CHR	CCA	184	
LR	IL8 TNF	15	ALGA0086631	108024616	T/G	46,70	0,01	CHR	CCA	184	
LR	IL8 TNF	15	ALGA0108737	108335353	G/A	48,80	0,04	GEN	CCA	184	
LR	IL12 IL8	15	H3GA0044814	108472427	A/G	53,70	0,04	CHR	PCA	184	
LR	IL12 IL8	15	DRGA0015357	108505209	C/A	53,00	0,04	CHR	PCA	184	
LR	RBC HMG HMT MCV MCH, MCV MCHC HAP	18	ALGA0096931	8587608	T/G	23,60	0,03	CHR	CCA, PCA	142	

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	IL8 TNF, PC2Cyto	15	ASGA0070317	108794926	G/C	32,30	0,05	CHR	CCA	185	
LR	IL8 TNF	15	H3GA0044820	108848114	C/T	39,60	0,04	CHR	CCA	185	
LR	IL8 TNF	15	ASGA0093834	109215027	T/C	14,30	0,05	CHR	CCA	185	
LR	IL8 TNF	15	ALGA0086678	109394965	G/A	50,70	0,05	GEN	CCA	185	
LR	IL8 TNF	15	ALGA0086703	109971469	C/T	60,00	0,01	CHR	CCA	186	DYTN
LR	BAS MON	15	ALGA0086800	112624977	C/T	90,10	0,01	GEN	CCA	187	UNC80
LW	BAS WBC NEU, LYM NEU MON EOS BAS	18	DRGA0016945	25162286	C/T	16,60	0,03	CHR	CCA	147	
LW	LYM NEU MON EOS BAS	15	ALGA0086932	117196535	G/A	47,70	0,01	CHR	CCA	189	
LR	IL8 TNF	15	H3GA0044951	119984036	T/C	59,10	0,06	CHR	CCA	190	TNS1
LR	IL8 TNF	15	ASGA0070560	119995203	A/G	40,00	0,06	CHR	CCA	190	
LW	RBC HMG HMT MCV MCH MCHC	NA	ALGA0014284	NA	T/C	57,50	0,03	CHR	CCA		
LR, LW	BAS MON, IL4 IL10 IL1b IL6, NEU RBC WBC MON BAS	NA	ALGA0073579	NA	C/T	10,50	0.01/3.22	GEN	CCA, TATES, mvBIMBAM		

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	NA	DRGA0006288	NA	NA	1,10	0,00	GEN	CCA, TATES		
LR	IL4 EOS IL10 IL1b TNF	NA	ALGA0046492	NA	C/T	84,90	0,02	CHR	CCA		
LR	HMT HMG MCHC	NA	ALGA0072783	NA	G/A	19,80	0,05	CHR	CCA		
LR	RBC HMG HMT MCV MCH, HMG MCHC IL10, HMT HMG MCHC	NA	INRA0020540	NA	NA	98,90	0,00	GEN	CCA, TATES		
LW	RBC HMG HMT MCV MCH MCHC	NA	ALGA0102592	NA	G/A	33,00	0,05	CHR	CCA		
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	NA	ALGA0031749	NA	C/T	32,50	0,03	CHR	CCA		
LW	LYM NEU MON EOS BAS	NA	ALGA0105830	NA	G/A	59,40	0,02	CHR	CCA		
LR	RBC HMG HMT MCV MCH, HMT HMG MCHC	NA	ALGA0031838	NA	G/T	30,50	0,04	CHR	CCA		
LW	RBC HMG HMT MCV MCH MCHC	NA	ALGA0120738	NA	G/A	92,80	0,02	CHR	CCA		
LR	WBC BAS	NA	ALGA0122704	NA	A/G	1,40	0,01	GEN	PCA		
LR	BAS MON	NA	ASGA0011563	NA	C/T	31,40	0,05	GEN	CCA		
LR	WBC NEU MON EOS BAS TNF	NA	ASGA0046381	NA	T/G	14,20	0,03	CHR	CCA		
LR	WBC NEU MON EOS BAS TNF	NA	ASGA0096826	NA	T/C	79,80	0,05	GEN	CCA		
LR	IL8 TNF	NA	ASGA0102483	NA	C/T	48,80	0,04	GEN	CCA		
LW	RBC HMG HMT MCV MCH MCHC	NA	ASGA0102908	NA	T/C	44,10	0,05	CHR	CCA		
LW	IFN IL8 TNF	NA	CASI0003808	NA	NA	1,00	0,03	GEN	PCA		
LR	RBC HMG HMT MCV MCH	NA	DBWU0000913	NA	G/A	49,70	0,01	CHR	CCA		
LR	IL6 IL10 IL1b	NA	DIAS0000434	NA	G/A	22,70	0,03	CHR	CCA		
LR	RBC HMG HMT MCV MCH	NA	DIAS0000994	NA	NA	98,00	0,04	CHR	CCA		
LR	IL4 EOS IL10 IL1b TNF	NA	DRGA0006061	NA	NA	1,60	0,01	GEN	CCA		

Breed	Trait	SSC	SNP	Position	m/M allele	MAF	P-value/ BF	Type of significance	Method	QTL	Nearest Gene within QTL
LW, LR	HMG MCH, WBC BAS, PLT RBC WBC	NA	H3GA0016899	NA	T/C	90,30	0,04	CHR	CCA, PCA		
LR	NEU RBC WBC MON BAS	NA	FBF0127SLC47A1	NA	NA	NA	0,06	CHR	CCA		
LW	RBC HMG HMT MCV MCH MCHC	NA	H3GA0000686	NA	G/A	24,20	0,05	CHR	CCA		
LW	RBC HMG HMT MCV MCH MCHC	NA	H3GA0000711	NA	G/A	25,90	0,05	CHR	CCA		
LR	WBC HMT EOS HAP IL8	NA	H3GA0009907	NA	A/G	9,40	0,02	CHR	CCA		
LW	HMG MCH, PLT RBC WBC	NA	ALGA0103880	NA	T/C	94,10	0,04	CHR	CCA		
LR	HMT HMG MCHC	NA	INRA0019232	NA	T/C	28,30	0,03	CHR	CCA		
LR	RBC HMG HMT MCV MCH	NA	INRA0020434	NA	T/C	50,90	0,06	CHR	CCA		
LW	HMG MCH, PLT RBC WBC	NA	ALGA0115368	NA	T/C	6,20	0,04	CHR	CCA		
LR	MCV MCHC HAP	NA	M1GA0023051	NA	T/C	39,40	0,01	CHR	PCA		
LR	IL4 EOS IL10 IL1b TNF	NA	MARC0001707	NA	T/C	25,90	0,02	CHR	CCA		
LR	WBC NEU MON EOS BAS TNF	NA	MARC0010639	NA	C/T	79,80	0,05	GEN	CCA		
LR	WBC HMT EOS HAP IL8	NA	MARC0013233	NA	C/T	90,70	0,02	CHR	CCA		
LR	LYM MON BAS	NA	MARC0030251	NA	T/C	76,70	0,03	CHR	PCA		
LW	RBC HMG HMT MCV MCH MCHC	8	rs323551662	41838395	C/G	NA	0,03	CHR	CCA		
LR	IFN IL12 IL8	NA	SIRI0000276	NA	NA	0,00	0,03	CHR	PCA		
LW	IFN IL8 TNF	NA	SIRI0001107	NA	NA	0,00	0,03	GEN	PCA		

SSC=*Sus scrofa* chromosome, SNP=single nucleotide polymorphism, m/M allele=minor/major allele, MAF=minor allele frequency, QTL nr.=Quantitative trait loci progressive number based on ±1Mbp distance from a significant SNP, LR=Landrace, LW=Large White, RBC=red blood cells, HMG=hemoglobin, HMT=hematocrit, MCV= mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, PLT=platelets, WBC=white blood cells, NEU=neutrophils, LYM=lymphocytes, MON=monocytes, EOS=eosinophils, BAS=basophils, HAP=haptoglobin, IFN-γ= interferon-γ, IL=interleukin, TNF-α= tumor necrosis factor- α , PC=principal component, CCA=canonical correlation analysis, PCA=principal component analysis.

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Roth K.; Pröll-Cornelissen M, J.; Heuß E. M.; Dauben C. M.; Henne H.; Appel A. K.; Schellander K., Tholen E.; Große-Brinkhaus C. (2022): Genetic parameters of immune traits for Landrace and Large White pig breeds. PLOS One.

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