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Genetic basis of reproductive performance and antibody response in pigs during a porcine reproductive and respiratory syndrome outbreak

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To my beloved parents, this is for you.

As the island of knowledge grows, so do the shores of our ignorance – the boundary between the known and unknown. Learning more about nature does not lead to a final destination but to more questions and mysteries. The more we know, the more exposed we are to our ignorance, and the more we know to ask. The goal of science then is to clarify, to the best of our knowledge, the way nature works.

- Marcelo Gleiser

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Nomenclature

APOBEC3B	Apolipoprotein B mRNA editing enzyme catalytic subunit 3B gene
Chr	Chromosome
EIF3L	Eukaryotic translation initiation factor 3 subunit L gene
ELISA	Enzyme-linked immunosorbent assay
E_{NBA}	Efficiency of correlated response to selection for increased NBA
FYW	Farrow-year-week
GALC	Galactosylceramidase enzyme
GEBV	Genomic estimated breeding value
GLIPR1L1	GLIPR1-like protein 1 gene
GLIPR1L2	GLIPR1-like protein 2 gene
GPA	Genomic prediction accuracy
GPS	Genomic prediction scenario
GPR65	G protein-coupled receptor 65
GRM	Genomic relationship matrix
GV	Genetic variance
GWAS	Genome-wide association studies
LD	Linkage disequilibrium
Mb	Megabase
MCMC	Markov Chain Monte Carlo
MHC	Major Histocompatibility Complex
MLV	Modified live virus
NBA	Number of piglets born alive
NBD	Number of piglets born dead
NM	Number of mummified piglets

NSB	Number of stillborn piglets
NW	Number of weaned piglets
PDGFB	Platelet-derived growth factor subunit B gene
PRRS	Porcine reproductive and respiratory syndrome
PRRSV	Porcine reproductive and respiratory syndrome virus
QTL	Quantitative trait loci
SNP	Single nucleotide polymorphisms
SOX10	SRY-box transcription factor 10 gene
SPATA17	Spermatogenesis associated 17 gene
S/P	Sample-to-positive ratio
SSC	*Sus scrofa* chromosome
TGVM	Total genetic variance accounted for by the markers
TNB	Total number of piglets born

Genetic basis of reproductive performance and antibody response in pigs during a porcine reproductive and respiratory syndrome outbreak[1]

Author: Felipe Mathias Weber Hickmann
Advisor: José Braccini Neto
Co-Advisor: Nick Serão

Abstract

Total antibody response, measured as sample-to-positive ratio (S/P ratio), has been proposed as an indicator trait to improve reproductive performance in pigs infected with the porcine reproductive and respiratory syndrome (PRRS) virus (PRRSV). The objectives of this work were to evaluate the genetic basis of reproductive performance in pigs and to perform host-genetic analyses for S/P ratio in Duroc and Landrace sows that experienced a PRRS outbreak. Serum samples were taken from 1231 purebred sows (690 Duroc and 541 Landrace) after a PRRS outbreak for subsequent PRRSV ELISA analysis and SNP genotyping. These sows had 29799 SNP genotypes one, with farrowing performance data during the outbreak on: number of piglets born alive (NBA), stillborn piglets (NSB), mummified piglets (NM), piglets born dead (NBD; NSB+NM), total number of piglets born (TNB; NBA+NBD), and piglets weaned (NW). Heritability and genome-wide association studies (GWAS) were performed for S/P ratio and reproductive traits, separately per breed. Genomic prediction accuracies (GPA) were obtained for each trait within and between breeds. Heritability estimates (±standard error) of S/P ratio during the PRRS outbreak were moderate, with 0.35±0.08 for Duroc and 0.34±0.09 for Landrace. For S/P ratio, the GWAS identified a major quantitative trait locus (QTL) on chromosome (chr) 7 [24-25 megabases (Mb)] explaining 15% of the genetic variance (GV), and one on chr 8 (25 Mb) explaining 2.4% GV for Duroc. For Landrace, GWAS identified a QTL on chr 7 (23-24 Mb) explaining 31% GV, and another one on chr 7 (108-109 Mb) explaining 2.2% GV. Heritability estimates for reproductive traits were overall low for both breeds. Favorable genetic correlations between S/P ratio with NBA (0.61±0.34) and NBD (-0.33±0.32) were observed for Landrace sows during the PRRS outbreak. Few QTL were identified in Duroc and Landrace sows for reproductive traits. GPA were moderate to high for S/P ratio for the within-breed prediction. On the other hand, GPA were low to moderate for most reproductive traits. The results indicate that reproductive traits are lowly heritable during a PRRS outbreak with few QTL identified in Duroc and Landrace sows. These results also validate previous studies that S/P ratio in PRRSV-infected sows is heritable and favorably genetically correlated with some reproductive traits during a PRRS outbreak. S/P ratio has then the potential to be used as an indicator trait to improve the reproductive performance of PRRSV-infected sows.

Keywords: PRRS, swine, genomics, S/P ratio, reproduction, antibody response

[1]Master of Science dissertation in Animal Science. Faculty of Agronomy, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil. (144 p.), May, 2020.

Bases genéticas do desempenho reprodutivo e da produção de anticorpos de matrizes durante um surto da síndrome reprodutiva e respiratória dos suínos[2]

Autor: Felipe Mathias Weber Hickmann
Orientador: José Braccini Neto
Coorientador: Nick Serão

Resumo

A produção total de anticorpos (*Sample-to-Positive ratio*; S/P ratio) vem sendo proposta como uma característica indicadora para melhorar o desempenho reprodutivo de porcas infectadas com o vírus da PRRS (PRRSV). Os objetivos deste trabalho foram avaliar a base genética do desempenho reprodutivo de matrizes suínas durante um surto de PRRS e a sua relação com o sistema imune. Amostras de sangue foram coletadas de 1231 porcas de raça pura (690 Duroc e 541 Landrace) após um surto de PRRS para a realização do teste ELISA e posterior genotipagem. Essas matrizes tiveram dados de desempenho reprodutivo coletados durante o surto da doença em relação ao número de leitões nascidos vivos (NBA), natimortos (NSB), mumificados (NM), nascidos mortos (NBD; NSB + NM), total de nascidos (TNB; NBA + NBD) e desmamados (NW), sendo genotipadas para 29799 marcadores do tipo SNPs. As estimativas de herdabilidade e os estudos de associação genômica ampla (GWAS) foram realizados para S/P ratio e características reprodutivas para cada raça separadamente. As estimativas de herdabilidade (±erro padrão) de S/P ratio durante o surto de PRRS foram moderadas, com 0,35±0,08 para Duroc e 0,34±0,09 para Landrace. Para S/P ratio, o GWAS identificou um importante *locus* de característica quantitativa (QTL) no cromossomo (chr) 7 [24-25 megabases (Mb)], explicando 15% da variação genética (VG) e outro no chr 8 (25 Mb) explicando 2,4% VG para Duroc. O GWAS também identificou dois QTLs no chr 7 (23-24 Mb; 108-109 Mb) explicando, respectivamente, 31% e 2.2% VG para Landrace. As estimativas de herdabilidade para as características reprodutivas foram, de modo geral, baixas nas duas raças. Correlações genéticas favoráveis foram observadas entre S/P ratio e NBA (0.61±0.34) e NBD (-0.33±0.32) em porcas da raça Landrace durante o surto da doença. Poucos QTL foram identificados para características reprodutivas em porcas das raças Duroc e Landrace. Acurácias de Predição Genômica (APG) foram medianas a altas para S/P ratio em SNP_{All}, SNP_{MHC} e SNP_{Rest} para a predição dentro da raça. No entanto, APG foram baixas para características reprodutivas. Os resultados indicam que as características reprodutivas apresentam baixa herdabilidade durante o surto de PRRS, com poucos QTL identificados. Estes resultados validam a utilização de S/P ratio como uma característica indicadora, herdável e geneticamente correlacionada com características reprodutivas de interesse durante um surto de PRRS.

Palavras-chave: PRRS, genômica, S/P ratio, reprodução, resposta imune

[2]Dissertação de mestrado em Zootecnia – Produção Animal, Faculdade de Agronomia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brasil. (144 p.), Maio, 2020.

Introduction

Pork production in the United States has consistently evolved over the past few decades and is predominated by indoor confinement systems in which pigs are raised in large operation sites (USDA, 2017). Pig farms in the US became larger in size, but fewer in numbers. Similar trend has been also reported in South America and Europe. This is the result of the rapid industrialization of pork production over the years driven mainly by advances in technology (Pork Checkoff, 2014).

Modern pork production happens through a chain of events that usually starts from the production of breeding stocks and ends with pork products being sold to the market. The efficient production of high-quality pork, however, has been disrupted by the occurrence of diseases and health problems several times (Rothschild, 2000). Health has been listed as the major area of concern by US pig farmers (Pork Checkoff, 2020). According to Holtkamp et al. (2013), Porcine Reproductive and Respiratory Syndrome (PRRS) has been reported as the most important swine disease in the US that causes substantial economic losses to the US swine industry every year. This disease affects the immune system of pigs of all ages and decreases the reproductive performance in breeding animals (Serão et al., 2014; Lunney et al., 2016; Putz et al., 2019; Montaner-Tarbes et al., 2019).

According to Rothschild (2020), genetics played a significant role to alter the pig industry in the past. The author states that the future holds much promise, too. It appears that the speed of technological changes applied to animal breeding and genetics has not reached a plateau. Modern technologies such as gene mapping, gene editing, and cloning will continue to advance, producing pigs of outstanding performance (Dekkers, Mathur & Knol, 2011). Scientists have already genetically engineered pigs immune to the PRRS virus (PRRSV), however, as of today, this editing technology has not been implemented into commercial operations. (Whitworth et al., 2016; Burkard et al., 2018).

On the other hand, there is still a need to explore other methods such as genetic and genomic selection for disease resistance to reduce the negative effects caused by diseases in swine. An alternative method to deal with swine diseases and resurgent outbreaks would be through the selection of animals that are genetically superior during exposure to diseases since traditional approaches such as vaccination, medication, sanitation, and biosecurity procedures have shown limited success (Dekkers et al., 2017). A greater level of understanding of how pigs genetically respond to diseases would help the swine industry not only increase its productivity, but also improve animal welfare and food security.

Chapter I. Literature review

Porcine Reproductive and Respiratory Syndrome (PRRS)

PRRS has consistently been reported as one of the most important swine diseases worldwide. In the US alone, the disease costs to producers more than $660 million annually (Holtkamp et al., 2013). The exact origin of the disease is still unknown, however, it emerged in the late 1980's in the US when veterinarians reported a mystery disease that was causing reproductive failure, pneumonia, and reduced growth performance in pigs (Loula, 1991).

The PRRS virus (PRRSV) is the etiological agent of the disease. Two strains of PRRSV that are biologically and genetically different have been reported (Nelson et al., 1993). The European strain (type 1) is associated with reproductive failure, while the North American strain (type 2) causes a systemic infection that affects the reproductive performance of sows and growth in younger pigs. Both strains share some clinical signs related to reproductive performance that have been widely reported in the literature (Figure 1.A). They include abnormal estrus cycle, late-term abortion, earlier farrow, and increased number of stillbirths and mummified fetuses (Rossow et al., 1999; Lunney et al., 2011).

A major symptom that is also associated with PRRS is febrile response, which usually occurs within 3-5 days of infection (Greiner et al. 2000). The increased core body temperature is a defense mechanism to reduce pathogen proliferation and survival that is energetically costly to animals (Earn, Andrews & Bolker, 2014). Additionally, PRRSV also replicates in blood vessels particularly in the umbilical cord and alveoli. This affects the pig's respiratory system, especially those at young age. PRRS has had several names over the years such as the mystery swine disease and the blue ear disease. Blue because of the discoloration that characterizes its respiratory form (Figure 1.B).

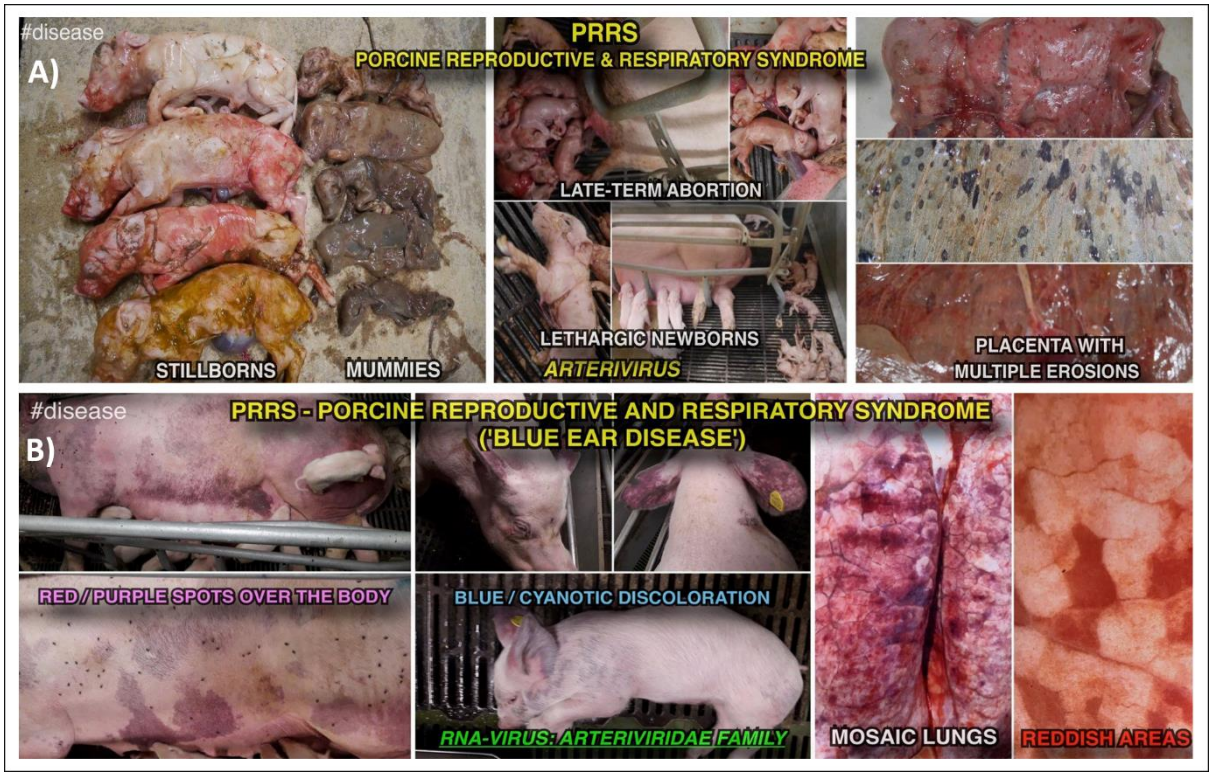

Figure 1. *Clinical signs of PRRS. Infection with PRRSV have two different sets of clinical signs: reproductive (A) and respiratory (B) syndromes. The reproductive performance in sows is affected by an increase in the number of stillbirths and mummified fetuses, late-term abortion, lethargic newborns, and placenta with multiple erosions following infection. Younger piglets have their respiratory system compromised after the replication of PRRSV in blood vessels (Shchetynskyi, 2019).*

The pattern of PRRS has changed over time from sudden outbreaks to constant occurrences (i.e., endemic stage) in the US. There is no single strategy to control the disease as well as no single treatment for PRRS. The current efforts to successfully control the disease have not meet expectations though. The main reasons for that are the failures in biosecurity procedures, limited success of vaccines, and the high mutation rate of PRRSV. Previously infected herds can have new outbreaks with different strains, which makes it even harder to control (Brar et al., 2014). Overall, a systematic approach to successfully deal with PRRSV is needed at both herd and individual level. In other words, identify desired goals, understand current constraints, develop solution options, and implement preferred ones.

Breeding for PRRSV-resilient pigs

In pig breeding programs, breeding for improved disease resistance is more challenging than breeding for improved performance traits. This is mainly due to the difficult in measuring the animal's resistance to a specific disease (Rothschild, 2000). Selection for improved health and welfare has traditionally been made for host resistance; however, the alternative concept of host tolerance has recently gained attention (Guy, Thomson & Hermesch, 2012). To avoid misunderstandings, it is necessary to be clear about the terminology being used. Resistance is associated with the ability of an animal to prevent infection or to limit the replication of a given pathogen (Best, White & Boots, 2008). On the other hand, tolerance has been defined as the host's ability to maintain performance at a given level of infection (Bishop et al., 2010). Another relatively new term to animal breeders is resilience. However, in contrast to resistance and tolerance that are based on the immunogenetics literature, resilience does not necessarily consider pathogen load, being associated with the capability of recovery. Resilience combines both resistance and tolerance concepts (Putz, 2019). Most terms listed are relative, not absolute. For instance, resistance does not mean animals completely resistant to infection due to the fact that it is almost impossible to have an animal that is resistant to all kind of pathogens.

Breeding for PRRSV-resilient pigs would help the US swine industry to maintain its high level of productivity, reducing the negative effects caused by this disease. Novel traits and efficient strategies that would allow the genetic selection for improved PRRSV-resilience are desirable. Antibody level is a trait that is often used in infectious disease studies due to the fact that antibodies are proteins of the immune system that present themselves when exposed to pathogens. Recent reports have shown that antibody response to PRRSV is a heritable trait that we can select for (Serão et al., 2014). It would be also desirable to select in uninfected pigs a trait that is correlated with response in PRRSV-infected animals, such as

antibody response to PRRSV vaccination, as suggested by Sanglard et al. (2020a). These novel traits and brand new breeding strategies were added to the breeding toolbox. They will offer in the feature a bunch of new opportunities to breed for disease resilience in swine.

Genetics of reproductive traits

Reproductive traits in pigs, such as litter size, ovulation rate, and age of puberty are important to modern pork production systems to maintain high levels of reproductive efficiency and performance (Bidanel, 2011). Genetics plays a significant role in the reproduction of the pig. Therefore, it is important to understand the genetic basis underlying these reproductive traits to maximize not only efficiency, performance, and profitability, but also animal welfare.

Almost all reproductive traits may be affected by infectious diseases. PRRS has gained a lot of attention in recent years because it greatly affects these traits. The use of genetics to select pigs that are resistant or more resilient to PRRS for improved reproductive performance have been recently reported (Serão et al., 2014; Serão et al., 2016; Putz et al., 2019; Scanlan et al., 2019; Sanglard et al., 2020b). These studies indicated that reproductive traits in commercial sows infected with PRRSV have low heritability estimates, which means that genetic selection for these traits is limited.

Commercial breeders and companies have developed maternal and terminal lines by crossing different breeds and lines for improved performance. Dam lines have been developed for improved reproductive performance, while sire lines for growth and performance (Rothschild, 1996). Sows have been selected for increased litter size with consequences for the welfare of both sows and piglets. There has been a steady increase in sow litter size over the last years resulted from improvements in breeding, use of superior

genetic lines, and crossbreeding to benefit from heterosis and complementarity (Soede & Kemp, 2019).

Advances in technology and new genetic discoveries applied to disease resistance and improved reproductive performance in pigs are expected. Genetic improvement of reproductive traits can be achieved if the genes controlling these traits could be manipulated directly. Gene editing is a promise that can potentially be used on a large scale, lowering costs; however, it is still depended on congressional approval, legal regulation, among others. On the other hand, genomic selection has been shown to improve the accuracy of traditional genetic evaluations (Van Eenennaam et al., 2014). It is no longer a promise. It is already a reality that is leading to structural changes in the swine industry (Meuwissen, Hayes & Goddard, 2001). Figure 2 exemplifies how the pig breeding pyramid has adapted for selection of pure lines for crossbred performance based on the advances in genomic selection.

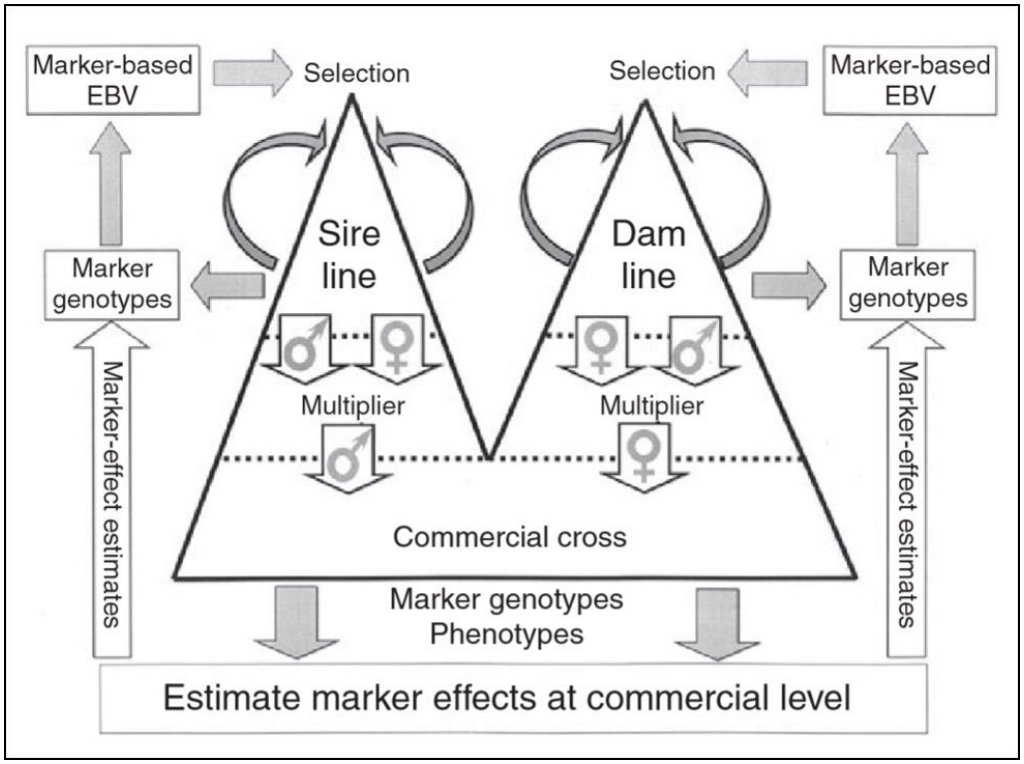

Figure 2. *Pig breeding pyramid adapted for selection of pure lines for crossbred performance to incorporate the advances in genomic selection (Dekkers, Mathur & Knol, 2011).*

Selection for improved reproductive performance under PRRS

In an attempt to improve reproductive traits in PRRSV-infected pigs and reduce the impacts caused by PRRS, the genetic improvement of pigs has been looking for characteristics that can be used to improve the accuracy of selection for reproduction, which has low heritability. An alternative approach to reduce the impact of PRRSV is through the genetic selection of animals that respond best when infected with PRRSV.

Recent work in breeding sows infected with PRRSV (Serão et al., 2014; Rashidi et al., 2014; Putz et al., 2019; Scanlan et al., 2019) show that reproductive traits are lowly heritable. However, Serão et al. (2014) found that total antibody response to PRRSV, measured as sample-to-positive (S/P) ratio, through a commercial enzyme-linked immunosorbent assay (ELISA), has high heritability (45%) and high positive genetic correlation (0.7) with the number of piglets born alive, which is a characteristic of low heritability (<0.10), during infection with PRRSV.

These authors thus suggested that S/P ratio has the potential to be used as a selection tool to improve the reproductive performance of animals infected with PRRSV. According to Serão et al. (2014), the genetic gain efficiency for reproduction is 64% higher when animals are selected based on S/P ratio compared to direct selection for reproductive performance. This indicates that genetic selection for reproductive performance is more effective when selecting for antibodies than directly for piglets born alive during infection.

In addition, using more than 50,000 markers of the Single Nucleotide Polymorphisms (SNP) type, Serão et al. (2014) also discovered two genomic regions (Quantitative Trait Loci; QTL) on swine chromosome 7 (*Sus scrofa*; SSC), which explained more than 40% of the genetic variance. One of the regions explained 25% of this variation, between megabases (Mb) 24 and 30, including the major histocompatibility complex (Major Histocompatibility Complex, MHC), the densest region of genes in the mammalian genome, which includes

genes with an important role for the immune and reproductive system in pigs (Lunney et al., 2009). The other QTL, located between 128 and 130 Mb, explained 15% of the genetic variance. Serão et al. (2014) reported few genes playing a role for reproduction within this region, with alleles in linkage disequilibrium (Serão et al., 2014).

Using a completely different data set than in Serão et al. (2014), Serão et al. (2016) validated the high heritability for total antibody response to PRRSV using the same ELISA test. These authors also discovered two QTL for S/P ratio on SSC7 when working with crossbred populations. Both Serão et al. (2014) and Serão et al. (2016) genome-wide association studies (GWAS) for S/P ratio are illustrated in Figure 3. Serão et al. (2016) also indicated that the majority of the farms used in their study (19 of 23) vaccinated their animals with a commercial modified live virus (MLV) vaccine, suggesting that the use of MLV vaccines for PRRS generates the same immune response from total antibody response to PRRSV. These results suggest that the genetic response to antibodies can also be used as a selection tool when animals are vaccinated, indicating that it is not necessary to wait for an infection to collect data for selection.

The use of molecular markers may increase the accuracy of genomic prediction for reproductive performance when analyzing the production of antibodies to PRRSV. According to Serão et al. (2016), the genomic prediction for response to PRRSV based on SNP markers is of great interest to the swine genetic industry because: (1) disease-related characteristics are generally not expressed in the nucleus and multiplier populations that are under selection, (2) in commercial herds, producers strive to maintain herd health by vaccinating animals to reduce the effects of the disease; thus, disease phenotypes are often not available, and (3) measuring disease phenotypes can be expensive (for example, antibody measurement and viremia level).

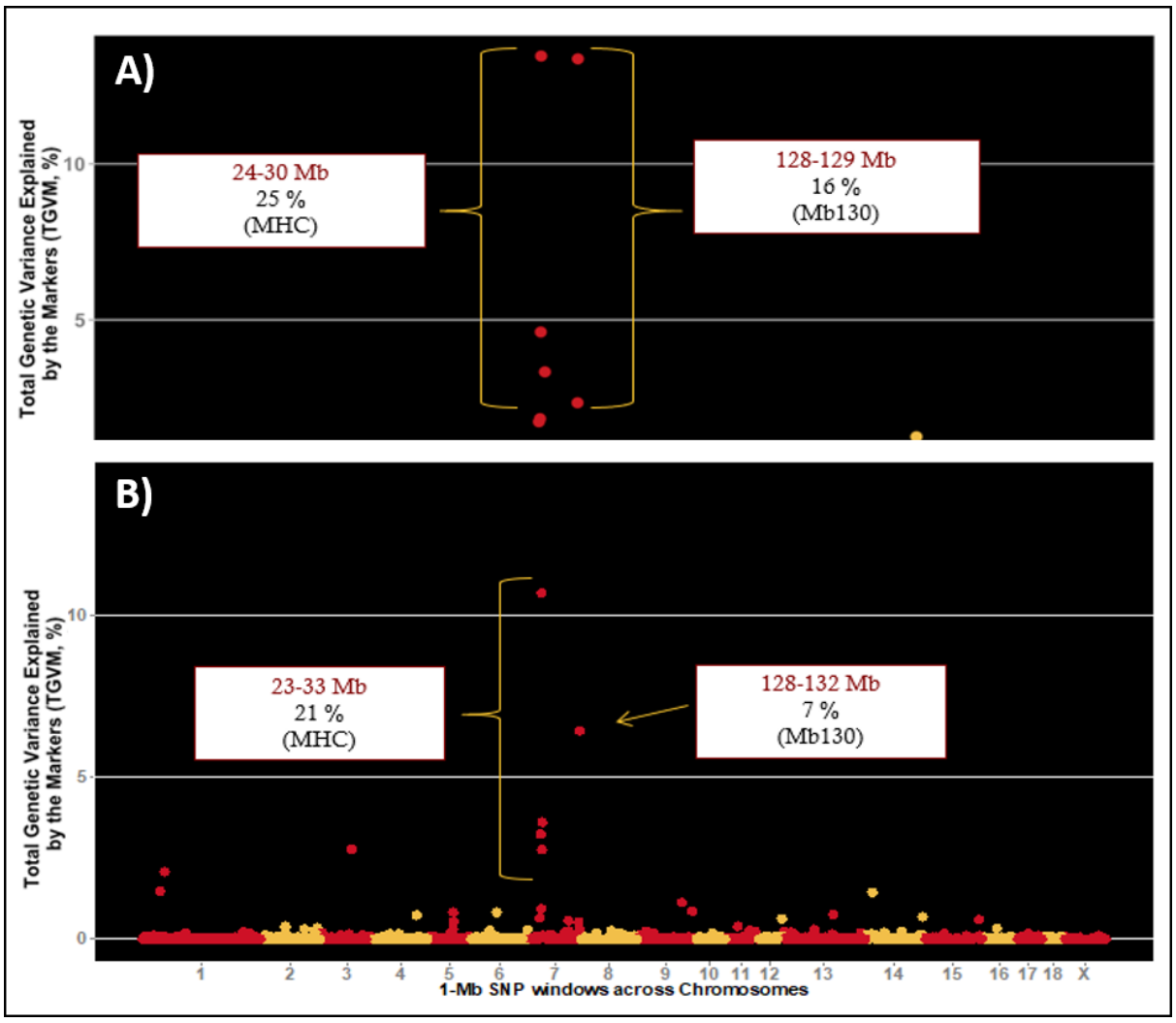

Figure 3. *Previous GWAS studies for S/P ratio. Serão et al. (2014) discovered two QTL on SSC 7 for S/P ratio when working with a purebred population and one breeding company (A). One of the regions (24-30 Mb) harbors the MHC region and explained 25% of the genetic variation, while the other QTL (128-130 Mb) explained 15% of the genetic variance. Serão et al. (2016) also found two QTL on SSC 7 for S/P ratio when working with crossbred populations from seven breeding companies (B). One of the regions (23-33 Mb) also harbors the MHC region, explaining 21% of the genetic variation. The other QTL (128-132 Mb) explained 7% of the genetic variance though.*

Recent studies have shown that reproductive performance between healthy and PRRSV-infected sows is highly genetically correlated (Putz et al., 2019; Scanlan et al., 2019). This suggests that selecting animals in a clean environment prior the occurrence of an outbreak may work. In other words, there is no need to wait for a PRRSV outbreak to start selecting animals for improved reproductive performance. On the other hand, Putz et al. (2019) also showed that the genetic correlation between reproductive performance prior and after a PRRSV infection in maternal breeds is low. This result indicates that response in

healthy animals previously exposed to PRRSV may have a different genetic control than in naïve animals. This relationship though has not been evaluated in other datasets, nor in terminal breeds, yet.

Genetic selection for improved reproductive performance in PRRSV-infected sows is still not a reality in the US swine industry, nor in other leading pork producing countries. This is mostly due to the fact that selection occurs in the nucleus, where a PRRSV infection is not expected. Novel and efficient strategies that would allow the genetic selection for improved reproductive performance in PRRSV-infected sows are needed. Since direct selection for farrowing traits is limited, we are constantly searching for potential proxies that could result in increased response to selection. However, a point to consider is the measurement of these proxies. It is far easier and cheaper to measure litter size traits than proxies such as uterine capacity, antibody response, microbiome, etc. Therefore, we need to find heritable traits that are more predictive of farrowing traits than themselves, while cheap, easy to measure, and collected in younger animals.

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Research problems addressed by this study

Objectives

Using a large commercial dataset with Landrace and Duroc sows that were infected with PRRSV, the objectives of this work were (1) estimate the heritability of reproductive traits in sows before, during, and after a PRRS outbreak; (2) estimate the heritability of S/P ratio during the PRRS outbreak; (3) estimate the genetic correlation between reproductive traits with S/P ratio during the PRRS outbreak; (4) Identify genomic regions associated with reproductive traits and S/P ratio during the PRRS outbreak; and (5) validate the use of S/P ratio as an indicator trait for improved reproductive performance during a PRRS outbreak.

Hypotheses

- Reproductive traits in sows are lowly heritable before, during, and after a PRRS outbreak;
- S/P ratio in PRRSV-infected sows is heritable;
- S/P ratio is genetically correlated with reproductive traits in sows during a PRRS outbreak;
- Genomic regions are associated with reproductive traits and S/P ratio in sows during a PRRS outbreak;
- S/P ratio can be used as an indicator trait to select pigs for improved reproductive performance during a PRRS outbreak.

Chapter II. Host genetics of response to porcine reproductive and respiratory syndrome in sows: reproductive performance[3]

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Host genetics of response to porcine reproductive and respiratory syndrome in sows: reproductive performance

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Abstract: Porcine Reproductive and Respiratory Syndrome (PRRS) is historically the most economically important swine disease worldwide that severely affects the reproductive performance of sows. However, little is still known about the genetic basis of reproductive performance in purebred herds during a PRRS outbreak through the comparison of maternal and terminal breeds. Thus, the objective of this work was to explore the host genetics of response to PRRS in purebred sows from two breeds. Reproductive data included 2546 Duroc and 2522 Landrace litters from 894 and 813 purebred sows, respectively, which had high-density genotype data available (29,799 single nucleotide polymorphisms; SNPs). The data were split into pre-PRRS, PRRS, and post-PRRS phases based on standardized farrow-year-week estimates. Heritability estimates for reproductive traits were low to moderate (≤0.20) for Duroc and Landrace across PRRS phases. On the other hand, genetic correlations of reproductive traits between PRRS phases were overall moderate to high for both breeds. Several associations between MARC0034894, a candidate SNP for response to PRRS, with reproductive performance were identified (P-value < 0.05). Genomic analyses detected few QTL for reproductive performance across all phases, most explaining a small percentage of the additive genetic variance (≤8.2%, averaging 2.1%), indicating that these traits are highly polygenic. None of the identified QTL within a breed and trait overlapped between PRRS phases. Overall, our results indicate that Duroc sows are phenotypically more resilient to PRRS than Landrace sows, with a similar return to PRRS-free

performance between breeds for most reproductive traits. Genomic prediction results indicate that genomic selection for improved reproductive performance under a PRRS outbreak is possible, especially in Landrace sows, by training markers using data from PRRS-challenged sows. On the other hand, the high genetic correlations with reproductive traits between PRRS phases suggest that selection for improved reproductive performance in a clean environment could improve performance during PRRS, but with limited efficiency due to their low heritability estimates. Thus, we hypothesize that an indicator trait that could be indirectly selected to increase the response to selection for these traits would be desirable and would improve the reproductive performance of sows during a PRRS outbreak.

Keywords: disease outbreak, genomics, GWAS, PRRS, QTL, reproduction, SNP, swine.

1. Introduction

Porcine Reproductive and Respiratory Syndrome (PRRS) is one of the most important swine diseases worldwide that affects the reproductive performance of sows and growth in young pigs. Some clinical signs of PRRS in sows include abnormal estrus cycle, late-term abortion, earlier farrow, and an increased number of stillbirths and mummified fetuses (Rossow et al., 1999; Lunney et al., 2011). The limited success in effectively controlling the PRRS virus (PRRSV) via traditional methods, such as vaccination and biosecurity procedures, has been reported to be due to the high mutation rate of PRRSV and the diversity of the strains circulating in the field (Brar et al., 2014; Montaner-Tarbes et al., 2019). Thus, exploring other methods, such as genetic and genomic selection, has been described as an additional and complementary tool to reduce the adverse effects caused by this pandemic (Dekkers et al., 2017).

Host genetics of response to PRRS in sows has been a subject of several studies over the last few years. These studies have indicated that reproductive performance traits in PRRSV-infected sows have low

heritability (Lewis et al., 2009b; Rashidi et al., 2014; Serão et al., 2014; Putz et al., 2019; Scanlan et al., 2019). It has been shown that reproductive performance between healthy and PRRSV-infected animals is highly genetically correlated (Putz et al., 2019; Scanlan et al., 2019). On the other hand, Putz et al. (2019) also showed that the genetic correlation between reproductive performance prior to and after PRRSV infection in maternal breeds is low. This result indicates that reproductive performance in animals previously exposed to PRRSV may have a different genetic control than in naïve animals; however, this relationship has not been evaluated in other datasets, nor terminal breeds.

Studies on genomics of response to PRRS have provided information on major QTL and accuracies of genomic prediction. However, most of these studies focused on growing pigs (Boddicker et al., 2012; Dunkelberger et al., 2017; Waide et al., 2018). To the best of our knowledge, Serão et al. (2014) and Orrett (2017) are the only studies that provided GWAS results for reproductive traits in PRRSV-infected sows. Using Landrace sows under a PRRSV wild-type infection, Serão et al. (2014) reported a major QTL on *Sus scrofa* chromosome (SSC) 1, explaining 11% of the additive genetic variance for the number of stillborn piglets (NSB). However, these authors did not perform genomic prediction analyses for reproductive traits. Additional datasets must be evaluated to validate these previous results as well as to evaluate terminal lines, which have not yet been investigated. Genomic studies investigating genomic regions and genetic markers associated with reproductive performance across different PRRS phases are still a gap in the literature. Thus, the objectives of this work were to estimate genetic parameters of reproductive traits in sows before, during, and after a PRRS outbreak, perform genomic analyses for reproductive performance in PRRSV-infected purebred sows, and evaluate differences in PRRS resilience for reproductive performance between a terminal and a maternal breed.

2. Material and Methods

The data used for this study were collected as part of routine data recording in a commercial breeding program from a farm that operates in line with regulations on animal protection.

2.1 Source of Data

Data were obtained from two commercial purebred populations (Duroc and Landrace) raised in the same farm separately, which experienced a PRRS outbreak during the Spring of 2018. Farrowing data included 2546 and 2522 litters from 894 Duroc and 813 Landrace sows, respectively, from June 2015 through July 2019. The Duroc and Landrace sows originated from 95 sires and 573 dams, and 114 sires and 502 dams, respectively. Traits used for this study were number of piglets born alive (NBA, pigs/litter), number of stillborn piglets (NSB, pigs/litter), number of mummified piglets (NBM, pigs/litter), number of piglets born dead (NBD, pigs/litter; the sum of NSB and NBM), total number of piglets born (TNB, pigs/litter; the sum of NBA and NBD), and number of piglets weaned (NW, pigs/litter). The net number of cross-fostered piglets (fostered in minus fostered out; XF) was also available. A total of 710 (28%) Duroc and 691 (27%) Landrace litters had cross-fostering. Prior to analyses, NSB, NBM, and NBD data were transformed as ln(phenotypeC1) because of right skewness observed in the data (Serão et al., 2014). Table 1 shows the summary statistics of these traits by breed.

All animals had follicular hair or ear tissue samples taken and shipped to Neogen GeneSeek (Lincoln, NE, United States) for genotyping. Genotype data were available on all Duroc and Landrace sows for 33,776 and 39,610 SNPs, respectively. Genotypes were obtained using the GGP Porcine HD panel (Neogen GeneSeek) and processed according to the breeding company's pipeline, which included removing non-segregating SNPs, SNPs with a minor allele frequency of less than 0.05, and minimum SNP call rate and animal call rate of 0.9. In addition, missing genotypes were imputed using Fimpute 2.2 (Sargolzaei et al., 2014). For subsequent analyses, only the 29,799 SNPs common to the genotype

data from both breeds that passed quality control were used. The Sscrofa 11.1 assembly was used for the SNP location. The genotype data were used to construct a genomic relationship matrix for each breed separately based on VanRaden (2008), method 1. The wild-type PRRSV strain was sequenced and identified as PRRSV 1-7-4, a highly pathogenic strain.

2.2 Identification of the PRRS outbreak

The dataset was split into pre-PRRS, PRRS, and post-PRRS phases, following Putz et al. (2019), based on farrow-year-week (FYW) estimates (Lewis et al., 2009b). The FYW estimates were obtained for each breed from the following linear mixed model for reproductive traits, with the exception of NW:

$$Y_{ijk} = \mu + PAR_i + fyw_j + sow_k + e_{ijk} \quad (1)$$

where Y_{ijk} is the observed phenotype; μ is the general mean; PAR_i is the fixed effect of the i^{th} parity; fyw_j is the random effect of the j^{th} farrow-year-week, assuming $fyw_j \sim N(0, I\sigma^2_{fyw})$, where I is the identity matrix; sow_k is the random effect of sow, assuming $sow_k \sim N(0, I\sigma^2_{sow})$; and e_{ijk} is the random residual term associated with Y_{ijk}, assuming $e_{ijk} \sim N(0, I\sigma^2_e)$. For NW, the model above was modified to include the fixed effect covariate of XF. Analyses were performed with the package *lme4* (Bates et al., 2015) in R (R Core Team, 2017).

The FYW estimates were then standardized by their respective standard deviations (SDs) to make all traits comparable. Outbreaks of PRRS were identified for each trait separately to assess the disease's impact on each reproductive trait, following Scanlan et al. (2019). For this, standardized FYW estimates that deviated 1.28 SD from the mean, representing a one-side probability threshold of 10%, were deemed extreme. The occurrence of two consecutive weeks of extreme values indicated the beginning of the PRRS phase. The end of the PRRS phase was defined by the return of standardized FYW estimates within 1.28 SD from the mean (i.e., from zero), followed by the occurrence of two

consecutive weeks without extreme values. The pre-PRRS, PRRS, and post-PRRS phases were then defined accordingly for each reproductive trait. Not all animals experienced all three PRRS phases.

2.3 Breed effect on PRRS resilience and return to PRRS-free performance

The reproductive data from both breeds across all phases were used to evaluate how each breed was impacted by the PRRS outbreak. Since the average reproductive performance between Duroc and Landrace is quite different, the data were analyzed as a rate (i.e., proportion; described below) to allow for a fair comparison between the breeds. For each trait, two analyses were performed to identify the statistical method that best fit the data. Hence, the data from each trait was analyzed using Poisson and negative binomial mixed model methodologies, according to the following statistical model:

$$\log(Y)_{ijklm} = \mu + Breed_i + Phase_j + (Breed * Phase)_{ij} + PAR_k + fyw_l + sow_m + \log(T)_{ijklm} \quad (2)$$

where μ, PAR_k, fyw_l, and sow_m are as previously defined; $\log(Y)_{ijklm}$ is the log of the observed phenotype of the trait analyzed; $Breed_i$ is the fixed effect of the i^{th} Breed (Duroc or Landrace); $Phase_j$ is the fixed effect of the j^{th} Phase (pre-PRRS, PRRS, or post-PRRS); $(Breed * Phase)_{ij}$ is the interaction between Breed and Phase; and $\log(T)_{ijklm}$ is the log of the trait used as the offset, described below.

The offset allowed the data to be analyzed as proportion, promoting fair comparison between breeds across phases. Depending on the trait analyzed, different offsets were used. TNB was used as the offset for all traits, with the exception of NW, as NW is also affected by XF. By using TNB as the offset, results represented the performance of the trait analyzed as a proportion of the litter size (i.e., TNB). The traits analyzed as proportion using TNB as an offset are referred to as NBA$_{TNB}$, NBD$_{TNB}$, NSB$_{TNB}$, and NBM$_{TNB}$. Two strategies were used in the analysis of NW. In the first, NW was analyzed using the

sum of TNB and XF as the offset ($NW_{TNB;XF}$). In this analysis, the proportion $NW_{TNB;XF}$ represented the sow's ability to wean all possible piglets that she could have farrowed (i.e., TNB) and had fostered in/out (i.e., XF). In the second strategy, NW was analyzed using the sum of NBA and XF as the offset ($NW_{NBA;XF}$). In this analysis, the proportion $NW_{NBA;XF}$ represented the sow's ability to wean all possible piglets nursed by her [i.e., the opportunity piglets (i.e., NBA) and those that fostered in/out (i.e., XF)].

In order to evaluate the effect of breed on PRRS resilience and on return to PRRS-free performance, two pre-defined contrasts were used when the effect of the interaction between Breed and Phase was significant (P-value ≤ 0.05). With the levels of the interaction denoted as (1) Duroc-pre-PRRS, (2) Landrace-pre-PRRS, (3) Duroc-PRRS, (4) Landrace-PRRS, (5) Duroc-post-PRRS, and (6) Landrace-post-PRRS, the following two contrasts were evaluated:

i. *PRRS resilience*, with coefficients of 1, -1, -1, 1, 0, and 0 for the six respective interaction levels. In this contrast, we evaluated the difference in the decline in relative reproductive performance from the pre-PRRS to the PRRS phase between the two breeds;
ii. *Return to PRRS-free performance*, with coefficients of 1, -1, 0, 0, -1, and 1 for the six respective interaction levels. In this contrast, we evaluated the difference in the rate of return to PRRS-free performance between the two breeds. In other words, we compared whether the relative reproductive performances between the pre-PRRS and post-PRRS phases were the same for both breeds.

Significance was declared at P-value ≤ 0.05, and a trend was declared at $0.05 <$ P-value < 0.10. For completeness, Tukey-Kramer separation was performed if the interaction between breed and phase was significant. Prior to the final analyses, for each trait, the dispersion parameter estimated using the negative binomial model was tested again at a value of 1 (representing a Poisson model) using a likelihood ratio test. Analyses indicated that the dispersion parameter was significant for NBD_{TNB},

NSB$_{TNB}$, NBM$_{TNB}$, and NW$_{NBA;XF}$, and hence, a negative binomial model was used for these traits. In contrast, NBA$_{TNB}$ and NW$_{TNB;XF}$ were analyzed using a Poisson model. Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, United States).

2.4. Genetic parameters

Heritabilities and genetic correlations were estimated separately for each breed and phase. Genetic correlations were estimated between phases within traits. Genetic correlations between traits within phases were not estimated because bivariate analyses within the PRRS phase had convergence issues due to the low sample size. For the pre-PRRS and post-PRRS phases, the following model was used to estimate heritabilities:

$$Y_{ijkl} = \mu + PAR_i + fyw_j + a_k + pe_l + e_{ijkl} \quad (3)$$

where Y_{ijkl}, μ, PAR_i, fyw_j, and e_{ijkl} are as previously defined; a_k is the animal genetic random effect, assuming $a_k \sim N(0, GRM\sigma_a^2)$, where GRM is the genomic relationship matrix; and pe_l is the random permanent environment effect, assuming $pe_l \sim N(0, I\sigma_{pe}^2)$. For NW, this model was modified to include the number of net cross-fostered piglets as a covariate. For the PRRS phase, pe and fyw were removed from the model as only one observation per animal was available for this phase. All analyses were performed in ASReml v4 (Gilmour et al., 2015).

2.5 Effect of SNPs previously associated with response to PRRS

The effects of the MARC0034894 / rs80841011 (1:28,912,680) (MARC) and WUR10000125 / rs80800372 (4:127,441,677) (WUR) SNPs, which were previously associated with NSB in PRRSV-infected Landrace sows (Serão et al., 2014) and with viremia and growth rate in PRRSV-infected nursery pigs (Boddicker et al., 2012, 2014b), respectively, were investigated by simultaneously fitting them as fixed effects in the model used for estimation of genetic parameters described above. Animals

with the BB genotype for the WUR SNP were combined with those with the AB genotype due to the dominance mode-of-action described for this SNP (Boddicker et al., 2014b). Analyses were performed separately for each PRRS phase and breed. All analyses were performed in ASReml v4 (Gilmour et al., 2015).

2.6 Genome-wide association studies

Genome-wide association studies (GWAS) Genome-wide association studies (GWAS) were performed separately for each PRRS phase and breed, using the BayesB method with p = 0.99 (Habier et al., 2011). Pre- and post-PRRS data were pre-adjusted for fixed effects due to repeated records on the same individuals. In other words, the adjusted phenotype (y*) was obtained for each animal as the sum of the estimated random animal effect, permanent environmental effect, and the average residuals from the model used for the estimation of genetic parameters. For the GWAS, residuals for a given trait were weighted based on the number of records on each animal and trait parameter estimates, with weights derived as in Garrick et al. (2009):

$$w_n = \frac{1 - h^2}{ch^2 + \frac{1 + (n-1)t}{n} - h^2}$$

where w_n represents the weighing factor for n observations; h^2 is the estimated heritability of the trait; c is the proportion of the genetic variance not accounted for by markers, which was assumed to be 0.75 for all traits; and t is the estimated repeatability of the trait. GWAS models for pre- and post-PRRS included only the intercept as fixed effect, with residuals being weighted according to the values obtained with the formula above, and the random allele substitution effects of SNPs. For the PRRS phase, the same models previously described for the PRRS phase were used but replacing the animal genetic effect by the random allele substitution effects of SNPs. For all analyses, additive genetic and residual variances obtained from the genetic parameter analyses were used as priors. A total of 50,000

Markov Chain Monte Carlo (MCMC) iterations were used, of which the first 10,000 iterations were used as burn-in. All analyses were performed using GenSel version 4.4 (Fernando and Garrick, 2009). Consecutive 1-Mb genomic regions that explained at least 0.5% of the total additive genetic variance accounted for by markers (TGVM) were combined. In the end, genomic regions that explained more than 1% of TGVM were deemed significant and further investigated to identify candidate genes. For the presentation of GWAS results, the start of the QTL region on a given SSC c was assumed to be c:Mbi,000,000, and the end of the QTL region as c:Mbf,999,999 where Mbi and Mbf represent the Mb where the identified QTL window started and ended, respectively. Thus, for example, if a QTL was identified in a given 1-Mb region r, the position of the QTL was expressed as rMb, such that Mbi = Mbf = r and the QTL encompassed c:r,000,000–r,999,999. In contrast, when closely located 1-Mb QTL regions were combined into a single window, the position of the QTL was expressed as r-r'Mb, such that Mbi = r < Mbf = r' and the QTL encompassed c:r,000,000–r',999,999.

2.7 Genomic prediction

Genomic prediction accuracies (GPA) were obtained using the same model as described for GWAS but using BayesB ($\pi = 0.99$), BayesC ($\pi = 0.99$), and BayesC0 (BayesC with $\pi = 0$), separately for each breed and trait. The overall objective of these analyses was to predict the performance of PRRSV-infected sows since information on GPA in PRRSV-infected sows in the literature is limited.

Five genomic prediction scenarios (GPS) were investigated according to different strategies used for the training datasets (i.e., the dataset used to estimate SNP effects). The training datasets differed according to the combination between the source of the dataset used for training (pre-PRRS phase and/or PRRS phase) and whether or not animals in the validation dataset were included in the training dataset. These five GPS are summarized below and in Table 2. In all GPS, data from the PRRS phase was used as the validation dataset. When multiple sources of data were used for training, estimation of

SNP effects was performed within each source of the data. In other words, estimation of marker effects was obtained separately using data from the pre-PRRS and PRRS phases.

1. GPS_{PRRS}: The training dataset included data from the PRRS phase only. In order to avoid using the same animal in the training and validation datasets, analyses were performed using a 4-fold cross-validation (4FCV). Thus, genomic estimated breeding values (GEBVs) in the validation set were calculated per fold. Details about the generation of the 4 folds are included below.
2. $GPS_{pre\text{-}PRRS}$: The training dataset included data from the pre-PRRS phase only. This approach was used since the two phases do not co-exist at the same time. Hence, in practice, GEBVs in the validation set (i.e., during PRRS) could be obtained using pre-PRRS data, in which the same animals are used in the training and validation datasets.
3. $GPS_{pre\text{-}PRRS\text{-}4FCV}$: The training dataset included only data from the pre-PRRS phase. In this GPS, we modified $GPS_{pre\text{-}PRRS}$ to represent cases where animals have data in one of the phases only (i.e., pre-PRRS or PRRS phase). Hence, GEBVs in the validation set were calculated per fold.
4. $GPS_{pre\text{-}PRRS,PRRS}$: The training datasets included data from both the pre-PRRS and PRRS phases. Since the two phases do not co-exist at the same time, all the pre-PRRS data were used. However, in order to avoid using the same animals in the PRRS phase for training and validation, the PRRS dataset was subjected to a 4FCV. Hence, GEBVs in the validation set were obtained as the average GEBV obtained from training SNPs using the pre-PRRS and PRRS phases.
5. $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$: The training dataset included data from both the pre-PRRS and PRRS phases. This strategy is a modification of the previous scenario ($GPS_{pre\text{-}PRRS;PRRS}$), in which a

4FCV was used for datasets. Hence, GEBVs in the validation set were obtained as the average GEBV obtained from training SNPs using the pre-PRRS and PRRS phases.

The folds used in the 4FCV analyses were created by randomly assigning sows from the same sire family to one of the four folds. This strategy was used to increase the relatedness of individuals between folds, which is expected in traditional breeding schemes. Then, three folds were used for training and the remaining fold for validation. This process was repeated until all four folds were used for validation. The number of records per fold, trait, and breed is presented in Supplementary Table 1. These folds were created using the PRRS data only, as this was the target dataset for prediction purposes. However, some animals in the pre-PRRS phase did not have data in the PRRS. Therefore, these animals were always used in the training datasets but never in the validation datasets. The number of records per fold differed between traits because the timing of the PRRS phase differed between traits.

The genomic prediction accuracy (GPA) for scenarios using Folds (i.e., all GPSs except $GPS_{pre\text{-}PRRS}$) were calculated as a weighted average as:

$$GPA = \frac{\sum_{i=1}^{4} n_i \, r_i(GEBV, y^*)}{\sqrt{h^2}}$$

where $r_i(GEBV, y^*)$ is the correlation between GEBVs and the phenotypes adjusted for fixed effects (y^*) in the i^{th} validation dataset, which was weighted by the proportion of records in the validation dataset of each fold (n_i); and h^2 is the estimate of heritability of the trait being analyzed during the PRRS phase. The GPA of the GPS using all the data from the pre-PRRS phase (i.e., $GPS_{pre\text{-}PRRS}$) was obtained as where $r_i(GEBV, y^*)/\sqrt{h^2}$, where all terms are as previously defined. Estimation of marker effects were obtained in GenSel v.4.4 (Fernando and Garrick, 2009).

3. Results

3.1 Identification of the PRRS outbreak

The standardized FYW estimates and 30-d RAs for all traits are shown in Figure 1 for both breeds. The extreme increase (over the 90th percentile) in standardized FYW estimates for NBD, NBM, and NSB, and an extreme decrease (under the 10th percentile) in standardized FYW estimates for NBA and NW were evident for both breeds in the same period as shown in Figures 1A,B for Duroc and Landrace, respectively. From these results, the beginning of the PRRS phase was set to be the 15th week of 2018 for all traits. All data prior to this date were defined as the pre-PRRS phase. The end of the PRRS phase was characterized by the return of standardized FYW estimates to be close to 0, which differed between traits. For mortality traits (NBD, NBM, and NSB), the end of the PRRS phase was set to be the 30th week of 2018 for both breeds, while for NBA, NW, and TNB, the end of the PRRS phase was set to be the 34th week of 2018 for both breeds. Visually, the same reduction pattern and return to normal production were observed for both breeds (Figures 1C,D for Duroc and Landrace, respectively). The summary statistics by phase and breed are shown in Table 3.

3.2 Breed effect on PRRS resilience and return to PRRS-free performance

Results for these analyses are presented in Table 4. With the exception of NSB_{TNB} (P-value = 0.300), there was a significant (P-value $\leq$ 0.026) interaction between PRRS phase and breed for all traits. For traits with this significant interaction, all traits but NSB_{TNB} (P-value = 0.161) and $NW_{NBA;XF}$ (P-value = 0.127) had a significant (P-value $\leq$ 0.039) PRRS resilience contrast. Results showed that, proportionally, the drop in reproductive performance from the pre-PRRS to the PRRS phase was greater in Landrace than in Duroc sows. Prior to the PRRS outbreak, Duroc and Landrace sows had proportionally similar (P-value > 0.05) NBA_{TNB} and NBM_{TNB}, with 0.866 ± 0.013 and 0.882 ± 0.011

NBA$_{TNB}$, respectively, and 0.039 ± 0.003 and 0.034 ± 0.003 NBM$_{TNB}$, respectively. However, during the PRRS phase, Duroc sows had, proportionally, better reproductive performance (P-value < 0.05) than Landrace sows, with 0.676 ± 0.017 and 0.590 ± 0.014 NBA$_{TNB}$, respectively and 0.150 ± 0.017 and 0.232 ± 0.025 NBM$_{TNB}$, respectively. Although Landrace had proportionally lower (P-value < 0.05) NBD$_{TNB}$ (0.106 ± 0.005) than Duroc sows (0.122 ± 0.007) prior to the PRRS outbreak, the relationship inverted during the PRRS phase, where Duroc sows had lower (P-value < 0.05) NBD$_{TNB}$ (0.299 ± 0.023) than Landrace (0.396 ± 0.030). Interestingly, Duroc had greater (P-value < 0.05) NW$_{TNB;XF}$ than Landrace sows in both pre-PRRS and PRRS phases. However, this superiority was more evident in the PRRS phase. Prior to the PRRS outbreak, the NW$_{TNB;XF}$ of Duroc and Landrace sows were 0.750 ± 0.019 and 0.700 ± 0.016, respectively, whereas in the PRRS phase, these were 0.371 ± 0.018 and 0.322 ± 0.015, respectively.

The return to PRRS-free performance contrast had a trend effect only for NW$_{NBA;XF}$ (P-value = 0.073). Although there were no differences in NW$_{NBA;XF}$ within breed between pre- PRRS and post-PRRS (P-value > 0.05), the return to PRRS-free performance contrast indicated that NW$_{NBA;XF}$ tended to have a greater reduction in Landrace sows from pre-PRRS to post-PRRS (0.716 ± 0.018 to 0.705 ± 0.023, respectively) than in Duroc sows (0.787 ± 0.021 to 0.742 ± 0.026, respectively). In both phases, Duroc had greater (P-value < 0.05) NW$_{NBA;XF}$ than Landrace sows. Overall, these results indicate that Duroc sows have greater PRRS resilience than Landrace sows.

3.3 Genetic parameters

Heritability (h^2) estimates for reproductive traits were low to moderate across datasets, as shown in Table 5. Overall, there was no consistency of estimates across PRRS phases for a given trait. Nonetheless, as expected, h2 estimates were overall low for all traits, breeds, and phases. From the pre-PRRS to the PRRS phase, there was a numerical increase in estimates of additive genetic variances for

litter mortality traits (i.e., NDB, NSB, and NBM) in both breeds. In contrast, residual variance estimates numerically increased during the PRRS phase for all traits and breeds. Most estimates of the additive genetic variance were numerically greater in the post-PRRS phase than in the pre-PRRS phase, while residual variance estimates were numerically lower in the post-PRRS than in the PRRS phase.

Estimates of genetic correlations (r_g) of each reproductive trait between the three phases are shown in Table 6. These estimates varied considerably between phases within the same trait, with large standard errors. Nonetheless, estimates were all positive. Between the pre-PRRS and PRRS phases, r_g estimates ranged from 0.06 ± 0.42 (TNB) to 0.94 ± 0.56 (NW) for Duroc, and from 0.47 ± 0.83 (NBA) to 0.84 ± 0.35 (NBD) for Landrace. Estimates of r_g between the pre-PRRS and post-PRRS phases ranged from 0.33 ± 0.46 (NSB) to 0.90 ± 0.38 (NW) for Duroc, and from 0.69 ± 0.63 (TNB) to 0.90 ± 0.47 (NBD) for Landrace. However, r_g estimates for NBA, NSB, and NW in Landrace, and for NBD in Duroc did not converge. Estimates of r_g between the PRRS and post-PRRS phases ranged from 0.10 ± 0.49 (NBA) to 0.94 ± 0.44 (NW) for Duroc, and from 0.10 ± 0.31 (NSB) to 0.96 ± 0.30 (TNB) for Landrace.

3.4 Effect of SNPs previously associated with response to PRRS

In this study, only a few associations of the MARC and WUR SNPs with reproductive traits were identified (Table 7). The only association (P-value = 0.037) of the WUR SNP with reproductive performance in Landrace sows was found for pre-PRRS NW, where AA animals had greater (9.61 ± 0.20) performance than AB animals (9.23 ± 0.24). For Duroc sows, there was a trending association (P-value = 0.095) of the WUR SNP with pre-PRRS NW, with AA animals also showing greater performance (7.32 ± 0.22) than AB animals (7.05 ± 0.19).

Many more associations were found for the MARC SNP, in particular for Landrace sows. In the pre-PRRS phase, this SNP was associated (P-value = 0.033) with NW, where AB sows (9.8 ± 0.21) weaned more (P-value < 0.05) piglets than AA sows (8.96 ± 0.37), with both not differing (P-value > 0.05)

337 from BB sows (9.50 ± 0.18). During the PRRS phase, MARC SNP was associated with the
338 reproductive performance of most traits in Landrace. For TNB (P-value = 0.033), BB (13.12 ± 0.29)
339 animals had greater (P-value < 0.05) performance than AA (11.74 ± 0.72) and AB (12.27 ± 0.36).
340 Interestingly, for NBA (P-value = 0.077), there were no differences (P-value > 0.10) between AA (8.26
341 ± 0.83) and BB (7.60 ± 0.34) animals, although both genotypes had greater (P-value < 0.10) NBA than
342 AB sows (6.75 ± 0.41). For NBD (P-value = 0.055) and NBM (P-value = 0.027), the same pattern was
343 observed, with better performance increasing with the number of the A allele. Sows with genotype AA
344 had better NBD (P-value < 0.10) and NBM (P-value < 0.05), with 2.29 ± 0.15 and 1.16 ± 0.16,
345 respectively, than BB sows (3.76 ± 0.06 and 2.33 ± 0.06, respectively). For both traits, AB sows did
346 not differ in NBD (3.61 ± 0.07; P-value > 0.10) and NBM (2.14 ± 0.08; P-value < 0.05) from the other
347 genotypes. No associations (P-value ≥ 0.302) were found between the MARC SNP and reproductive
348 performance post-PRRS in Landrace sows.

349 In contrast, the MARC SNP was only associated with post-PRRS performance in Duroc sows.
350 Associations were found for TNB (P-value = 0.023), NBA (P-value = 0.003), and NW (P-value =
351 0.055). In all associations, better performance was observed as the number of A alleles increased. Sows
352 with the AA genotype had greater TNB (9.58 ± 0.35), NBA (8.70 ± 0.32), and NW (7.29 ± 0.35) than
353 BB sows, who had 8.54 ± 0.20, 7.53 ± 0.19, and 6.47 ± 0.23, respectively. These did not differ from
354 sows with AB genotype.

355 **3.5 Genomic regions associated with reproductive traits**

356 Genomic regions that explained more than 1% of TGVM in reproductive performance across PRRS
357 phases are displayed in Table 8. In general, these QTL explained a low %TGVM of the traits. For
358 Duroc pre-PRRS, there were nine QTL identified, with two for TNB, NBA, NBD, and NW, and one
359 for NBM. Of these, the largest QTL was identified for NBA on SSC 7 (31–33 Mb), close to the MHC

region, explaining 2.8% TGVM. For Duroc PRRS, there were four QTL identified, one for each trait (TNB, NBA, NSB, and NW). The largest QTL was found for TNB on SSC 5 (36–41 Mb), explaining 7.2% TGVM. For Duroc post-PRRS, there were seven QTL identified, with three for TNB, two for NBA, and one for NBM and NW. The largest QTL was identified for NBA (8.2% TGVM) on SSC 11 (22 Mb), which was also identified for TNB (2.0% TGVM) and NW (1.4% TGVM).

For Landrace pre-PRRS, there were eight QTL identified, three for TNB and NBA, two for NBM, and one for NSB. The largest identified QTL was for NSB on SSC 6 (41–43 Mb), explaining 7.4% TGVM. TNB and NBA shared two QTL: one on SSC 9 (8–10 Mb), explaining 1.5 and 4.3% TGVM for TNB and NBA, respectively, and one on SSC 16 (2–5 MB), explaining 1.1 and 1.4% TGVM for TNB and NBA, respectively. In addition, a QTL on SSC 5 was identified for these two traits without a complete overlap between the QTL regions of these traits, on 4–8 Mb (1.4% TGVM) for TNB and on 7–10 Mb (1.3% TGVM) for NBA. For Landrace PRRS, five QTL were identified, with two for NBA and NBD, and one for NBM. The largest QTL was for NBA on SSC 13 (156–160 Mb), explaining 1.5% TGVM. For Landrace post-PRRS, there were five QTL identified, with the largest QTL (SSC 3, 1–2 Mb) explaining 3.1% TGVM for NW. TNB and NBA had the same QTL on SSC 8 (111–113 Mb), explaining 1.7 and 2.9% TGVM, respectively. Although many QTL were identified, they were not consistent across traits and phases within a breed. Several candidate genes were identified in these regions and will be discussed below.

3.6 Genomic prediction accuracies

Overall, genomic prediction accuracies (GPAs) were similar across Bayesian methods, and thus, results presented in the main text are just for one method (BayesB). These are shown in Figure 2, whereas results from all methods are available in Supplementary Table 2. In general, there was no consistency in GPAs between traits, breeds, and GPSs. In general, GPAs were better in Landrace than in Duroc.

In Duroc, although there was considerable variation in GPAs across GPSs within a trait, in general, results obtained from scenarios combining data from the pre-PRRS and PRRS phases for training yielded better GPAs. Among the given GPSs, $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$ is the only scenario that resulted in positive GPAs for all traits. In addition, this GPS yielded the highest GPAs (SD across the four folds) for NBA (0.61 ± 0.48), NBD (0.55 ± 0.73), NSB (0.98 ± 2.05), and NBM (1.19 ± 2.55). For TNB, the highest GPAs were obtained in scenarios $GPS_{pre\text{-}PRRS}$ (0.60) and $GPS_{pre\text{-}PRRS;PRRS}$ (0.60 ± 0.12), whereas for NW, the highest GPA was obtained in GPS_{PRRS} (0.69 ± 0.06). However, some negative GPAs were obtained in these analyses. Of these, large negative GPAs (< -0.3) were obtained using GPS_{PRRS} for NSB (-0.57 ± 0.04) and NBM (-0.46 ± 0.12), $GPS_{pre\text{-}PRRS}$ for NBD (-0.63), NSB (-0.50), NBM (-1.03), and NW (-0.31), and $GPS_{pre\text{-}PRRS\text{-}4FCV}$ for TNB (-0.39 ± 0.6).

In contrast, all GPAs were positive in Landrace. Results across GPSs within a trait were similar, with the exception of TNB. For this trait, the highest GPA was obtained using $GPS_{pre\text{-}PRRS}$ (1.16), although a high GPA was also obtained using $GPS_{pre\text{-}PRRS\text{-}4FCV}$ (0.77 ± 1.95). Interestingly, GPS_{PRRS} showed the lowest GPA for TNB (0.09 ± 0.09), whereas for the other traits, this GPS yielded the highest or second highest GPAs. GPS_{PRRS} had the highest GPAs for NBA (0.37 ± 0.03), NBD (0.55 ± 0.12), and NBM (0.41 ± 0.14). For NSB, the GPA for GPS_{PRRS} was 0.46 ± 0.08, whereas the highest GPA was obtained in $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$, with 0.48 ± 0.29. Finally, for NW, the GPA for GPS_{PRRS} was 0.44 ± 0.14, whereas the highest GPA was also obtained in $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$, with 0.45 ± 0.31. Overall, the GPAs in Landrace were better and more consistent across GPS and traits than in Duroc. In general, combining data from the pre-PRRS and PRRS phases did not substantially yield better GPAs in Landrace.

4. Discussion

4.1 Identification of the PRRS outbreak

We used standardized FYW estimates to identify when the PRRS outbreak occurred to split the reproductive data into three different datasets. Although the beginning of the PRRS phase was set to be April 9th, 2018, animals were probably infected with PRRSV prior to that date, before the reproductive performance of sows was affected. Increases in abortions and piglet mortality traits, such as NSB and NBM, are usually reported as the first clinical signs of a PRRS outbreak (Rossow et al., 1999; Lunney et al., 2011). There was an increased incidence of mortality traits under PRRS for both breeds, which reinforced the severity of the disease. Survival traits, such as NBA and NW, had a decrease in means during the PRRS phase, which is in line with what other studies had previously found using this approach (Serão et al., 2014; Putz et al., 2019; Scanlan et al., 2019). With the exception of TNB, all traits showed improved mean performance after the outbreak, reaching similar performance to the production levels prior to the outbreak.

4.2 Breed effect on PRRS resilience and return to PRRS-free performance

Breed differences play an important role when it comes to PRRS-resilience. Many studies have reported that growing pigs from lines selected for improved reproductive performance (e.g., Landrace, Meishan, Large White) are more resilient to the effects of PRRS than pigs from lines selected for carcass traits and growth (e.g., Duroc, Pietran) because of the severe effects of a PRRSV infection on the lungs of animals selected for lean growth (Halbur et al., 1998; Petry et al., 2005; Vincent et al., 2006). On the other hand, Lewis et al. (2009a) reported that Meishan sows, commonly selected for improved reproductive performance and maternal ability, had greater susceptibility to PRRS than sows from terminal lines.

426 We evaluated how proportionally each breed changed its performance between PRRS phases to
427 evaluate the impact of breed on PRRS resilience and on return to PRRS-free performance. For this, we
428 performed analyses using an offset, so the count data for each trait would be adjusted to its total count
429 (TNB for most traits). This approach was used to allow a fair comparison between breeds, as their
430 performance is different since Landrace animals are selected to have improved reproductive
431 performance, whereas Duroc is used as a terminal line. Results from these analyses indicated that
432 Duroc has greater PRRS resilience than Landrace sows.

433 For most traits, the decrease in performance from pre-PRRS to PRRS was lower in Duroc than in
434 Landrace sows. For instance, the decrease in NBA$_{TNB}$ was 21.9 2.2% in Duroc and 33.1 1.7% in
435 Landrace. As expected, this reduction in NBA$_{TNB}$ due to the PRRS outbreak was accompanied by an
436 increase in piglet mortality traits for both breeds. There was an increase in NBD$_{TNB}$ of 144.7 22.4% in
437 Duroc and 275.1 32.4% in Landrace sows. For both breeds, this increase in NBD$_{TNB}$ was driven by an
438 increase in NBM since there was a significant difference in NBM$_{TNB}$ and not in NSB$_{TNB}$ for the PRRS
439 resilience contrast. NBM$_{TNB}$ increased by 285.6 52.6% in Duroc and 575.6 86.4% in Landrace sows
440 from pre-PRRS to PRRS.

441 An increase in NBD is one of the traditional signs of a PRRS outbreak in a commercial farm (Rossow
442 et al., 1999; Lunney et al., 2011). Depending on the timing of PRRSV infection during pregnancy,
443 sows are expected to show differences in NSB and NBM. As shown in Figures 1C,D for Duroc and
444 Landrace, respectively, there was a numerically greater average of NSB than NBM within the first 6
445 weeks of the PRRS phase. This is expected, as it indicates that potentially viable piglets had recently
446 died in the uterus due to the PRRSV infection. In contrast, NBM increased after 6 weeks, as they died
447 during pregnancy at earlier development stages, resulting in their mummification. In addition, the
448 distribution of farrowing events was very similar between Duroc and Landrace over the PRRS period.
449 About 25% of the farrowing events from each breed occurred within the first 6 weeks of the PRRS

phase. Hence, the lack of significant PRRS resilience contrast effect for NSB_{TNB} should be due to the clear effect of PRRSV infection during the first weeks, without significant differences between breeds. In contrast, due to the delayed effect on performance, our analyses were powerful enough to detect differences in PRRS resilience for NBM_{TNB}.

Among all traits evaluated, NW was the only one in which two approaches were used. In $NW_{TNB;XF}$, we evaluated the weaning performance of sows with respect to her maximum biological limit to produce piglets (i.e., TNB). Similar to the results presented for the other traits, from pre-PRRS to PRRS, Duroc sows had a lower reduction in $NW_{TNB;XF}$ than Landrace sows, with reductions of 50.6 2.5 and 54.1 2.3%, respectively. However, the same was not observed for $NW_{NBA;XF}$, in which the PRRS resilience contrast was not significant, although, numerically, there was a lower reduction observed in Duroc (56.6 2.2%) than in Landrace (59.0 2.2%). In $NW_{NBA;XF}$ we evaluated the weaning performance of sows with respect to her realized potential to produce piglets (i.e., NBA). In other words, in $NW_{NBA;XF}$ we considered only the opportunity piglets she could have weaned, as those that were born dead could not have been weaned by her. This lack of significant PRRS resilience contrast for $NW_{NBA;XF}$ could be due to the significant breed effect in NBA_{TNB}, indicating that, proportionally, the two breeds differ in NBA. Hence, by using NBA as part of the offset for NW, the difference in NBA_{TNB} should have removed the breed difference for $NW_{NBA;XF}$. Thus, the different results obtained in $NW_{TNB;XF}$ and $NW_{NBA;XF}$ for the PRRS resilience contrast indicate a breed difference in perinatal (i.e., TNB) resilience, rather than resilience from farrowing to weaning.

Results suggest that Duroc sows have overall greater PRRS resilience for reproductive traits than Landrace sows. The applicability of these results for the industry, however, is limited since commercial sows are usually Landrace x Large White crosses. Nevertheless, if these traits are genetically correlated with terminal traits, such as feed efficiency, commercial hogs may benefit from this overall superiority observed in Duroc sows since these hogs are usually made up of 50% Duroc. These results further

474 suggest that Duroc sows have lower drop in reproductive performance than Landrace sows from pre-
475 PRRS to PRRS. Second, our analyses did not consider within-breed genetic effects due to the overall
476 small sample size for genetic analyses using generalized models. Although we were able to identify
477 differences in reproductive performance between the two breeds across PRRS phases, by not fitting a
478 random animal effect in the model, these results were not adjusted for within-breed differences, nor
479 the degrees of freedom of the test statistics evaluated were corrected by the complex pedigree
480 relationships. Nonetheless, breed differences are due to genetic factors. Thus, the phenotypic
481 superiority of Duroc sows compared to Landrace sows with regards to PRRS resilience should be due
482 to the genetic make-up of these animals.

483 **4.3 Genetic parameters**

484 Ranges of h^2 estimates for reproductive traits in this study were consistent with previous estimates
485 found for healthy and PRRSV-infected sows (Lewis et al., 2009b; Serão et al., 2014; Putz et al., 2019;
486 Scanlan et al., 2019). For most traits, h2 estimates for litter mortality traits were higher during the
487 PRRS outbreak. Putz et al. (2019) suggested that the increased incidence of these traits could explain
488 these higher h2 estimates during the PRRS phase. In most cases, this increase in h2 estimates was
489 accompanied by an increase in the estimate of additive genetic variance. This increase was much
490 clearer in Landrace sows than in Duroc ones. The increase in additive genetic variance for mortality
491 traits from the pre-PRRS to the PRRS phase observed in this study for Landrace sows is in accordance
492 with the literature (Serão et al., 2014; Putz et al., 2019), even in F1 (Landrace x Large White) sows
493 (Scanlan et al., 2019). In Duroc, estimates of additive genetic variance for NBA and TNB were similar
494 across phases. This aligns with the overall greater phenotypic resilience observed in this study for
495 Duroc sows.

It is expected that the additive genetic variance of traits that have been selected in a clean and healthy environment will be higher in diseased animals compared to healthy animals (Berghof et al., 2019). Terminal lines such as Duroc are selected for higher feed efficiency, carcass, and growth traits, not for maternal traits, in contrast to Landrace (Bishop et al., 2010). In this study, the presence of this pattern, however, varied between breeds and traits. For Duroc, the estimates for TNB and NBA were very similar across phases, whereas, for NBD, NSB, NBM, and NW, these estimates substantially increased from the pre-PRRS to the PRRS phase, and then decreased during the post-PRRS phase. For Landrace, estimates of additive genetic variances increased from the pre-PRRS to the PRRS phase for NBD, NSB, NBM, and NW too. During the post-PRRS phase, these estimates generally decreased for these traits.

Most studies that included r_g estimates between PRRS phases partitioned data into only two phases (healthy and disease phases), combining data from prior to and after the outbreak as one phase only (Lewis et al., 2009b; Rashidi et al., 2014; Scanlan et al., 2019). On the other hand, Putz et al. (2019) reported r_g estimates between traits across different PRRS phases (pre-PRRS, PRRS, and post-PRRS). We also split data into three phases to better understand changes over time, to analyze how litter size traits eventually return to their production levels after the outbreak, and to identify differences between breeds in their ability to recover from the PRRS outbreak. Putz et al. (2019) and Scanlan et al. (2019) have shown that the reproductive performance of healthy and PRRSV-infected sows is highly genetically correlated. The r_g estimates between litter mortality traits in this study prior to and during a PRRSV infection were consistent with those previous findings. These results suggest that selecting animals in a clean environment for improved reproductive performance before an outbreak would also improve the reproductive performance of animals infected with PRRSV. However, h2 estimates for reproductive performance are still low, and the use of an indicator trait to indirectly increase response to selection for these traits would be desirable.

Putz et al. (2019) estimated low r_g between reproductive performance prior to and after a PRRSV infection in maternal breeds. They also indicated that the reproductive performance in healthy sows previously exposed to PRRSV might have a different genetic control than in naïve animals. In contrast, we found much higher r_g estimates between survival traits prior to and after a PRRSV infection than Putz et al. (2019) for both breeds, suggesting that reproductive traits in naïve animals and healthy animals after infection share a common genetic control. These conflicting results indicate that additional studies are needed to understand this relationship better. Nonetheless, in our study and in Putz et al. (2019), the standard errors associated with estimates of genetic correlation were large, suggesting that results might not be real. Some r_g estimates for litter mortality traits between PRRS phases had convergence issues in our study, partially explained by the low sample size and the large standard errors.

Overall, these results indicate that selection for improved reproductive performance during a PRRS outbreak is possible, but with limited efficiency because of the low heritability estimates of these traits, regardless of the PRRS phase. Therefore, the identification of an indicator trait, such as antibody response to PRRSV as proposed by Serão et al. (2014), would greatly benefit the swine industry to accelerate the rate of genetic improvement for these traits under a PRRS outbreak. Antibody response to PRRSV, measured as S/P ratio, was shown to be moderately heritable in Landrace and Duroc sows during a PRRS outbreak. In combination with the high genetic correlation between S/P ratio and NBA in Landrace (0.61) and the negative genetic correlations with mortality traits, Hickmann et al. (2021) validated the use of S/P ratio as an indicator trait for improved reproductive performance under a PRRS outbreak in Landrace populations. In addition, Sanglard et al. (2020) demonstrated that antibody response to PRRSV vaccination in gilts is highly genetically correlated with subsequent reproductive performance in the absence of a PRRS outbreak. Nonetheless, the high genetic correlations between PRRS phases suggest that selection for improved reproductive performance in a clean environment

(i.e., in the absence of PRRS) could result in improved response during a PRRS outbreak, but with limited efficiency due to their low heritability estimates. In addition, the large standard errors associated with these estimates must be taken into consideration.

4.4 Effect of SNPs previously associated with response to PRRS

The WUR SNP on SSC 4 has been associated with PRRSV tolerance in growing pigs, in which AB piglets had favorable performance compared to those with the AA genotype (Boddicker et al., 2012; Hess et al., 2018). Serão et al. (2014) identified associations (P-value $\leq$ 0.057) between WUR genotype and NBA and NW during the pre-PRRS phase in an outbreak study, with AB sows having better performance than AA sows. In our study, the only association (P-value = 0.037) between the genotype at WUR SNP and reproductive performance was found for pre-PRRS NW in Landrace sows. Contrary to Serão et al. (2014), AA animals had greater performance (9.61 ± 0.20) than AB (9.23 ± 0.24) animals. Serão et al. (2014) did not find associations (P-value > 0.10) within the PRRS phase, neither did we (P-value $\geq$ 0.266). In our study, there were no associations (P-value $\geq$ 0.363) between the WUR SNP and reproductive performance in both Duroc and Landrace sows during the post-PRRS phase. Although the effect of the WUR SNP has been well validated in multiple studies in PRRSV-exposed growing pigs (Abella et al., 2016; Dunkelberger et al., 2017; Hess et al., 2018), its association with reproductive traits is limited in the literature. It could be that its effect on these traits is very small or, in fact, not existing. Our results could suggest the latter, although a much larger sample size might be needed to better understand this relationship, and we cannot accept the null hypothesis of lack of associations. Finally, with the large number of comparisons performed in this study for this marker (2 breeds X 3 phases X 6 traits = 36 tests), which was not accounted for in the significance tests, the association with NW in Duroc during the pre-PRRS phase could be a false positive.

Serão et al. (2014) found an association (P-value < 0.001) between the MARC SNP on SSC 1 with NSB in reproductive sows during the PRRS phase, with BB sows showing favorable performance. In our study, there were no associations between this SNP and NSB (P-value = 0.571). However, there were associations with other reproductive traits (TNB, NBM, NBA, and NBD) in Landrace sows during the PRRS phase. As in Serão et al. (2014), we also found favorable associations for sows with the BB genotype for the MARC SNP. With the exception of NBA, in which AA (8.26 ± 0.83) and BB (7.60 ± 0.34) animals had greater performance than AB (6.75 ± 0.41) sows, greater performance in TNB, NBM, and NBD was obtained as the number of the B allele increased in Landrace sows. There were no associations with reproductive traits in Duroc sows during the PRRS phase. This lack of associations could be because Duroc sows are selected for different traits than Landrace sows, and thus, the linkage disequilibrium between this marker and the QTL might be weak. On the other hand, during the post-PRRS phase, there were significant associations (P-value ≤ 0.055) between the MARC SNP and reproductive traits (TNB, NBA, and NW) for Duroc sows but not for Landrace sows. Interestingly, these associations for Duroc were not found during the pre-PRRS phase, although pre-PRRS traits were highly genetically correlated with the corresponding post-PRRS traits. Furthermore, the QTL that harbors this SNP on SSC1 for NSB during the PRRS phase in Serão et al. (2014) was not identified in this study for any of the traits, further supporting that this region might not be important in the populations used in our study. Altogether, the MARC SNP seems to have a much greater potential to be used as a genetic marker for improved reproductive performance than the WUR SNP. Nonetheless, the significant associations observed for the MARC SNP in this independent dataset bring new possibilities for marker-assisted selection for improved reproductive performance under a PRRS outbreak in Landrace sows or following a PRRS outbreak in Duroc sows. Further research is needed to pinpoint the reasons for the opposite results in these two populations, while focusing on identifying the quantitative trait nucleotide responsible for this effect.

590 **4.5 Genome-wide association studies**

591 Reports on GWAS for reproductive traits in PRRSV-infected sows are scarce in the literature. Most
592 studies have performed GWAS analyses to investigate genomic regions associated with host response
593 to experimental PRRSV infection in growing pigs (Boddicker et al., 2012, 2014a,b; Waide et al., 2018).
594 These studies have provided information about major QTL associated with viremia and weight gain in
595 pigs. Lewis et al. (2009c) reported SNPs associated with reproductive traits during a PRRS outbreak
596 in sows but did not report the specific genomic regions associated with these traits. Orrett (2017) also
597 reported several QTL associated with reproductive performance in PRRSV-infected sows: on SSC 1
598 (220–226 Mb) for NBM, on SSC 5 (89–93 Mb), SSC 6 (78–80 Mb), and SSC 9 (127–137) for NSB,
599 on SSC 10 (69–70 Mb) for NBD, and on SSC 3 (28–30 Mb), SSC 4 (137–140 Mb), SSC 7 (107–113
600 Mb), and SSC 8 (26–28 Mb) for NBA. None of these genomic regions were identified in our study.
601 Serão et al. (2014) reported a QTL on SSC 1 (32–35 Mb) that explained 11% of TGVM for NSB and
602 1% TGVM for NBD during the PRRS phase in Landrace sows. In our study, there were no QTL
603 associated with NSB in the PRRS phase in Landrace, but we did find a QTL for this trait in Duroc
604 sows (Table 8).

605 We also found other QTL associated with reproductive traits during the PRRS outbreak in both breeds
606 that were not previously reported. Two QTL appeared to be associated with more than one trait: the
607 QTL on SSC 13 (189–190 Mb) that was associated with NBD and NW in Duroc sows, and the QTL
608 on SSC 9 (11–13 Mb) that was associated with NBD and NBM in Landrace sows. The 6-Mb region
609 on SSC 5 associated with TNB in Duroc sows has not previously been associated with reproductive
610 traits in sows. This region had the largest %TGVM in this study, with 7.2%. Two candidate genes in
611 this region play a role in reproduction; the GLIPR1-like protein 1 gene (*GLIPR1L1*) involved with
612 fertilization, with a potential role in sperm-oocyte binding (Gibs et al., 2010), and the GLIPR1-like
613 protein 2 gene (*GLIPR1L2*) that plays a role in a great variety of processes, including immune response

614 and membrane development (Ren et al., 2006). Zhang et al. (2019) reported two QTL on SSC 5 (9 and
615 67 Mb) associated with litter size traits at birth in non-PRRS-infected Duroc sows. These two regions
616 are in a different position than the 36–41 Mb region associated with TNB in our study; however, the
617 QTL located at 9 Mb overlaps with the region associated with NSB in our study for Duroc. Four genes
618 in this 1-Mb interval are related to reproductive development and energy metabolism that may play a
619 role during a viral infection. The apolipoprotein B mRNA editing enzyme catalytic subunit 3B gene
620 (*APOBEC3B*) acts as an inhibitor of retrovirus replication and retrotransposon mobility. This gene
621 protects the cell or organism in the presence of a virus with species specific interactions (Schröfelbauer
622 et al., 2004). The Eukaryotic translation initiation factor 3 subunit L gene (*EIF3L*) plays a role in the
623 process of viral translational termination-reinitiation and is required for several steps in the initiation
624 of protein synthesis (Masutani et al., 2007; Lee et al., 2015). Both Platelet-derived growth factor
625 subunit B (*PDGFB*) and SRY-box transcription factor 10 (*SOX10*) genes are also located within this
626 1-Mb region and regulate embryonic development, being involved in the cell response to growth factor
627 stimulus as well (Sekido and Lovell-Badge, 2009). Another region including a reproductiverelated
628 gene is the 3-Mb region on SSC 10 associated with NBA in Landrace sows, which harbors a gene
629 associated with spermatogenetic failures, the spermatogenesis associated 17 gene (*SPATA17*; Deng et
630 al., 2006). We did not find any candidate genes that play a role in reproduction within the QTL on SSC
631 14 (125–126 Mb) for NW in Duroc sows, or within the QTL on SSC 13 (156–160 Mb) for NBA in
632 Landrace sows.

633 A large number of QTL have been reported in the literature for reproductive traits in non-infected pigs
634 (Onteru et al., 2011; Verardo et al., 2016; Suwannasing et al., 2018). These QTL considerably varied
635 depending on the trait being considered. We identified several QTL associated with reproductive traits
636 for the pre-PRRS phase that were not previously reported. Two QTL were associated with two traits:
637 the QTL on SSC 9 (8–10 Mb) and the QTL on SSC 16 (2–5 Mb), both of them associated with TNB

638 and NBA in Landrace sows. Other QTL associated with more than one trait had some overlapping
639 regions, such as the QTL on SSC 5 (4–8 Mb) and the QTL on SSC 5 (7–10 Mb) associated with TNB
640 and NBA, respectively, in Landrace sows. Interestingly, the same genomic regions controlling TNB
641 were also associated with NBA in Landrace sows. The QTL found on SSC 15 (119 Mb) for NW in
642 Duroc sows was also found in Landrace sows, however, for NBM. In this region, there is a candidate
643 gene that plays a role in reproduction: the transition protein 1 gene (TNP1) involved with
644 spermatogenesis in mammals (Khattri et al., 2011). Another region including a reproductive-related
645 gene is the 3- Mb region on SSC 7 (31–33 Mb) close to the MHC region that was associated with NBA
646 in Duroc sows during the pre-PRRS phase, which harbors a gene associated with sperm capacitation,
647 the T-complex protein 11 gene (TCP11; Castaneda et al., 2020).

648 Several QTL with relatively small effects were found in this study for both breeds in each PRRS phase.
649 However, none of the identified QTL overlapped between phases for either breed. This result was
650 somewhat unexpected because genetic correlation estimates of reproductive traits between PRRS
651 phases were generally high and positive, indicating similar genetic control for them, regardless of the
652 PRRS phase. However, the power of detecting QTL in GWAS is impacted by the heritability of the
653 trait and sample size. Thus, the low heritability estimates of these traits and the small sample size
654 limited the identification of QTs for the same trait being identified between PRRS phases.

655 The number of identified QTL was much greater for the pre-PRRS phase than for the PRRS phase for
656 both breeds. Although the number of animals used in the analyses were similar between these two
657 phases, they were overall low. In addition, lowly heritable traits have a lower statistical power of
658 GWAS to detect QTL, and thus, it could be that a larger dataset would result in more similar results
659 between phases. Additionally, we were not able to identify specific SNPs that explained most of the
660 %TGVM of the identified QTL. Most QTL identified in this study explained a low % TGVM of the
661 traits, further supporting the general perception that reproductive traits are highly polygenic.

662 **4.6 Genomic prediction accuracies**

663 Studies on genomics of response to PRRS have provided information on accuracies of genomic
664 prediction but, to date, only results using growing piglets have been reported (Boddicker et al., 2014a;
665 Waide et al., 2018). These authors reported high genomic prediction accuracies based on the WUR
666 region associated with viremia and weight gain in pigs. To the best of our knowledge, our study is the
667 first one to report GPAs of reproductive traits in PRRSV-infected sows.

668 Multiple scenarios were evaluated to perform genomic prediction of reproductive traits in PRRSV-
669 infected sows. Due to the high r_g estimates for reproductive traits between pre-PRRS and PRRS phases,
670 we evaluated how accuracies changed according to using data from only the PRRS phase, from only
671 the pre-PRRS, or a combination of both. Furthermore, with the exception of GPSpre□PRRS, all
672 analyses were performed using cross-validation (i) to avoid biased GPAs when using data from the
673 PRRS phase for training SNP effects, and (ii) to better represent how genomic selection is done in
674 practice. All these strategies resulted in a different number of animals used for training and validation,
675 as seen in Supplementary Table 1. Finally, we used different statistical methods for genomic prediction;
676 however, results were very similar across methods, further suggesting that no major QTL control the
677 traits evaluated in this study. In general, there was not consistency in results according to GPSs across
678 traits and breeds. Nonetheless, GPA results for Landrace were all positive and less variable compared
679 to Duroc, which had large variation in GPAs with positive and negative values within traits and GPSs.

680 The GPAs of reproductive traits during a PRRS outbreak using marker estimates during the outbreak
681 (i.e., GPSPRRS) were generally low to moderate. However, compared to the other GPSs, this scenario
682 had overall lower variation in GPAs across folds. In Duroc, GPAs using GPSPRRS were low and
683 positive for TNB (GPA ± SD across folds = 0.32 ± 0.05), NBA (0.31 ± 0.01), and NBD (0.09 ± 0.06),
684 and moderate and negative for NSB (-0.57 ± 0.04) and NBM (-0.46 ± 0.12). The only trait that had a

substantial favorable GPA for this scenario in Duroc was NW, with 0.69 ± 0.06. In fact, this GPS was the best one for NW in Duroc. In Landrace, with the exception of TNB that had a very low GPA (0.09 ± 0.09), this scenario resulted in the largest or comparable GPAs for the other traits compared to the other GPSs. This scenario had the best GPA for NBA (0.37 ± 0.03), NBD (0.55 ± 0.12), and NBM (0.41 ± 0.14), and the second best for NSB (0.46 ± 0.08) and NW (0.44 ± 0.14). Therefore, genomic prediction of reproductive performance during a PRRS outbreak seems to be worthwhile in Landrace sows only.

In general, the r_g estimates of reproductive traits were moderate-high and positive between pre-PRRS and PRRS phases. Hence, we would expect high GPAs using $GPS_{pre\text{-}PRRS}$ and $GPS_{pre\text{-}PRRS\text{-}4FCV}$; however, this was not the case in these analyses. In Duroc, with the exception of NBA, all other traits had contrasting results between $GPS_{pre\text{-}PRRS}$ and $GPS_{pre\text{-}PRRS\text{-}4FCV}$, where GPAs were negative for one GPS and positive for the other. For example, training markers in the pre-PRRS phase using the same animals for training and validation (i.e., $GPS_{pre\text{-}PRRS}$) was only beneficial for TNB (GPA = 0.60), whereas NBA had a very low GPA (~0) and the other traits had substantially negative GPAs, ranging from -0.31 for NW to -1.03 for NBM. Interestingly, when a 4FCV was used when training markers in the pre-PRRS phase (i.e., $GPS_{pre\text{-}PRRS\text{-}4FCV}$), all results improved, with the exception for TNB (GPA = -0.39 ± 0.60). However, these remained negative for NBD (-0.03 ± 0.71) and NBM (-0.02 ± 1.93), and it was very low and positive for NW (0.02 ± 0.90). In contrast, the GPA for NSB in $GPS_{pre\text{-}PRRS\text{-}4FCV}$ was high and positive (0.84 ± 1.42), albeit very variable across folds. Finally, the GPA for NBA (0.31 ± 0.55) was the same level as in GPS_{PRRS} (0.31 ± 0.01), although the latter had a much lower variation across folds than the former. These results did not align with the r_g estimates of reproductive traits in Duroc between pre-PRRS and PRRS phases in Table 6. This could be due to the overall low sample size used in this study, which resulted in wide standard errors for the r_g estimates, as well as large SD of GPAs across folds (Supplementary Table 2).

In Landrace, results between $GPS_{pre\text{-}PRRS}$ and $GPS_{pre\text{-}PRRS\text{-}4FCV}$ were much more consistent across traits. The only exception was for TNB. The GPA for this trait using $GPS_{pre\text{-}PRRS}$ (1.16) was the highest across all traits and GPSs in Landrace. Although the GPA of TNB using $GPS_{pre\text{-}PRRS\text{-}4FCV}$ was also high (0.77 ± 1.95), it was very variable across folds. For other traits, GPAs were moderate low for NBD, NSB, and NW, and close to zero for NBA and NBM. Moreover, these were consistently lower than the GPAs obtained when only the PRRS data were used for analyses (i.e., GPS_{PRRS}). Contrary to what was seen in Duroc, the genomic prediction analyses of reproductive traits during a PRRS outbreak in Landrace sows were much more aligned with the r_g estimates between the pre-PRRS and PRRS phases in Table 6. Hence, phenotypic and genomic data from healthy sows could be used to promote improved reproductive performance during a PRRS outbreak.

The other two GPSs evaluated in this study (i.e., $GPS_{pre\text{-}PRRS;PRRS}$ and $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$) aimed to evaluate the use of data from both pre-PRRS and PRRS phases to predict reproductive performance during a PRRS outbreak. In both scenarios, marker estimates were obtained separately using data from the pre-PRRS and PRRS phases. Then, GEBVs in the validation sets were calculated as the average GEBV based on the estimates from each phase. This strategy was used because GWAS and r_g estimates results within a breed did not indicate that the genomic control of reproductive traits is the same between pre-PRRS and PRRS phases. Therefore, we expected that the results for $GPS_{pre\text{-}PRRS;PRRS}$ would be a combination of the results based on GPS_{PRRS} and $GPS_{pre\text{-}PRRS}$, whereas for $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$ would be a combination of the results based on GPS_{PRRS} and $GPS_{pre\text{-}PRRS\text{-}4FCV}$. In fact, this was observed in most cases.

In most analyses, GPAs using $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$ were greater than using $GPS_{pre\text{-}PRRS;PRRS}$. This is in accordance with the previous results shown for $GPS_{pre\text{-}PRRS\text{-}4FCV}$, which had overall greater GPAs than for $GPS_{pre\text{-}PRRS}$, especially in Duroc sows. In Duroc, these two GPSs had overall the best results across all GPSs. $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$ resulted in the highest GPAs in Duroc for NBA (0.61 ± 0.48), NBD

(0.55 ± 0.73), NSB (0.98 ± 2.05), and NBM (1.19 ± 2.55), whereas $GPS_{pre\text{-}PRRS;PRRS}$ had the highest GPA for TNB (0.60 ± 0.12; which was the same as using $GPS_{pre\text{-}PRRS}$). Among these results, the GPA for NBM was the only unexpected one since the GPAs for this trait using GPS_{PRRS} and $GPS_{pre\text{-}PRRS}$ were moderate to high and negative, with -0.46 ± 0.12 and -1.03, respectively. In addition, this analysis had the largest SD of GPAs across folds using BayesB, with 2.55. In fact, $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$ had the overall greater variability in GPAs across folds (average SD of 1.24) in Duroc compared to all other GPS, followed by $GPS_{pre\text{-}PRRS\text{-}4FCV}$ (average SD = 1.02). Although this GPS resulted in overall better GPAs than all other GPS, this large variability in results suggests that such strategy might not be used to accurately obtain GEBVs for reproductive performance during a PRRS outbreak in Duroc.

In contrast, $GPS_{pre\text{-}PRRS\text{-}4FCV}$ had the second lowest variability in GPAs across folds (average SD = 0.49), behind only GPS_{PRRS} (average SD = 0.1). In general, differences in GPAs between $GPS_{pre\text{-}PRRS;PRRS}$ and $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$ were small. Furthermore, with the exception of TNB, results were consistently better than for $GPS_{pre\text{-}PRRS}$ and $GPS_{pre\text{-}PRRS\text{-}4FCV}$, and similar to those in GPS_{PRRS}. Although GPAs for NSB (0.48 ± 0.29) and NW (0.45 ± 0.31) in $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$ were numerically greater than in GPSPRRS (0.46 ± 0.08 and 0.44 ± 0.14 for NSB and NW, respectively), the latter had a much lower GPA SD across folds than the former. This was also the case for the GPAs of the other traits that were similar between GPS_{PRRS} and these two GPS ($GPS_{pre\text{-}PRRS;PRRS}$ and $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$): (i) for NBA, GPAs were 0.37 ± 0.03 and 0.35 ± 0.27 for GPS_{PRRS} and $GPS_{pre\text{-}PRRS\text{-}4FCV;PRRS}$, respectively; (ii) for NBD, GPAs were 0.55 ± 0.12 and 0.54 ± 0.31 for GPS_{PRRS} and $GPS_{pre\text{-}PRRS;PRRS}$, respectively; and (iii) for NBM, GPAs were 0.41 ± 0.14 and 0.34 ± 0.51 for GPS_{PRRS} and $GPS_{pre\text{-}PRRS;PRRS}$, respectively. Therefore, the marginal increase in GPAs when pre-PRRS data were used in combination with PRRS data for some of the traits does not seem to offset the greater variability in GPAs using this strategy.

The genomic prediction results presented in this study indicate that reproductive performance under a PRRS outbreak can be improved through genomic selection. However, Duroc results were highly

757 variable across GPSs and traits, without a clear pattern, indicating that additional research is needed to
758 evaluate the use of genomic selection for improved reproductive performance under a PRRS outbreak
759 for this breed. However, it is important to note that this is a terminal breed, and hence, little emphasis
760 is put on maternal traits in its selection index. In contrast, results for Landrace were more consistent.
761 In general, using only data from the PRRS phase had similar results to those in which GEBVs were
762 based on those obtained from the separate analyses using the pre-PRRS and PRRS phases. However,
763 the high variability in GPAs when the data were combined does not support the use of this strategy to
764 promote genetic gains for reproductive performance under a PRRS outbreak. Hence, the use of PRRS
765 data only to train marker estimates is indicated. Nonetheless, additional strategies should be
766 exanimated in the future, such as combining both pre-PRRS and PRRS phases when estimating marker
767 effects. However, this strategy assumes that marker estimates are the same in both phases. Although
768 this is a strong assumption, the overall high r_g estimates of reproductive performance between the pre-
769 PRRS and PRRS phases indicate that there is potential in using this strategy to increase the size of the
770 training set, which should then increase the accuracy of the marker estimates. Nonetheless, the
771 proportion of data from each phase used in the training set should impact these results.

772 **5. Conclusions**

773 Our results indicate that heritabilities are overall low for most reproductive traits, regardless of PRRS-
774 phase. The high genetic correlations with reproductive traits between PRRS phases suggest that
775 selection for improved reproductive performance in a clean environment (i.e., in the absence of PRRS)
776 would improve response during a PRRS outbreak, but with limited efficiency due to their low
777 heritability estimates. Thus, an indicator trait that we can indirectly use to increase the response to
778 selection for these traits is then desirable. Our results also indicate that, phenotypically, Duroc sows
779 are less impacted by PRRS than Landrace sows, indicating that they have overall greater PRRS
780 resilience than Landrace sows. The MARC0034894 SNP previously associated with NSB during a

PRRSV infection was associated with most traits in our study. Associations between this SNP and reproductive performance were found depending on the trait, breed, and PRRS phase. Nonetheless, results indicate that this marker has the potential to be used to improve reproductive performance. In contrast, the lack of substantial associations between the WUR10000125 SNP with reproductive performance does not support the use of this marker for reproductive performance. Genomic analyses showed that several QTL control reproductive performance, most of them explaining a very small percentage of the additive genetic variance, indicating that these traits are highly polygenic. Our study is the first one to provide genomic prediction accuracies for reproductive traits during a PRRS outbreak. Although results were overall variable in Duroc, those from Landrace indicate that genomic selection for improved reproductive performance during a PRRS outbreak might be more accurate by training markers using data from PRRSV-infected sows. Overall, this study helped to understand better the genetic basis of PRRS response to potentially improve the reproductive performance of sows.

6. Conflict of Interest

The authors declare that this study received funding from Smithfield Premium Genetics, NC, United States. The funder had the following involvement with the study: providing performance and genotype data and collection of blood samples. In addition, YH and KG are employed by the company Smithfield Premium Genetics, NC, United States. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7. Author Contributions

FH performed statistical analyses, interpreted results, prepared figures and tables, and drafted the manuscript. JB, LK, and JD were involved in the interpretation and discussion of results. YH and KG provided the data, led the collection of blood samples, and interpreted results. LS provided help and

guidance for statistical analyses, being involved in the discussion of results as well. NS assisted with data analysis, interpretation of results, and drafted the manuscript. All authors read and approved the final version of the manuscript.

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9. Abbreviations

APOBEC3B: apolipoprotein B mRNA editing enzyme catalytic subunit 3B gene; *EIF3L*, eukaryotic translation initiation factor 3 subunit L gene; FYW, Farrow-year-week; GEBV, genomic estimated breeding value; *GLIPR1L1*, GLIPR1-like protein 1 gene; *GLIPR1L2*, GLIPR1-like protein 2 gene; GPA, genomic prediction accuracy; GPS, genomic prediction scenarios; GWAS, genome-wide association studies; MARC, MARC0034894; Mb, megabases; MCMC, Markov Chain Monte Carlo; NBA, number of piglets born alive; NBA_{TNB}, number of piglets born alive with total number of piglets born used as the offset; NBD, number of piglets born dead; NBD_{TNB}, number of piglets born dead with total number of piglets born used as the offset; NBM, number of mummified piglets; NBM_{TNB}, number of mummified piglets with total number of piglets born used as the offset; NSB, number of stillborn piglets; NSB_{TNB}, number of stillborn piglets with total number of piglets born used as the offset; NW, number of piglets weaned; $NW_{TNB;XF}$, number of piglets weaned with total number of piglets born and number of cross-fostered pigs used as the offset; $NW_{NBA;XF}$, number of piglets weaned with number of piglets born alive and number of cross-fostered pigs used as the offset; *PDGFB*, platelet-derived growth factor subunit B gene; PRRS, porcine reproductive and respiratory syndrome; PRRSV; porcine

827 reproductive and respiratory syndrome virus; QTL, quantitative trait loci; SNP, single nucleotide
828 polymorphisms; *SOX10*, SRY-box transcription factor 10 gene; *SPATA17*, spermatogenesis associated
829 17 gene; SSC, *Sus scrofa* chromosome; TGVM, total additive genetic variance accounted for by
830 markers; TNB, total number of piglets born; XF, net number of cross-fostered pigs; XV, cross-
831 validation; WUR, WUR10000125 SNP.

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835 of the first author.

836 **11. Data Availability Statement**

837 The datasets presented in this article are not readily available because the data that support the findings
838 of this study are not publicly available. Data may be available from authors upon reasonable request
839 and authorization from the company that generated the data.

840 **12. Supplementary material**

841 The Supplementary Material for this article can be found online at:
842 https://www.frontiersin.org/articles/10.3389/fgene.2021.707870/full#supplementary-material

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14. Figures

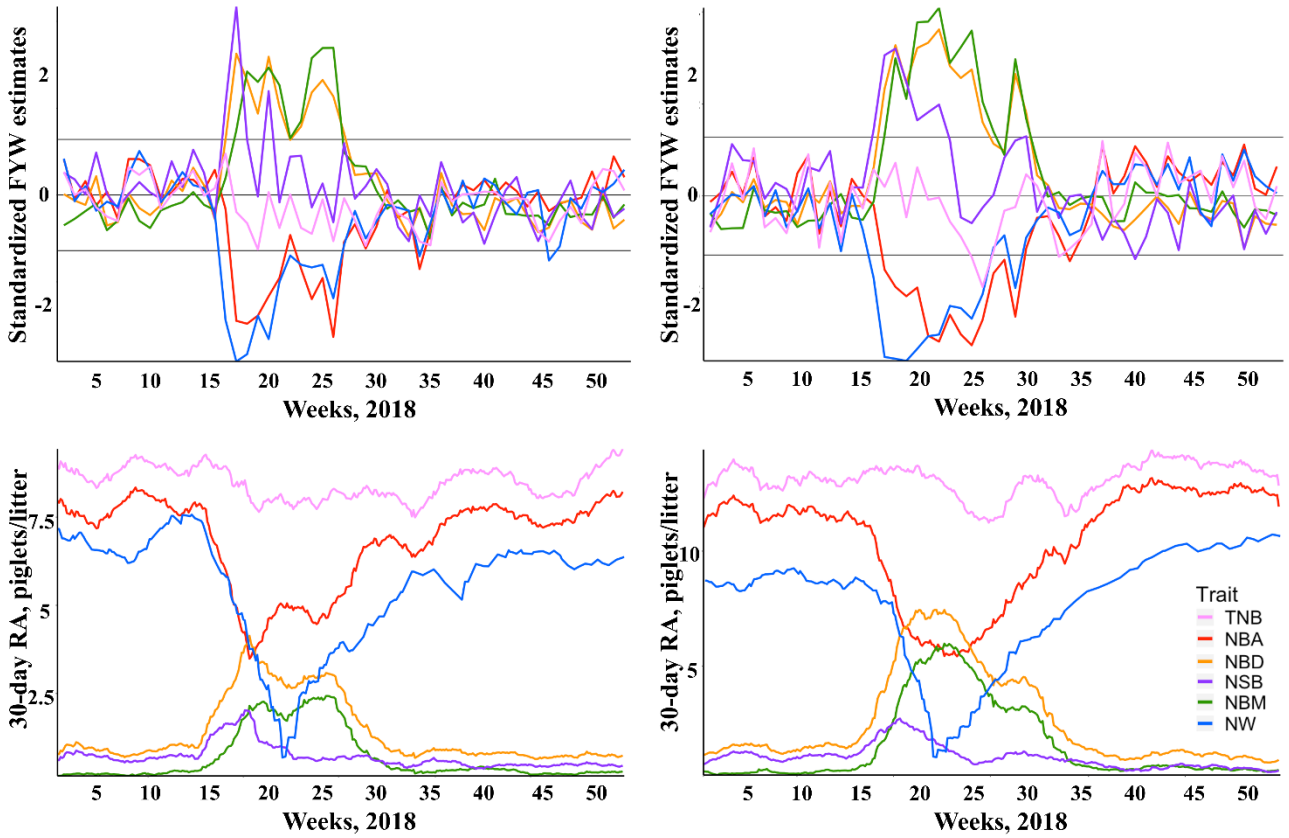

Figure 1. Impact of Porcine Reproductive and Respiratory Syndrome (PRRS) on herd average reproductive performance. Standardized estimates of farrow-year-week (FYW) during 2018 for each reproductive trait for Duroc **(A)** and Landrace **(B)** sows. Thirty-day rolling averages (RA) of reproductive traits for Duroc **(C)** and Landrace **(D)** sows.

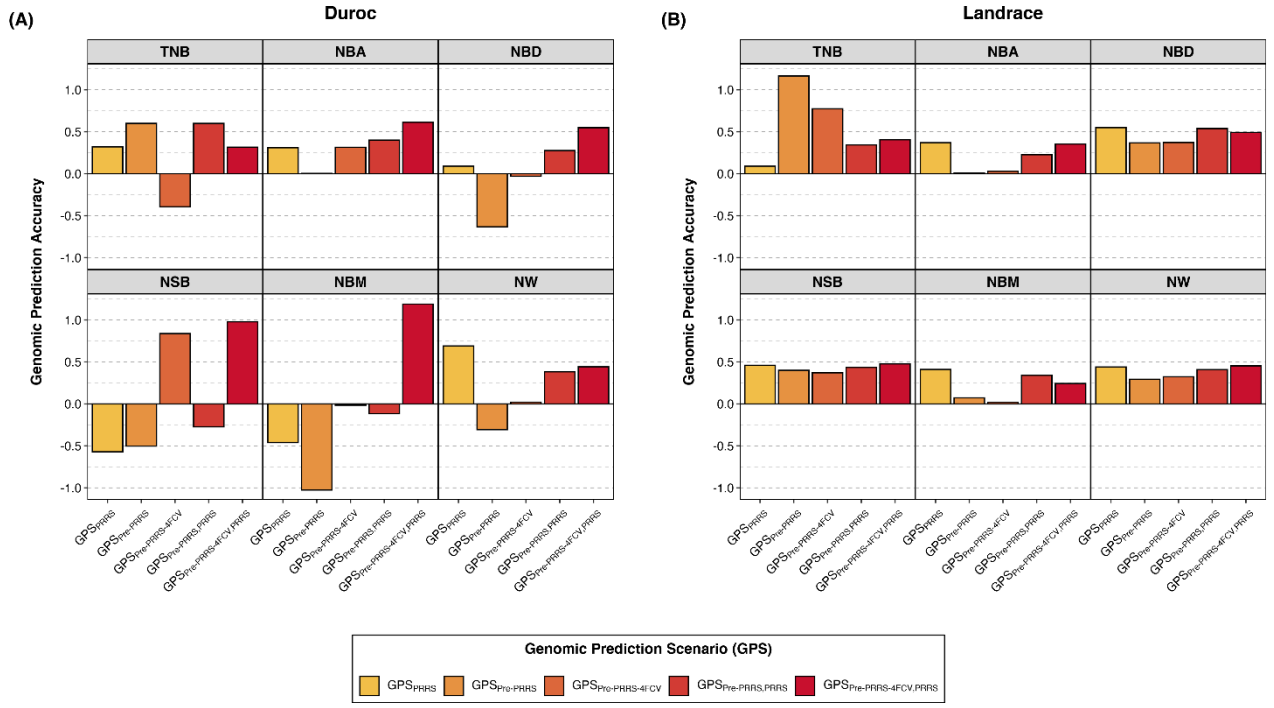

Figure 2. Genomic prediction accuracies of reproductive traits during a Porcine Reproductive and Respiratory Syndrome (PRRS) outbreak. Results are presented for Duroc **(A)** and Landrace **(B)** across genomic prediction scenarios (GPS) for total number born (TNB), number born alive (NBA), number born dead (NBD), number of stillborn (NSB), number born mummified (NBM), and number of piglets weaned (NW) using BayesB. The y-axis represents the genomic prediction accuracy and the x-axis the GPS. Details for the different GPS are available in **Table 2**. Results for all methods and standard deviations across folds are available in **Supplementary Table 2**

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15. Tables

Table 1. Summary statistics of reproductive traits[1] by breed.

	Duroc				Landrace			
Trait[2]	N[3]	Mean (SD)	Min	Max	N[3]	Mean (SD)	Min	Max
TNB	2511	8.61 (2.96)	3	19	2505	13.36 (4.00)	3	24
NBA	2546	7.41 (3.00)	0	17	2522	11.47 (4.08)	0	22
NBD	2511	1.15 (2.96)	0	15	2505	1.89 (2.78)	0	23
NSB	2546	0.62 (1.10)	0	15	2522	0.89 (1.43)	0	22
NBM	2511	0.52 (1.32)	0	15	2505	0.99 (2.21)	0	22
NW	2504	6.36 (3.07)	0	23	2476	9.04 (3.82)	0	26

[1]Expressed as number of piglets/litter (standard errors in parenthesis);
[2]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NBM, number of mummified piglets; NW, number of piglets weaned;
[3]Number of litters that have the trait recorded out of 2546 and 2522 litters from 894 Duroc and 813 Landrace sows, respectively.

Table 2. Summary of genomic prediction scenarios (GPS) evaluated.

	Training datasets[1]			Validation dataset (PRRS)[2]		Calculation of GEBVs[3,4]	
	Pre-PRRS						
Scenario	All	Folds	PRRS (Folds)	All	Folds	All	Folds
GPS_{PRRS}	-	-	✓	-	✓		✓
$GPS_{pre\text{-}PRRS}$	✓	-	-	✓	-	✓	
$GPS_{pre\text{-}PRRS\text{-}4FCV}$	-	✓	-	-	✓		✓
$GPS_{pre\text{-}PRRS,PRRS}$	✓	-	✓	-	✓	½	½
$GPS_{pre\text{-}PRRS\text{-}4FCV,PRRS}$	-	✓	✓	-	✓	½	½

[1]Source of data used in the training dataset. In GPSs including both phases (pre-PRRS and PRRS), marker effects were estimated separately for each source of data;
[2]In all analyses, data from the PRRS phase was used for validation;
[3]Genomic estimated breeding values (GEBVs);
[4]In the last two GPSs ($GPS_{pre\text{-}PRRS,PRRS}$ and $GPS_{pre\text{-}PRRS\text{-}4FCV,PRRS}$), the GEBV of each individual was calculated as the average GEBV obtained from the marker effects estimates using each training set (i.e., pre-PRRS and PRRS phases).

Table 3. Summary statistics of reproductive traits[1] by PRRS[2] phase and breed.

	Duroc				Landrace			
Trait[3]	N[4]	Mean (SD)	Min	Max	N[4]	Mean (SD)	Min	Max
Pre-PRRS phase								
TNB	1004 (478)	8.94 (2.88)	3	19	1096 (461)	13.36 (3.79)	3	24
NBA	1004 (478)	7.90 (2.67)	0	18	1096 (461)	11.81 (3.33)	0	22
NBD	978 (468)	1.03 (1.37)	0	13	1073 (450)	1.55 (1.87)	0	18
NSB	978 (468)	0.66 (1.02)	0	9	1073 (450)	1.01 (1.44)	0	13
NBM	978 (468)	0.37 (0.80)	0	10	1073 (450)	0.54 (0.99)	0	13
NW	1004 (478)	6.98 (2.51)	0	24	1096 (461)	9.37 (2.96)	0	26
PRRS phase								
TNB	494 (494)	7.89 (3.13)	3	19	429 (429)	12.59 (3.98)	3	24
NBA	501 (501)	5.50 (3.30)	0	15	432 (432)	7.53 (4.73)	0	19
NBD	494 (494)	1.40 (1.19)	0	15	429 (429)	3.24 (1.47)	0	23
NSB	501 (501)	0.59 (0.75)	0	12	432 (432)	0.93 (0.90)	0	12
NBM	494 (494)	0.75 (1.11)	0	15	429 (429)	1.99 (1.61)	0	22
NW	501 (501)	3.92 (3.19)	0	12	432 (432)	4.84 (4.15)	0	14
Post-PRRS phase								
TNB	1028 (542)	8.63 (3.03)	3	17	980 (513)	13.75 (3.82)	3	24
NBA	1028 (542)	7.82 (2.79)	0	17	980 (513)	12.55 (3.46)	0	22
NBD	1079 (558)	0.78 (1.19)	0	15	1025 (527)	1.26 (1.96)	0	23
NSB	1079 (558)	0.50 (0.92)	0	15	1025 (527)	0.75 (1.47)	0	22
NBM	1079 (558)	0.28 (0.68)	0	9	1025 (527)	0.51 (1.19)	0	22
NW	1028 (542)	6.69 (3.21)	0	23	980 (513)	10.05 (3.59)	0	26

[1]Expressed as number of piglets (standard errors in parenthesis);
[2]Porcine Reproductive and Respiratory Syndrome (PRRS);
[3]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NBM, number of mummified piglets; NW, number of piglets weaned;
[4]Number of litters (number of sows).

Table 4. Effect[1] of PRRS[2] phase and breed on reproductive traits.[3]

Phase	*Breed*	NBA_{TNB}	NBD_{TNB}	NSB_{TNB}	NBM_{TNB}	$NW_{TNB, XF}$	$NW_{NBA, XF}$
Pre-PRRS	Duroc	0.866^{b} (0.013)	0.122^{c} (0.007)	0.083^{c} (0.005)	0.039^{b} (0.003)	0.750^{a} (0.019)	0.787^{a} (0.021)
	Landrace	0.882^{ab} (0.011)	0.106^{b} (0.005)	0.070^{b} (0.004)	0.034^{ab} (0.003)	0.700^{bc} (0.016)	0.716^{bc} (0.018)
PRRS	Duroc	0.676^{c} (0.017)	0.299^{d} (0.023)	0.125^{d} (0.011)	0.150^{c} (0.017)	0.371^{d} (0.018)	0.342^{d} (0.017)
	Landrace	0.590^{d} (0.014)	0.396^{e} (0.030)	0.124^{d} (0.011)	0.232^{d} (0.025)	0.322^{e} (0.015)	0.294^{e} (0.015)
Post-PRRS	Duroc	0.895^{ab} (0.014)	0.093^{ab} (0.005)	0.063^{b} (0.004)	0.030^{a} (0.003)	0.722^{ab} (0.024)	0.742^{ab} (0.026)
	Landrace	0.905^{a} (0.012)	0.087^{a} (0.005)	0.053^{a} (0.003)	0.033^{ab} (0.003)	0.689^{c} (0.023)	0.705^{c} (0.023)
ANOVA P-values							
Breed		0.001	0.483	0.011	0.010	<0.001	<0.001
Phase		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Breed*Phase		<0.001	<0.001	0.300	<0.001	0.026	0.018
Contrast P-values[5]							
Resilience		<0.001	<0.001	0.161	<0.001	0.039	0.127
Return to PRRSV-free Performance		0.712	0.329	0.969	0.103	0.307	0.073

[1]Results represented as proportions based on total number of piglets born (TNB), with or without the number of cross-fostered pigs (XF), or number of piglets born alive (NBA) with XF. Standard errors in parenthesis;

[2]Porcine Reproductive and Respiratory Syndrome (PRRS);

[3]NBA_{TNB}: NBA with TNB used as the offset; NBD_{TNB}: Number of piglets born dead (NBD) with TNB used as the offset; NSB_{TNB}: Number of stillborn piglets (NSB) with TNB used as the offset; NBM_{TNB}: Number of mummified piglets (NBM) with TNB used as the offset; NW: Number of piglets weaned; $NW_{TNB,XF}$: NW with the sum of TNB and the net number of cross-fostered pigs (XF) used as the offset; $NW_{NBA,XF}$: NW with the sum of NBA and XF used as the offset;

[4]Resilience, contrast representing the differences between breeds for the difference between pre-PRRS and PRRS; Return to PRRSV-free performance, contrast representing the differences between breeds for the difference between pre-PRRS and post-PRRS;

[a-e] Means lacking the same superscript within a column indicate differences at *P*-value < 0.05.

Table 5. Estimates of genetic parameters[1,2] for reproductive traits by PRRS[3] phase and breed.

	Pre-PRRS phase			PRRS phase			Post-PRRS phase		
Trait[4]	h^2 (SE)	σ_a^2	σ_e^2	h^2 (SE)	σ_a^2	σ_e^2	h^2 (SE)	σ_a^2	σ_e^2
					Duroc				
TNB	0.01 (0.01)	1.08	6.48	0.11 (0.07)	1.03	8.38	0.15 (0.04)	1.36	7.49
NBA	0.01 (0.02)	1.36	5.60	0.12 (0.07)	1.33	9.56	0.13 (0.04)	1.01	6.66
NBD	<0.01 (0.01)	<0.01	0.29	0.09 (0.06)	0.05	0.54	0.11 (0.03)	0.03	0.24
NSB	<0.01 (0.01)	0.01	0.21	0.02 (0.05)	0.01	0.30	0.07 (0.03)	0.01	0.18
NBM	0.01 (0.02)	<0.01	0.13	0.02 (0.05)	0.01	0.53	0.06 (0.03)	0.01	0.11
NW	0.06 (0.03)	0.36	3.37	0.12 (0.06)	1.20	9.08	0.14 (0.04)	1.07	5.97
					Landrace				
TNB	0.05 (0.02)	1.82	12.63	<0.01 (0.05)	0.07	15.32	0.20 (0.04)	2.76	10.74
NBA	0.07 (0.02)	1.57	9.16	0.06 (0.06)	1.45	20.83	0.16 (0.04)	1.94	9.66
NBD	<0.01 (0.01)	0.02	0.35	0.13 (0.08)	0.10	0.71	0.10 (0.03)	0.03	0.32
NSB	0.01 (0.01)	0.03	0.25	0.16 (0.08)	0.06	0.35	0.12 (0.03)	0.03	0.22
NBM	0.02 (0.02)	<0.01	0.18	0.08 (0.07)	0.07	0.84	0.01 (0.02)	<0.01	0.19
NW	0.12 (0.03)	0.51	5.10	0.08 (0.07)	1.40	15.87	0.13 (0.04)	1.30	8.29

[1]Heritability, h^2; additive genetic variance, σ_a^2; residual variance, σ_e^2;
[2]Expressed as piglets^2 for TNB, NBA, and NW, and ln(piglets+1)^2 for the other traits;
[3]Porcine Reproductive and Respiratory Syndrome (PRRS);
[4]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NBM, number of mummified piglets; NW, number of piglets weaned.

Table 6. Estimates of genetic correlations of reproductive traits between PRRS[1] phases by breed.

Trait[2]	Pre-PRRS/PRRS	Pre-PRRS/Post-PRRS	PRRS/Post-PRRS
		Duroc	
TNB	0.06 (0.42)	0.85 (0.36)	0.81 (0.26)
NBA	0.73 (0.30)	0.87 (0.36)	0.10 (0.49)
NBD	0.38 (0.36)	NC[3]	0.71 (0.19)
NSB	0.73 (0.97)	0.33 (0.46)	NC[3]
NW	0.94 (0.56)	0.90 (0.38)	0.94 (0.44)
		Landrace	
TNB	0.70 (0.68)	0.69 (0.63)	0.96 (0.30)
NBA	0.47 (0.83)	NC[3]	0.68 (0.42)
NBD	0.84 (0.35)	0.90 (0.47)	0.31 (0.33)
NSB	0.83 (0.22)	NC[3]	0.10 (0.31)
NW	0.73 (0.53)	NC[3]	0.93 (0.47)

[1]Porcine Reproductive and Respiratory Syndrome (PRRS);
[2]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NW, number of piglets weaned;
[3]NC, Not Converged. Number born mummified (NBM) did not converge for both breeds.

Table 7. Least squares means[1] (SE) for reproductive traits across PRRS[2] phases for genotypes at the WUR10000125 and MARC0034894 SNP[3] in Duroc and Landrace sows.

	WUR10000125			MARC0034894			
Trait[4]	*AA*	*AB*	*P*-value	*AA*	*AB*	*BB*	*P*-value
Pre-PRRS phase							
Duroc							
TNB	9.62 (0.29)	9.38 (0.24)	0.308	9.70 (0.35)	9.50 (0.26)	9.29 (0.25)	0.386
NBA	8.46 (0.28)	8.22 (0.23)	0.290	8.61 (0.34)	8.30 (0.25)	8.10 (0.24)	0.273
NBD[5]	0.77 (0.05)	0.79 (0.04)	0.794	0.72 (0.06)	0.81 (0.05)	0.80 (0.04)	0.633
NSB[5]	0.52 (0.05)	0.53 (0.04)	0.847	0.50 (0.06)	0.54 (0.04)	0.53 (0.04)	0.832
NBM[5]	0.23 (0.04)	0.24 (0.03)	0.788	0.20 (0.04)	0.24 (0.03)	0.25 (0.03)	0.574
NW	7.32^{A} (0.22)	7.05^{B} (0.19)	0.095	7.33 (0.26)	7.17 (0.20)	7.06 (0.19)	0.465
Landrace							
TNB	13.58 (0.30)	13.31 (0.36)	0.365	13.12 (0.58)	13.75 (0.30)	13.48 (0.27)	0.428
NBA	12.15 (0.26)	11.84 (0.31)	0.236	11.71 (0.51)	12.27 (0.27)	12.01 (0.24)	0.393
NBD[5]	1.01 (0.04)	1.07 (0.05)	0.508	1.03 (0.09)	1.03 (0.04)	1.06 (0.04)	0.949
NSB[5]	0.72 (0.04)	0.72 (0.05)	0.899	0.73 (0.08)	0.70 (0.04)	0.73 (0.03)	0.934
NBM[5]	0.27 (0.03)	0.32 (0.04)	0.189	0.27 (0.06)	0.30 (0.03)	0.30 (0.03)	0.918
NW	9.61^{a} (0.20)	9.23^{b} (0.24)	0.037	8.96^{b} (0.37)	9.80^{a} (0.21)	9.50^{ab} (0.18)	0.033
PRRS phase							
Duroc							
TNB	8.73 (0.37)	8.72 (0.29)	0.969	8.99 (0.47)	8.76 (0.32)	8.42 (0.32)	0.372
NBA	5.49 (0.37)	5.44 (0.30)	0.861	5.35 (0.48)	5.56 (0.32)	5.49 (0.32)	0.898
NBD[5]	1.91 (0.08)	2.02 (0.07)	0.613	2.04 (0.11)	2.01 (0.07)	1.84 (0.07)	0.654
NSB[5]	0.65 (0.06)	0.76 (0.05)	0.266	0.65 (0.08)	0.70 (0.05)	0.77 (0.05)	0.624
NBM[5]	1.21 (0.08)	1.18 (0.06)	0.826	1.43 (0.10)	1.16 (0.07)	1.02 (0.07)	0.184
NW	3.68 (0.40)	3.68 (0.32)	0.990	3.79 (0.48)	3.56 (0.35)	3.69 (0.36)	0.837
Landrace							
TNB	12.51 (0.34)	12.24 (0.41)	0.484	11.74^{b} (0.72)	12.27^{b} (0.36)	13.12^{a} (0.29)	0.033
NBA	7.69 (0.40)	7.38 (0.48)	0.507	8.26^{A} (0.83)	6.75^{B} (0.41)	7.60^{A} (0.34)	0.077
NBD[5]	3.16 (0.07)	3.17 (0.09)	0.980	2.29^{B} (0.15)	3.61^{AB} (0.07)	3.76^{A} (0.06)	0.055
NSB[5]	1.02 (0.05)	1.00 (0.07)	0.870	0.87 (0.11)	1.05 (0.06)	1.11 (0.05)	0.571
NBM[5]	1.82 (0.07)	1.84 (0.09)	0.945	1.16^{b} (0.16)	2.14^{ab} (0.08)	2.33^{a} (0.06)	0.027

NW	5.11 (0.33)	4.89 (0.41)	0.562	5.60 (0.67)	4.44 (0.35)	4.96 (0.30)	0.158
Post-PRRS phase							
Duroc							
TNB	8.95 (0.25)	8.93 (0.18)	0.946	9.58[a] (0.35)	8.70[ab] (0.21)	8.54[b] (0.20)	0.023
NBA	8.00 (0.23)	7.99 (0.17)	0.969	8.70[a] (0.32)	7.74[ab] (0.20)	7.53[b] (0.19)	0.003
NBD[5]	0.63 (0.04)	0.65 (0.03)	0.784	0.62 (0.06)	0.66 (0.03)	0.64 (0.03)	0.900
NSB[5]	0.45 (0.03)	0.44 (0.03)	0.770	0.41 (0.05)	0.46 (0.03)	0.46 (0.03)	0.733
NBM[5]	0.16 (0.03)	0.19 (0.02)	0.363	0.21 (0.04)	0.17 (0.02)	0.16 (0.02)	0.688
NW	6.80 (0.27)	6.72 (0.22)	0.740	7.29[A] (0.35)	6.51[AB] (0.23)	6.47[B] (0.23)	0.055
Landrace							
TNB	13.73 (0.24)	13.63 (0.29)	0.745	13.86 (0.51)	13.38 (0.25)	13.79 (0.20)	0.312
NBA	12.46 (0.23)	12.34 (0.27)	0.656	12.63 (0.47)	12.10 (0.24)	12.45 (0.20)	0.302
NBD[5]	0.87 (0.04)	0.84 (0.04)	0.771	0.82 (0.08)	0.86 (0.04)	0.89 (0.03)	0.833
NSB[5]	0.53 (0.03)	0.53 (0.04)	0.977	0.53 (0.07)	0.52 (0.03)	0.54 (0.03)	0.945
NBM[5]	0.29 (0.02)	0.29 (0.03)	0.953	0.24 (0.05)	0.31 (0.03)	0.32 (0.02)	0.599
NW	9.95 (0.23)	9.85 (0.26)	0.710	10.24 (0.44)	9.84 (0.23)	9.63 (0.20)	0.371

[1]Expressed as number of piglets;
[2]Porcine Reproductive and Respiratory Syndrome (PRRS);
[3]Frequencies of the *A* and *B* alleles for the WUR10000125 SNP were 0.51 and 0.49, respectively for Duroc, and 0.81 and 0.19, respectively for Landrace, while for the MARC0034894 SNP were 0.31 and 0.69, respectively for Duroc, and 0.25 and 0.75, respectively for Landrace for the PRRS-phase;
[4]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NBM, number of mummified piglets; NW, number of piglets weaned;
[5]Results were back-transformed from ln(phenotype+1);
[a-b] Means lacking the same superscript indicate differences at *P*-value < 0.05 between genotypes with an SNP;
[A-B] Means lacking the same superscript indicate differences at *P*-value < 0.10 between genotypes with an SNP.

Table 8. Genomic regions associated[1] with reproductive performance across PRRS[2] phases for Duroc and Landrace sows.

Trait[3]	%TGVM	SSC	Mb	#SNPs
Pre-PRRS phase				
Duroc				
TNB	1.3	6	41-42	30
	1.2	14	103-104	29
NBA	2.8	7	31-33	46
	1.2	16	70-73	61
NBD	1.8	4	114-116	63
	1.0	5	83-86	36
NBM	1.6	9	120-123	61
NW	1.3	15	119	35
	2.2	15	125-129	152
Landrace				
TNB	1.4	5	4-8	176
	1.5	9	8-10	89
	1.1	16	2-5	55
NBA	1.3	5	7-10	108
	4.3	9	8-10	89
	1.4	16	2-5	55
NSB	7.4	6	41-43	39
NBM	1.2	6	0-2	54
	1.1	15	119-122	97
PRRS phase				
Duroc				
TNB	7.2	5	36-41	39
NBD	2.0	13	189-190	43
NSB	1.2	5	5-9	131
NW	2.9	13	189-190	21
Landrace				
NBA	1.2	10	7-9	50
	1.5	13	156-160	40

NBD	1.2	3	13-15	112
	1.0	9	11-13	90
NBM	1.1	9	11-13	90
Post-PRRS phase				
Duroc				
TNB	1.9	4	86-87	36
	1.2	9	128-130	92
	2.0	11	22	21
NBA	1.9	9	128-131	115
	8.2	11	22	21
NBM	1.8	2	46-47	21
NW	1.4	11	22	21
Landrace				
TNB	1.7	8	111-113	37
	1.3	12	55-56	35
NBA	1.3	2	11-12	54
	2.9	8	111-113	37
NW	3.1	3	1-2	49

[1]Genomic regions explaining more than 1% of the total additive genetic variance accounted for by markers (%TGVM). Traits not included on the table did not have any genomic region explaining more than 1% of TGVM;
[2]Porcine Reproductive and Respiratory Syndrome (PRRS);
[3]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NBM, number of piglets born mummified; NW, number of piglets weaned;
SSC, *Sus scrofa* chromosome;
Mb, location of the SNP window within the SSC, in megabases;
#SNPs, number of SNPs in the region.

Supplementary Material

Supplementary table 1. Number of records used for training and validation in each fold (F) across genomic prediction scenarios (GPS)[1] of reproductive traits[2] during a Porcine Reproductive and Respiratory Syndrome (PRRS) outbreak by breed.

GPS$_{PRRS}$

	Duroc								**Landrace**							
	Training (PRRS)				*Validation*				*Training (PRRS)*				*Validation*			
Trait	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4
TNB	372	372	372	372	124	124	124	124	321	321	321	321	107	107	107	107
NBA	372	372	372	372	124	124	124	124	321	321	321	321	107	107	107	107
NBD	315	315	315	315	105	105	105	105	275	275	275	276	92	92	92	91
NSB	315	315	315	315	105	105	105	105	275	275	275	276	92	92	92	91
NBM	309	312	308	310	104	101	105	103	275	275	275	276	92	92	92	91
NW	372	372	372	372	124	124	124	124	321	321	321	321	107	107	107	107

GPS$_{pre\text{-}PRRS}$

	Duroc		**Landrace**	
Trait	*Training (Pre-PRRS)*	*Validation*	*Training (Pre-PRRS)*	*Validation*
TNB	478 (239)[3]	496 (257)[4]	459 (213)[3]	428 (215)[4]
NBA	478 (239)[3]	496 (257)[4]	461 (213)[3]	428 (215)[4]
NBD	475 (239)[3]	420 (181)[4]	459 (213)[3]	367 (154)[4]
NSB	478 (239)[3]	420 (181)[4]	461 (213)[3]	367 (154)[4]
NBM	475 (239)[3]	413 (174)[4]	459 (213)[3]	367 (154)[4]
NW	478 (239)[3]	496 (257)[4]	461 (213)[3]	428 (215)[4]

GPS$_{pre\text{-}PRRS\text{-}4FCV}$

	Duroc								**Landrace**							
	Training (Pre-PRRS)				*Validation*				*Training (Pre-PRRS)*				Validation			
Trait	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4
TNB	432 (239)[5]	432 (239)[5]	432 (239)[5]	431 (239)[5]	124	124	124	124	375 (213)[5]	374 (213)[5]	374 (213)[5]	374 (213)[5]	107	107	107	107
NBA	432 (239)[5]	432 (239)[5]	432 (239)[5]	431 (239)[5]	124	124	124	124	375 (213)[5]	374 (213)[5]	374 (213)[5]	374 (213)[5]	107	107	107	107
NBD	375 (239)[5]	375 (239)[5]	375 (239)[5]	374 (239)[5]	105	105	105	105	329 (213)[5]	328 (213)[5]	328 (213)[5]	329 (213)[5]	92	92	92	91
NSB	375 (239)[5]	375 (239)[5]	375 (239)[5]	364 (239)[5]	105	105	105	105	329 (213)[5]	328 (213)[5]	328 (213)[5]	329 (213)[5]	92	92	92	91
NBM	370 (239)[5]	370 (239)[5]	369 (239)[5]	369 (239)[5]	104	101	105	103	329 (213)[5]	328 (213)[5]	328 (213)[5]	329 (213)[5]	92	92	92	91
NW	432 (239)[5]	432 (239)[5]	432 (239)[5]	431 (239)[5]	124	124	124	124	375 (213)[5]	374 (213)[5]	374 (213)[5]	374 (213)[5]	107	107	107	107

$GPS_{pre\text{-}PRRS,PRRS}$

	Duroc									Landrace								
	Training				*Validation*					*Training*				*Validation*				
		PRRS									*PRRS*							
Trait	*Pre-PRRS*	F1	F2	F3	F4	F1	F2	F3	F4	*Pre-PRRS*	F1	F2	F3	F4	F1	F2	F3	F4
TNB	478 (239)[3]	372	372	372	372	124	124	124	124	459 (213)[3]	321	321	321	321	107	107	107	107
NBA	478 (239)[3]	372	372	372	372	124	124	124	124	461 (213)[3]	321	321	321	321	107	107	107	107
NBD	475 (239)[3]	315	315	315	315	105	105	105	105	459 (213)[3]	275	275	275	276	92	92	92	91
NSB	478 (239)[3]	315	315	315	315	105	105	105	105	461 (213)[3]	275	275	275	276	92	92	92	91
NBM	475 (239)[3]	309	312	308	310	104	101	105	103	459 (213)[3]	275	275	275	276	92	92	92	91
NW	478 (239)[3]	372	372	372	372	124	124	124	124	461 (213)[3]	321	321	321	321	107	107	107	107

$GPS_{pre\text{-}PRRS\text{-}4FCV,PRRS}$

	Duroc												Landrace											
	Training								*Validation*				*Training*								*Validation*			
	Pre-PRRS				*PRRS*								*Pre-PRRS*				*PRRS*							
Trait	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4	F1	F2	F3	F4
TNB	432 (239)[5]	432 (239)[5]	432 (239)[5]	431 (239)[5]	372	372	372	372	124	124	124	124	375 (213)[5]	374 (213)[5]	374 (213)[5]	374 (213)[5]	321	321	321	321	107	107	107	107
NBA	432 (239)[5]	432 (239)[5]	432 (239)[5]	431 (239)[5]	372	372	372	372	124	124	124	124	375 (213)[5]	374 (213)[5]	374 (213)[5]	374 (213)[5]	321	321	321	321	107	107	107	107
NBD	375 (239)[5]	375 (239)[5]	375 (239)[5]	374 (239)[5]	315	315	315	315	105	105	105	105	329 (213)[5]	328 (213)[5]	328 (213)[5]	329 (213)[5]	275	275	275	276	92	92	92	91
NSB	375 (239)[5]	375 (239)[5]	375 (239)[5]	364 (239)[5]	315	315	315	315	105	105	105	105	329 (213)[5]	328 (213)[5]	328 (213)[5]	329 (213)[5]	275	275	275	276	92	92	92	91
NBM	370 (239)[5]	370 (239)[5]	369 (239)[5]	369 (239)[5]	309	312	308	310	104	101	105	103	329 (213)[5]	328 (213)[5]	328 (213)[5]	329 (213)[5]	275	275	275	276	92	92	92	91
NW	432 (239)[5]	432 (239)[5]	432 (239)[5]	431 (239)[5]	372	372	372	372	124	124	124	124	375 (213)[5]	374 (213)[5]	374 (213)[5]	374 (213)[5]	321	321	321	321	107	107	107	107

[1]GPS described in the Materials and Methods section and in Table 2 of the manuscript;

[2]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NBM, number of mummified piglets; NW, number of piglets weaned;

[3]Number of animals with pre-PRRS data included in the training dataset that did not have PRRS data included in the validation dataset;

[4]Number of animals with PRRS data included in the validation dataset that did not have pre-PRRS data included in the training dataset;

[5]Number of animals with pre-PRRS data included in the training dataset for this fold that did not have PRRS data included in the validation dataset.

Supplementary table 2. Genomic prediction accuracies[1] of reproductive traits[2] during a Porcine Reproductive and Respiratory Syndrome (PRRS) outbreak by breed and Bayesian method across genomic prediction scenarios (GPS)[3].

GPS$_{PRRS}$

	Duroc			**Landrace**		
Trait[1]	*BayesB*	*BayesC*	*BayesC0*	*BayesB*	*BayesC*	*BayesC0*
TNB	0.32 (0.05)	0.27 (0.05)	0.27 (0.04)	0.09 (0.09)	0.09 (0.09)	0.07 (0.06)
NBA	0.31 (0.01)	0.33 (0.02)	0.34 (0.02)	0.37 (0.03)	0.38 (0.04)	0.37 (0.04)
NBD	0.09 (0.06)	0.09 (0.05)	0.08 (0.06)	0.55 (0.12)	0.56 (0.12)	0.55 (0.12)
NSB	-0.57 (0.04)	-0.61 (0.04)	-0.66 (0.04)	0.46 (0.08)	0.47 (0.08)	0.47 (0.08)
NBM	-0.46 (0.12)	-0.45 (0.12)	-0.45 (0.12)	0.41 (0.14)	0.40 (0.14)	0.42 (0.14)
NW	0.69 (0.06)	0.65 (0.06)	0.64 (0.05)	0.44 (0.14)	0.43 (0.14)	0.43 (0.14)

GPS$_{pre\text{-}PRRS}$

	Duroc			**Landrace**		
Trait	*BayesB*	*BayesC*	*BayesC0*	*BayesB*	*BayesC*	*BayesC0*
TNB	0.60	0.30	0.31	1.16	1.09	1.08
NBA	~0	~0	-0.01	0.01	0.07	0.07
NBD	-0.63	-0.57	-0.52	0.37	0.38	0.40
NSB	-0.50	0.14	0.15	0.40	0.45	0.48
NBM	-1.03	-0.60	-0.60	0.07	0.03	0.03
NW	-0.31	-0.17	-0.17	0.29	0.32	0.32

GPS$_{pre\text{-}PRRS\text{-}4FCV}$

	Duroc			**Landrace**		
Trait	*BayesB*	*BayesC*	*BayesC0*	*BayesB*	*BayesC*	*BayesC0*
TNB	-0.39 (0.60)	-0.36 (0.58)	-0.36 (0.58)	0.77 (1.95)	0.75 (1.91)	0.77 (1.97)
NBA	0.31 (0.55)	0.29 (0.54)	0.25 (0.51)	0.03 (0.57)	0.04 (0.52)	0.05 (0.50)
NBD	-0.03 (0.71)	-0.02 (0.73)	-0.07 (0.63)	0.37 (0.17)	0.39 (0.16)	0.41 (0.16)
NSB	0.84 (1.42)	0.92 (1.39)	0.93 (1.42)	0.37 (0.23)	0.43 (0.23)	0.45 (0.23)
NBM	-0.02 (1.93)	-0.02 (1.88)	0.02 (1.95)	0.02 (0.32)	-0.01 (0.28)	-0.01 (0.28)
NW	0.02 (0.90)	0.03 (0.91)	0.04 (0.93)	0.32 (0.09)	0.28 (0.11)	0.28 (0.09)

GPS$_{pre\text{-}PRRS,PRRS}$

	Duroc			Landrace		
Trait	*BayesB*	*BayesC*	*BayesC0*	*BayesB*	*BayesC*	*BayesC0*
TNB	0.60 (0.12)	0.28 (0.14)	0.27 (0.14)	0.34 (2.08)	0.27 (2.20)	0.23 (2.29)
NBA	0.40 (0.46)	0.29 (0.20)	0.30 (0.19)	0.23 (0.62)	0.32 (0.54)	0.32 (0.52)
NBD	0.28 (0.60)	0.26 (0.59)	0.27 (0.60)	0.54 (0.31)	0.54 (0.30)	0.54 (0.29)
NSB	-0.27 (0.25)	-0.31 (0.44)	-0.55 (0.36)	0.44 (0.25)	0.46 (0.22)	0.48 (0.23)
NBM	-0.12 (0.51)	-0.18 (0.76)	-0.15 (0.78)	0.34 (0.51)	0.37 (0.48)	0.38 (0.48)
NW	0.38 (0.19)	0.27 (0.18)	0.27 (0.18)	0.41 (0.26)	0.44 (0.39)	0.44 (0.38)

	$GPS_{pre\text{-}PRRS\text{-}4FCV,PRRS}$					
	Duroc			**Landrace**		
Trait	*BayesB*	*BayesC*	*BayesC0*	*BayesB*	*BayesC*	*BayesC0*
TNB	0.32 (0.68)	0.46 (0.76)	0.50 (0.67)	0.41 (1.19)	0.32 (1.24)	0.30 (1.31)
NBA	0.61 (0.48)	0.65 (0.46)	0.67 (0.45)	0.35 (0.27)	0.38 (0.25)	0.38 (0.22)
NBD	0.55 (0.73)	0.44 (0.68)	0.63 (0.92)	0.49 (0.37)	0.50 (0.37)	0.49 (0.38)
NSB	0.98 (2.05)	1.15 (2.10)	0.78 (1.85)	0.48 (0.29)	0.53 (0.31)	0.55 (0.32)
NBM	1.19 (2.55)	1.17 (2.85)	1.27 (2.81)	0.24 (0.51)	0.30 (0.47)	0.32 (0.47)
NW	0.44 (0.93)	0.33 (1.08)	0.29 (1.07)	0.45 (0.31)	0.45 (0.43)	0.45 (0.42)

[1]Numbers in parenthesis represent the standard deviation of genomic prediction accuracies across the 4 folds;

[2]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NBM, number of mummified piglets; NW, number of piglets weaned;

[3]GPS described in the Materials and Methods section and in Table 2 of the manuscript.

Chapter III. Host genetics of response to porcine reproductive and respiratory syndrome in sows: Antibody response as an indicator trait for improved reproductive performance[4]

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Host genetics of response to porcine reproductive and respiratory syndrome in sows: Antibody response as an indicator trait for improved reproductive performance

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Abstract

Antibody response to porcine reproductive and respiratory syndrome (PRRS) virus (PRRSV) infection, measured as sample-to-positive (S/P) ratio, has been proposed as an indicator trait for improved reproductive performance during a PRRS outbreak in Landrace sows. However, this result has not yet been validated in Landrace sows or evaluated in terminal sire lines. The main objectives of this work were to validate the use of S/P ratio as an indicator trait to select pigs during a PRRS outbreak and to explore the genetic basis of antibody response to PRRSV. Farrowing data included 2,546 and 2,522 litters from 894 Duroc and 813 Landrace sows, respectively, split into pre-PRRS, PRRS, and post-PRRS phases. Blood samples were taken from 1,231 purebred sows (541 Landrace and 690 Duroc) following a PRRS outbreak for subsequent PRRSV ELISA analysis for S/P ratio measurement. All animals had high-density genotype data available (29,799 single nucleotide polymorphisms; SNPs). Genetic parameters and genome-wide association studies (GWAS) for S/P ratio were performed for each breed separately. Heritability estimates (± standard error) of S/P ratio during the PRRS outbreak

were moderate, with 0.35 ± 0.08 for Duroc and 0.34 ± 0.09 for Landrace. During the PRRS outbreak, favorable genetic correlations of S/P ratio with the number of piglets born alive (0.61 ± 0.34), number of piglets born dead (-0.33 ± 0.32), and number of stillborn piglets (-0.27 ± 0.31) were observed for Landrace sows. For Duroc, the GWAS identified a major quantitative trait locus (QTL) on chromosome (Chr) 7 (24-15 megabases; Mb) explaining 15% of the total genetic variance accounted for by markers (TGVM), and another one on Chr 8 (25 Mb) explaining 2.4% of TGVM. For Landrace, QTL on Chr 7 (24–25 Mb) and Chr 7 (108–109 Mb), explaining 31% and 2.2% of TGVM, respectively, were identified. Some of the SNPs identified in these regions for S/P ratio were associated with reproductive performance but not during the PRRS outbreak. Genomic prediction accuracies for S/P ratio were moderate to high for the within-breed analysis. For the between-breed analysis, these were overall low. These results further support the use of S/P ratio as an indicator trait for improved reproductive performance during a PRRS outbreak in Landrace sows.

Keywords: genomics, GWAS, swine, QTL, outbreak, reproduction, PRRS, S/P ratio

1. Introduction

Recent studies have shown that reproductive performance traits in commercial sows infected with porcine reproductive and respiratory syndrome (PRRS) virus (PRRSV) have low heritability estimates (Rashidi et al., 2014; Serão et al., 2014; Putz et al., 2019; Scanlan et al., 2019; Hickmann et al., 2021). Therefore, identifying an indicator trait highly heritable and highly genetically correlated with reproductive performance under a PRRS outbreak could be used to select for reproductive performance in PRRSV-infected sows.

Antibody response to PRRSV infection, measured as sample-to-positive (S/P) ratio using a commercial ELISA, has been proposed as an indicator trait to improve litter size traits in sows infected with

PRRSV. Serão et al. (2014) reported a moderately high estimate of heritability for S/P ratio (0.45) measured approximately 46 days after the beginning of the PRRS outbreak. These authors also estimated large genetic correlations of S/P ratio with the number of piglets born alive (NBA; 0.73) and stillborn piglets (NSB; -0.72) during a PRRS outbreak. These results indicate that selection for increased S/P ratio would result in a correlated response to selection in NBA and NSB under PRRS that is 63% and 97% more efficient than direct selection for NBA and NSB, respectively. The high heritability of S/P ratio has been validated by Serão et al. (2016). In contrast, Putz et al. (2019) reported a relatively low heritability estimate (0.17) for S/P ratio measured at approximately 60 days after the predicted start of the PRRS outbreak. However, the method of measuring S/P ratio in their study was not the same as in others (Serão et al., 2014, 2016; Abella et al., 2019; Sanglard et al., 2020). Nonetheless, Putz et al. (2019) found a high genetic correlation of S/P ratio with NSB under PRRS (-0.73), supporting the findings of Serão et al. (2014).

Genomic analyses for S/P ratio following a PRRSV infection are scarce in the literature, with Serão et al. (2014, 2016) being the only studies that have reported QTL for this trait in PRRSV-infected sows. Serão et al. (2014) identified two major QTL on *Sus scrofa* chromosome (SSC) 7 that together explained 40% of the total genetic variance accounted for by markers (TGVM) for S/P ratio. The two QTL identified by Serão et al. (2014) were further validated by Serão et al. (2016). One of these QTL explained 25% of the TGVM and was located in the Major Histocompatibility Complex (MHC) region, a gene-rich region in the genome that harbors several genes playing essential roles in the immune system of mammals (Hammer et al., 2020). In addition, Sanglard et al. (2020) also identified the MHC QTL in gilts vaccinated with a commercial modified live virus vaccine. In addition, Serão et al. (2014, 2016) also identified specific single nucleotide polymorphisms (SNPs) associated with S/P ratio, indicating that key SNPs can be used to select for this trait.

Serão et al. (2016) reported moderate genomic prediction accuracies for S/P ratio in commercial gilts. This indicates that phenotypic and genomic information collected at the commercial level can be used to estimate marker effects accurately and breeding values for nucleus herds to genetically select animals with increased S/P ratio when exposed to PRRSV. Although S/P ratio has potential as an indicator trait for genetic improvement of litter size traits in PRRSV-infected sows, the high genetic correlation between these traits and S/P ratio reported by Serão et al. (2014) requires validation in other datasets and breeds. Therefore, the main objectives of this work were to validate the use of S/P ratio as an indicator trait for improved reproductive performance during a PRRS outbreak, to perform genomic analyses of S/P ratio, and to evaluate the effects of key SNPs on S/P ratio and reproductive performance in Landrace and Duroc sows.

2. Material and Methods

All animal experimental procedures used in this study were followed according to international guidelines on Animal Care under industry standard conditions (IACUC, Iowa State University, protocol number 6-17-8551-S).

2.1 Source of data

The data used in this study were obtained from two commercial purebred herds (Duroc and Landrace) that experienced a PRRS outbreak during the spring of 2018. The PRRS outbreak was identified based on a combination of previous methodologies (Lewis et al., 2009; Putz et al., 2019; Scanlan et al., 2019), as described by Hickmann et al. (2021). The wild-type PRRSV strain was sequenced and identified as PRRSV 1-7-4, a highly pathogenic strain. The focus of the study performed by Hickmann et al. (2021) was on the genomic basis of reproductive performance in healthy and PRRSV-infected sows. In contrast, this study focuses on the genomic basis of S/P ratio and its relationship with reproductive performance in healthy and PRRSV-infected sows. Briefly, the farrowing data included 2,546 and

2,522 litters from 894 Duroc and 813 Landrace sows, respectively, split into pre-PRRS, PRRS, and post-PRRS phases. The number of animals (litters) included in the pre-PRRS, PRRS, and post-PRRS datasets were 478 (1,004), 501 (501), and 558 (1,079), respectively, for Duroc, and 461 (1,096), 429 (429), and 527 (1,025), respectively, for Landrace. Not all animals experienced all three PRRS phases. The reproductive data included farrowing performance for the number of piglets born alive (NBA, pigs/litter), number of stillborn piglets (NSB, pigs/litter), number of mummified piglets (NBM, pigs/litter), number of piglets born dead (NBD, pigs/litter; the sum of NSB and NBM), total number of piglets born (TNB, pigs/litter; the sum of NBA and NBD), and number of piglets weaned (NW, piglets/litter). The net number of cross-fostered piglets (fostered in minus fostered out) was also available. A total of 450 (23%) Duroc and 433 (23%) Landrace litters had cross-fostering. Prior to analyses, NSB, NBM, and NBD were transformed as ln(phenotypeC1), following Serão et al. (2014), because of the right skewness observed in the data. Sows from Duroc and Landrace herds originated from 71 sires and 446 dams, and 92 sires and 365 dams, respectively.

Following the appearance of typical signs of PRRSV infection, such as changes in reproductive performance and clinical symptoms, sows on the farm were bled using Lavender Top Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, United States) on June 1st, 2018, approximately 54 days after the detection of PRRS (Hickmann et al., 2021). Blood samples were shipped to the Veterinary Diagnostic Laboratory at Iowa State University (Ames, IA, United States), where sera from these samples were used to quantify PRRSV antibody by ELISA (PRRS X3 Ab Test, IDEXX, Westbrook, ME, United States). The PRRSV antibody assay produced a quantitative result (i.e., S/P ratio) of the adjusted sample optical density (OD) divided by the adjusted kit positive control serum OD. These OD adjustments subtracted the average negative control OD from the sample OD and the average positive control OD. The S/P ratio data consisted of 690 Duroc and 541 Landrace sows. Of these, 644 Duroc and 528 Landrace sows also had reproductive data available.

All animals had follicular hair or ear tissue samples taken and shipped to Neogen GeneSeek (Lincoln, NE, United States) for genotyping using the GGP PorcineHDpanel (Neogen GeneSeek) for 45,536 SNPs. The genotype data were processed according to the breeding company's pipeline, including the removal of non-segregating SNPs, SNPs with a minor allele frequency of less than 0.05, and minimum SNP call rate and animal call rate of 0.9. In addition, missing genotypes were imputed using Fimpute 2.2 (Sargolzaei et al., 2014). These steps were performed within bread, resulting in 29,799 SNPs common to both breeds used in the final analyses, with the Sscrofa 11.1 assembly being used for the SNP location.

2.2 Genetic parameters

Heritability estimates of S/P ratio were estimated using a univariate model, while correlations of S/P ratio with reproductive traits were estimated using a bivariate model. A genomic relationship matrix (***GRM***) was derived for each breed separately based on VanRaden (2008), method 1. Analyses were performed for each breed separately. Heritability estimates of S/P ratio were obtained from the following univariate animal model:

$$Y_{ij} = \mu + PAR_i + a_j + e_{ij} \quad (1)$$

where Y_{ij} is the observed phenotype; μ is the general mean; PAR_i is the fixed-effect of the i^{th} parity ($i = 1,\ldots6$); a_j is the animal random effect, assuming $a_j \sim N(0, \boldsymbol{GRM}\sigma_a^2)$, where σ_a^2 is the additive genetic variance; and e_{ij} is the random residual term associated with Y_{ij}, assuming $e_{ij} \sim N(0, \boldsymbol{I}\sigma_e^2)$, where $\boldsymbol{I}$ is the identity matrix and σ_e^2 is the residual variance. Heritability estimates of reproductive performance traits were obtained from a bivariate model with S/P ratio. The bivariate model used included the same effects as the univariate model for each trait. The models used for reproductive traits are described in Hickmann et al. (2021). All analyses were performed in ASReml 4.0 (Gilmour et al., 2015).

2.3 Genome-wide association studies

Genome-wide association studies (GWAS) were performed for S/P ratio for each breed separately using the BayesB method (Habier et al., 2011). In the GWAS, we used $\pi = 0.9973$ to fairly compare our results with those reported by Serão et al. (2014), i.e., including the same expected number of SNPs in the model (80 SNPs). The GWAS model included the fixed effects of intercept and parity, and the random allele substitution effects for the SNP markers. For all analyses, additive genetic and residual variances from the genetic parameter analyses were used as priors. A total of 50,000 Markov Chain Monte Carlo (MCMC) iterations were used, with 10,000 iterations used as burn-ins and MCMC samples stored at every 100th iteration, resulting in 500 posterior MCMC samples. Results from this analysis are presented as the posterior mean of the %TGVM of non-overlapping 1-Mb regions based on the Sscrofa11.1 genome build. Genomic regions explaining ≥ 2 %TGVM were considered significant. For a given 1-Mb region *i* including m SNPs, its %TGVM was calculated as:

$$\%\, TGVM_i = \sum_{k=1}^{500} var\left(\frac{\sum_{j=1}^{n} M'_{ij}\alpha_{ik}}{\sum_{i=1}^{w}\sum_{j=1}^{n} M'_{ij}\alpha_{ik}}\right)k \quad (2)$$

where $\%TGVM_i$ represents the vector of calculated %TGVM of the i^{th} 1-Mb region including *m* SNPs; M'_{ij} represents the row vector of reference allele counts (coded -1, 0, 1) of the *m* SNPs included in the i^{th} 1-Mb region of the genome for the j^{th} animal (j = 1 to *n*, where *n* changed across breeds and traits); and α_{ik} represents the column vector of allele-substitution effects of the *m* SNPs included in the i^{th} 1-Mb region of the genome in the k^{th} stored MCMC sample. For both breeds, the number *w* of 1-Mb non-overlapping windows was 2,211 and the average (SD) number m of SNPs within each 1-Mb region was 13.5 (8).

159 Before final results, 1-Mb windows showing %TGVM ≥ 0.5% within 3 Mb from significant regions
160 (i.e., ≥ 2 %TGVM) were combined into one larger window and its %TGVM was recalculated as
161 described in Eq. (2). This strategy was used due to the resolution of Bayesian GWAS methods, where
162 simulations have shown that quantitative loci nucleotides are expected to be located within 3 Mb of
163 the identified QTL regions (Garrick and Fernando, 2013). For the presentation of GWAS results in
164 figures and tables, the start of the QTL region on a given SSC *c* was assumed to be *c*:Mbi,000,000, and
165 the end of the QTL region as *c*:Mbf,999,999 where Mbi and Mbf represent the Mb where the identified
166 QTL window started and ended, respectively. Thus, for example, if a QTL was identified in a given 1-
167 Mb region *r*, the position of the QTL was expressed as *r*Mb, such that Mbi = Mbf = *r* and the QTL
168 encompassed *c*:*r*,000,000–*r*,999,999. In contrast, when closely located 1-Mb QTL regions were
169 combined into a single window, the position of the QTL was expressed as *r*-*r*'Mb, such that Mbi = *r* <
170 Mbf = *r*' and the QTL encompassed *c*:*r*,000,000–*r*',999,999. All analyses were performed using
171 GenSel version 4.4 (Fernando and Garrick, 2009). The linkage disequilibrium (LD) among SNPs in
172 identified QTL regions for S/P ratio was estimated using the Haploview software (Barrett, 2009).

173 **2.4 Effects of selected SNPs associated with S/P ratio**

174 We investigated the effects of SNPs identified to be associated with S/P ratio in this study and by Serão
175 et al. (2014). Based on results from this study, SNPs showing the largest estimated allele substitution
176 effects within identified QTL in the GWAS for S/P ratio were further evaluated. SNPs selected based
177 on the study of Serão et al. (2014) were ASGA0031860 (7:22,075,114), MARC0058875
178 (7:24,865,378), and ASGA0032151 (7:25,967,157), based on the Sscrofa11.1 genome build. Although
179 two additional SNPs were also associated with S/P ratio in Serão et al. (2014), these SNPs were not
180 present in the genotype data in this study. The effect of these selected SNPs on S/P ratio and
181 reproductive traits was tested with separate analyses for each breed and PRRS phase by simultaneously
182 fitting all selected SNPs as categorical fixed effects in the model used for estimation of genetic

parameters. Significance of the effect of a SNP was declared at a p-value < 0.05, and a trend was declared at 0.05 < p-value < 0.10. Analyses were performed using ASReml 4.0.

2.5 Genomic prediction of S/P ratio

Genomic prediction analyses for S/P ratio were performed with the model described for GWAS, using BayesB (π = 0.9973) in GenSel v.4.4 (Fernando and Garrick, 2009). Analyses were performed both within-breed and between breeds. For the within-breed analysis, 5-fold cross-validation was performed for each breed separately, where each animal was randomly assigned to one of five folds. In this approach, markers were trained using four folds and validated using the remaining fold. This was repeated five times until all validation datasets were used for validation. There were 138 and 108 animals in each fold for Duroc and Landrace, respectively (one fold for Landrace had 109 observations). Genomic prediction accuracies (GPAs) were calculated as a weighted average as:

$$GPA = \frac{\sum_{i=1}^{5} n_i r_{i(GEBV,y^*)}}{\sum_{i=1}^{5} n_i \sqrt{h^2}} \quad (3)$$

where $r_i(GEBV, y^*)$ is the correlation between the genomic estimated breeding value (GEBV) and phenotypes adjusted for fixed effects (y^*) in the i^{th} validation dataset, which is weighted by the number of records in each validation dataset (n_i); and h^2 is the heritability of S/P ratio for the whole dataset of the breed being analyzed.

For the between-breed analysis, all data for one breed were used as training to validate the other breed. GPA was calculated as the correlation between $GEBV$ and y^*, divided by the square root of the estimate of heritability based on the whole dataset for the breed used for validation. Both the within- and between-breed analyses were performed using three sets of SNPs, as proposed by Serão et al. (2016):

- All 29,799 SNPs across the genome (SNP_{All});
- Only SNPs in the QTL that harbors the MHC region (SNP_{MHC});

- All SNPs across the genome excluding those in the MHC region (SNP_{Rest}).

The SNPs in the MHC region were defined based on the GWAS results of each breed. For SNP_{Rest}, a 2-Mb window surrounding the QTL found in the MHC region was removed to avoid having any SNPs in LD with this QTL that could affect results.

3. Results

3.1 Genetic parameters

The estimate of heritability of S/P ratio was moderately high for both breeds (Table 1). For Duroc, the estimate (0.35 ± 0.08) was numerically greater than for Landrace (0.34 ± 0.09). In general, variance component estimates were very similar between breeds. Landrace sows had a numerically greater additive genetic variance estimate (0.033) than Duroc sows (0.032). On the other hand, the residual variance estimate (0.059) was slightly lower for Duroc than for Landrace (0.063).

Heritability estimates of reproductive traits and genetic correlations (rg) of S/P ratio with farrowing traits are shown in Table 1. Only results that converged are shown. Genetic correlation estimates of reproductive traits with S/P ratio in Duroc sows were moderate to low, ranging from -0.38 ± 0.31 (NBM) to 0.48 ± 0.24 (NSB) for pre-PRRS, -0.24 ± 0.30 (NBA) to 0.30 ± 0.25 (NW) for PRRS, and -0.22 ± 0.17 (NBA) to -0.04 ± 0.22 (NSB) for post-PRRS. For Landrace, these were also moderate to low and ranged from -0.18 ± 0.25 (NBD) to 0.15 ± 0.20 (NBA) for pre-PRRS, -0.33 ± 0.32 (NBD) to 0.61 ± 0.34 (NBA) for PRRS, and -0.33 ± 0.54 (NBM) to 0.06 ± 0.18 (NBA) for post-PRRS. Pre-PRRS and PRRS in Landrace sows showed favorable genetic correlation estimates of S/P ratio with reproductive performance, whereas for Duroc, these relationships were not strong.

3.2 Genomic regions in the pig genome associated with S/P ratio

Few genomic regions that explained a substantial proportion of TGVM were identified in Duroc and Landrace sows for S/P ratio (Figure 1). For Duroc, two 1-Mb regions within 1 Mb from each other on SSC 7 explained 11.2% (24 Mb; i.e., 7:24,000,000:24,999,999) and 3.5% (25 Mb) of TGVM, and one on SSC8 (25 Mb) that explained 2.4% of TGVM were identified (Figure 1A). Once the two regions on MHC region were combined and its %TGVM recalculated, the QTL (24–25 Mb; i.e., 7:24,000,000–25,999,999) explained 15% of TGVM. For Landrace, four 1-Mb regions on SSC 7 were identified (Figure 1B). Two of these were located within 1 Mb, with one explaining 29.5% of TGVM(24 Mb) and the other 0.6% of TGVM (25 Mb). Once combined, this QTL (24–25 Mb) explained 31% of TGVM. The other two QTL on SSC 7 were also located within 1 Mb of each other, with one explaining 0.5% of TGVM (Mb 108) and the other 2.2% of TGVM (109 Mb). Once combined (108–109 Mb), this QTL explained 2.2% of TGVM. The QTL located on SSC 7 (24–25 Mb) for both breeds harbors the MHC region, the most important genomic region controlling immune response in mammals. We also investigated the LD in this region for each breed (Figure 2). In general, LD in this region was much lower for Landrace (Figure 2B) sows than for Duroc (Figure 2A) sows.

3.3 Effects of selected SNPs associated with S/P ratio

The SNPs within the two QTL regions found for each breed were subjected to additional investigation to identify SNPs with large effects that could be responsible for the %TGVM explained for by these regions. From this, we identified one SNP for Duroc (MARC0089437; 7:24,217,931) and one for Landrace (ASGA0032063; 7:24,247,099), both located on the MHC region. These two SNPs were combined with the three previously reported by Serão et al. (2014), and their associations with S/P ratio were investigated in this study. Results of these associations are presented in Table 2. For Duroc sows, the MARC0089437 SNP explained 9.2% of TGVM, while all other SNPs explained less than

0.3% of TGVM. Of the five selected SNPs, MARC0089437 and MARC0058875 were significantly (p-value ≤ 0.018) associated with S/P ratio. For Landrace sows, the ASGA0032063 SNP explained 29.1% of TGVM, while all other SNPs explained less than 0.7% of TGVM. Of the five selected SNPs, ASGA0032063, MARC0089437, and ASGA0032151 were significantly (p-value ≤ 0.054) associated with S/P ratio. These results provide information on key SNPs associated with S/P ratio for Duroc and Landrace sows during a PRRS outbreak.

3.4 Effects of selected SNPs associated with S/P ratio on reproductive traits

Estimates of the association of the five selected SNPs with reproductive performance are shown in Table 3. Overall, few associations were found to be significant. Interestingly, there were no associations (p-value ≥ 0.370) of these selected SNPs with reproductive traits in Landrace sows during the PRRS phase. For both breeds, most associations were found for the post-PRRS period. Starting with pre-PRRS, the MARC0089437 SNP had a trending association with NBA (p-value = 0.089) in Duroc sows, with heterozygotes showing greater performance than both homozygotes. In Landrace sows, this SNP had a trending association with NW(p-value = 0.063), with BB animals having greater NW than AB animals, while no AA animals were observed in the dataset. The ASGA0032063 SNP had a trending effect (p-value ≤ 0.067) for two mortality traits (NBD and NSB) in Landrace sows during pre-PRRS, with AA animals showing lower NBD and NSB than animals with the other two genotypes. For the PRRS phase in Duroc sows, the ASGA0031860 SNP had a trending association with NBD (p-value = 0.058), with BB sows having greater NBD than AA and AB sows. For the post-PRRS phase, the ASGA0031860 SNP was associated (p-value = 0.05) and had a trending effect (p-value = 0.09) for NW in Landrace and Duroc sows, respectively, with AA animals showing greater performance than the other genotypes for both breeds. The ASGA0032151 SNP also had a trending effect for NW (p-value = 0.057) and NSB (p-value = 0.089) in Landrace sows only, with AA sows showing overall greater performance for both traits. The MARC0089437 SNP was associated with

several traits (TNB, NBA, NBM, and NW; p-value ≤ 0.068) in Duroc sows in the post-PRRS period. Although AA sows had greater NBM than AB and BB sows, they also had greater TNB, NBA, and NW. However, differences for TNB, NBA, and NW were between BB with AA and AB, indicating that heterozygote animals have overall better reproductive performance than the other genotypes. This same SNP had a trending effect for TNB (p-value = 0.081) in Landrace sows, with AA sows showing greater performance than AB sows. On the other hand, the AA genotype of the MARC0058875 SNP in Duroc sows was associated not only with greater TNB (p-value = 0.037) and NW (p-value = 0.069) but also greater NBM (p-value = 0.013) compared with the other genotypes. These results provide additional information on key SNPs associated with S/P ratio in Duroc and Landrace sows during a PRRS outbreak and their associations with reproductive performance across PRRS phases.

3.5 Genomic prediction

Genomic prediction accuracies (GPA ± standard deviation) were moderate to high for the within-breed analyses (Figure 3), showing that genomic selection for increased S/P ratio is feasible. GPAs were moderate to high, with greater values for SNP_{All}, then SNP_{MHC}, and then SNP_{Rest}. These GPAs were 0.73 ± 0.06 for Landrace and 0.60 ± 0.08 for Duroc (SNP_{All}), 0.60 ± 0.05 for Landrace and 0.50 ± 0.09 for Duroc (SNP_{MHC}), and 0.41 ± 0.10 for Landrace and 0.45 ± 0.07 for Duroc (SNP_{Rest}), indicating that genomic selection for S/P ratio, regardless of the genomic information used, is feasible. On the other hand, for the between-breed analysis, GPAs were low and sometimes negative. For SNP_{All}, SNP_{MHC}, and SNP_{Rest}, these were -0.03, -0.32, and 0.10, respectively, when training on Duroc and validating on Landrace, and 0.08, 0.09, and 0.03, respectively, when training on Landrace and validating on Duroc. These results indicate that between-breed genomic selection has limited usefulness.

4. Discussion

4.1 Genetic parameters

Heritability estimates of S/P ratio were overall lower than in Serão et al. (2014), who reported a high heritability estimate (0.45 ± 0.13) for S/P ratio following a PRRS outbreak in purebred Landrace sows. There were differences in collection dates between our study and Serão et al. (2014). While in Serão et al. (2014), blood samples were taken from purebred Landrace sows at approximately 46 days after the estimated beginning of the PRRS outbreak, in our study it was at about 54 days. Thus, this difference in the collection dates between both studies might have affected results since antibody response is time sensitive. Differences in estimates could also be due to differences in genetic background between populations, random variation in the estimation of the parameters, or inaccuracy in identifying the PRRS outbreak period.

Other studies have also estimated the heritability of S/P ratio. Serão et al. (2016) reported a high heritability of S/P ratio (0.47) measured at an average of 40.8 days (SD = 16.3) after F1 gilts entered the commercial farm (no confirmation on whether vaccination or PRRSV wild-type infection was obtained in their study). Using PRRSV-infected purebred sows, Putz et al. (2019) reported a heritability estimate of 0.17 for S/P ratio measured at about 60 days after the outbreak. However, these authors did not use the same method to measure S/P ratio as in our study. Abella et al. (2019) and Sanglard et al. (2020) reported heritability estimates of 0.69 and 0.33 for S/P ratio in F1 gilts after vaccinating animals with a modified live PRRSV vaccine (MLV) at 42 and 52 days, respectively. Although there are major differences between these estimates, S/P ratio was measured in young gilts in Abella et al. (2019), with 6–7 weeks of age, whereas S/P ratio was measured in more mature gilts in Sanglard et al. (2020) with 26 weeks of age. Therefore, differences in heritability estimates available in the literature may be due to several factors, including the time of collection, the method used to measure S/P ratio, the age of the

316 animals, type of exposure (vaccination or natural infection), and random error. Our results further
317 support the idea that S/P ratio has a sizeable genetic component.

318 Estimates of genetic correlations of S/P ratio with litter size traits during the PRRS outbreak were,
319 overall, consistent with the results of Serão et al. (2014) for Landrace sows. This is the first study
320 reporting results using a terminal sire line (i.e., Duroc sows) to the best of our knowledge. Serão et al.
321 (2014) reported that S/P ratio had strong favorable genetic correlations with NSB (-0.72 ± 0.28) and
322 NBA (0.73 ± 24) during a PRRS outbreak. In our study, there was also a high favorable genetic
323 correlation of S/P ratio with NBA (0.61 ± 0.34), but not for NSB (-0.27 ± 0.31). We also found a
324 favorable genetic correlation of S/P ratio with TNB (0.47 ± 1.47) in Landrace sows. However, this
325 estimate had a large standard error, probably due to the low heritability estimate of TNB (0.01 ± 0.05)
326 and the small sample size. The genetic correlations of S/P ratio with mortality traits were in a favorable
327 direction (negative) but not as strong (≤ -0.33) as results from Serão et al. (2014). Putz et al. (2019)
328 only found a large genetic correlation of S/P ratio with NSB (-0.73 ± 0.29), in contrast to our study.
329 These results indicate that S/P ratio can be used as an indicator trait for improved reproductive
330 performance in Landrace sows during a PRRS outbreak.

331 As reported in Serão et al. (2014), an indirect response to selection on reproductive performance during
332 a PRRS outbreak based on S/P ratio is expected to be 63% more effective than a direct response to
333 selection for increased NBA during a PRRS outbreak. Based on our genetic parameters, the
334 corresponding estimate would be 22%, further supporting the use of S/P ratio as an indicator trait for
335 reproductive performance under a PRRSV infection, as illustrated in Figure 4. It is important to note
336 that this is a simplistic comparison, assuming that selection is performed on own phenotypes. Results
337 for Duroc were not as promising. In addition to having lower estimates of genetic correlation of S/P
338 ratio with reproductive traits, we had convergence issues for genetic correlations with mortality traits.

Under the conditions described in this study, Serão et al. (2014), and Putz et al. (2019), the use of S/P ratio as a genetic indicator trait for improved reproductive performance under a PRRS outbreak has some limitations. For instance, these studies reported a high genetic correlation of S/P ratio with and reproductive performance using (i) purebred animals (ii) under a natural PRRS outbreak. In practice, breeding companies do not want to have PRRSV-positive purebred animals, as this can impact the additive genetic response to other traits measured in these animals that are included in their breeding goals, impacting the actual meaning of their (G)EBVs, as well as limiting the use of purebred animals for breeding. In addition, it is not expected that purebred herds undergo a PRRS outbreak due to the high biosecurity in these hers. However, they can happen in practice, such as for the populations used in this and other studies. Furthermore, although several studies have demonstrated that, in PRRSV-infected purebred sows, S/P ratio has sizable heritability and genetic correlation with reproductive performance, a large number of animals is needed to obtain accurate (G)EBVs for animals to be selected based on S/P ratio to improve reproductive performance under a PRRS outbreak. Finally, the overall goal of purebred selection is to improve the performance of crossbred animals, which was not evaluated in this study. Hence, the applicability of such a tool under these scenarios is limited. Nonetheless, the validation of the results reported by Serão et al. (2014) brings new opportunities to develop and evaluate feasible strategies to use S/P ratio as an indicator trait.

For instance, based on the results reported by Abella et al. (2019) and Sanglard et al. (2020), potential strategies are feasible. These authors reported that their studies were driven by the results reported by Serão et al. (2014) and proposed evaluating the use of S/P ratio as an indicator trait for reproductive performance in PRRSV-vaccinated F1 gilts. These authors reported moderate-to-high heritability estimates of S/P ratio (0.69 and 0.33, respectively). Furthermore, Sanglard et al. (2020) showed that S/P ratio due to vaccination was highly genetically correlated with NBA in F1 animals, while no PRRS outbreak was present during pregnancy or farrowing of these animals. Although the use of PRRSV

363 vaccination is a standard procedure in the U.S. swine industry (Arruda et al., 2016), this strategy
364 requires a close genetic relationship between F1 animals and nucleus animals. For example, F1 animals
365 should have pedigree information available to estimate the breeding values of nucleus animals for S/P
366 ratio and reproductive performance. Another strategy is to genotype F1 animals, which is desirable but
367 still cost limiting. Nonetheless, investigating the relationships among S/P ratio and reproductive
368 performance, under or not PRRSV infection or vaccination, is needed to further evaluate this strategy.

369 Sanglard et al. (2021) combined the S/P ratio data from the PRRSV-vaccinated F1 animals in Sanglard
370 et al. (2020) and the Landrace population used in this study to investigate the genetic relationships
371 between S/P ratio and reproductive performance under several conditions. These authors reported that
372 S/P ratio due to vaccination in F1 gilts and PRRSV infection in Landrace nucleus sows was high (0.72),
373 indicating that the host genetic response to PRRS challenge is similar. Furthermore, these authors
374 reported a favorable and moderate genetic correlation (0.50) of S/P ratio in PRRSV-vaccinated gilts
375 with NBA in nucleus animals before the PRRS outbreak. However, contrary to our expectations, the
376 estimate between S/P ratio in PRRSV-vaccinated gilts and NBA in purebred Landrace during the PRRS
377 outbreak was close to zero (0.07). Nonetheless, when this relationship was evaluated between S/P ratio
378 in PRRSV-infected Landrace and NBA in F1 gilts, a favorable, albeit low, estimate of genetic
379 correlation was observed (0.23). Hence, the use of S/P ratio data collected in Landrace nucleus herds
380 during a PRRS outbreak could be used to predict reproductive performance in commercial F1 animals.
381 Finally, Hickmann et al. (2021), using the same animals of this study, reported high genetic correlation
382 estimates for reproductive performance before and during the PRRS outbreak. Therefore, combining
383 the results from Hickmann et al. (2021), Sanglard et al. (2021), and the current study, the use of S/P
384 ratio, either from collecting data in PRRSV-infected nucleus Landrace animals or PRRSV-infected F1
385 gilts, as an indicator trait for reproductive performance (under or not PRRSV infection) is possible.

In summary, antibody response to PRRSV, measured as S/P ratio, was shown to be moderately heritable in Landrace and Duroc sows during a PRRS outbreak. In combination with the high genetic correlation of S/P ratio with NBA in Landrace (0.61) and the negative genetic correlations with mortality traits, our results validate and further support the use of S/P ratio as an indicator trait for improved reproductive performance under a PRRS outbreak in Landrace populations. However, in Duroc, the weak genetic correlation estimates and the large standard errors do not allow us to make conclusions for this population.

4.2 Genomic regions in the pig genome associated with S/P ratio

In this study, the QTL for S/P ratio identified on SSC7 (24–25 Mb) for S/P ratio in Duroc and Landrace sows is located within the MHC region, as previously reported by Serão et al. (2014, 2016) and Sanglard et al. (2020). The MHC region is widely recognized as the most important genomic region controlling the immune response in mammals (Hammer et al., 2020). The MHC QTL explained 25% of TGVM for S/P ratio in Landrace sows in Serão et al. (2014) and 20% of TGVM for S/P ratio in F1 replacement gilts in Serão et al. (2016). In our study, this QTL explained a greater proportion of TGVM in Landrace (31%) but lower in Duroc (15%). Their genetic background could partially explain the difference between these breeds since Landrace pigs have been intensively selected for a different set of traits (i.e., maternal traits) than Duroc pigs (i.e., terminal traits). In addition, it could be that the LD between SNPs and QTL in this region may differ between the two populations, affecting the power to detect the QTL.

Previous studies also reported a QTL for S/P ratio at 128–132 Mb on SSC7 that explained 15% (Serão et al., 2014) and 7% (Serão et al., 2016) of TGVM. In these reports, the older version of the swine genome assembly was used (i.e., *Sscrofa*10.2). The QTL identified by these authors around 130 Mb on the draft genome assembly (*Sscrofa*10.2) was not identified in our study, but these authors indicated

409 that this region shows high LD. However, there are some errors in the *Sscrofa*11.1 assembly in the part
410 of SSC 7 corresponding to 128–132 Mb in the *Sscrofa*10.2 assembly, with most of the missing content
411 now located on an unplaced scaffold (AEMK02000452) in the *Sscrofa*11.1 assembly (Warr et al.,
412 2020). Nonetheless, a GWAS using the older assembly version still did not identify this QTL in our
413 data (results not shown). Interestingly, Sanglard et al. (2020), using PRRSV-vaccinated F1 gilts
414 genetically related to the Landrace animals used in this study, also did not find this QTL in their
415 analyses of S/P ratio, while they did identify the MHC QTL. Thus, the reason why the 130-Mb QTL
416 on SSC7 detected by Serão et al. (2014, 2016) was not detected by Sanglard et al. (2020) and in the
417 current study could be because this QTL is segregating in our population or due to the lack of LD
418 between SNPs and the QTL. Serão et al. (2016) detected this QTL using data from seven breeding
419 companies. However, analyses performed by each breeding company did not identify this QTL for all
420 companies (unpublished results), further suggesting that this QTL may not be segregating or lack SNP-
421 QTL LD in all populations.

422 We also found novel QTL on SSC8 (25 Mb) in Duroc and on SSC7 (108–109 Mb) in Landrace sows.
423 However, they explained a much smaller proportion of TGVM, 2.4 and 2.2%, respectively. The QTL
424 at 108–109 Mb on SSC 7 had two candidate genes associated with reproduction or immune response.
425 The G protein-coupled receptor 65 (*GPR65*), a protein-coding gene that has been associated with
426 immune response in humans by regulating the cytokine production of T cells and macrophages
427 (Onozama et al., 2012), and the *GALC* gene, which has been associated with spermiogenesis and with
428 sperm abnormalities in mouse when deficient (Luddi et al., 2005). These candidate genes further
429 support that this region may play a role in immune response and reproduction. No candidate genes
430 were identified for the SSC8 QTL found for Duroc.

4.3 Effects of selected SNPs associated with S/P ratio

We performed additional analyses using the SNPs associated with S/P ratio that accounted for most of the TGVM observed in our study, along with those reported by Serão et al. (2014). These authors evaluated the effect of SNPs on S/P ratio measured in Landrace sows that experienced a PRRS outbreak. They reported five SNPs within the MHC QTL found in their study (SSC7, 24–30 Mb) that accounted for 25.1% of TGVM. Of their SNPs, three of them are located within the MHC QTL in our study: ASGA0032151, ASGA0031860, and MARC0058875. In Serão et al. (2014), the ASGA0032151 and MARC0058875 SNPs were associated with S/P ratio, with the AB and BB genotypes having a greater S/P ratio than the AA genotype at both SNPs.

In Duroc sows, the MHC QTL that explained 15% of TGVM explained only 1.5% of TGVM after removing these five SNPs from the MHC QTL, indicating that these SNPs accounted for most of the effect in the MHC region. Similarly, for Landrace sows, the MHC QTL that explained 31% of TGVM explained < 0.1% of TGVM after these five SNPs were accounted for. This indicates that these SNPs were capable of accounting for the TGVM of S/P ratio within this region. The MARC0089437 SNP was the only SNP that was associated with S/P ratio in both populations. Interestingly, this SNP was only identified as a key SNP in the GWAS using Duroc sows.

Furthermore, the direction of the effects for this SNP was opposite in the two populations. Although a greater S/P ratio was obtained in Duroc sows with the AB and BB genotypes, Landrace sows with the BB genotype had a lower S/P ratio than AB sows. Also, the A allele had a very low frequency (0.04) in Landrace sows but a much higher frequency (0.41) in Duroc. In fact, only one Landrace sow had the AA genotype, and this individual was removed from the analysis. We found a similar situation for the ASGA0032063 SNP identified in the GWAS for Landrace, for which the B allele had a very low frequency (0.05) in Duroc sows, but a much greater frequency (0.69) in Landrace sows. Heterozygote

Landrace sows had a greater S/P ratio than homozygote sows, indicating an overdominance effect for this SNP. This has some limitations in breeding schemes in the nucleus, as selection for improved performance results in fixation of the favorable allele, limiting the number of AB animals for this SNP. Nonetheless, AA Landrace sows had a greater S/P ratio than BB sows for this SNP, which indicates that selection for an increase in the frequency of the A allele in purebred Landrace sows may increase the S/P ratio of the population.

For the SNPs selected based on the results of Serão et al. (2014), MARC0058875 was associated with S/P ratio in Duroc sows and ASGA0032151 in Landrace sows during the PRRS outbreak. Duroc sows with the AB genotype at the MARC0058875 SNP had a lower S/P ratio than homozygous animals, indicating a negative dominance effect for this SNP. Serão et al. (2014), using Landrace sows, observed the superiority of AB and BB compared with AA sows at the MARC0058875 SNP. This contrasting result indicates a complex relationship between this marker and the QTL in these distinct populations. For ASGA0032151, the BB genotype had a greater S/P ratio than AA in Landrace animals. This is partially in accordance with Serão et al. (2014), who also worked with Landrace animals during a PRRS outbreak. However, these authors also observed a greater S/P ratio in BB sows than AB genotypes, whereas no differences in S/P ratio were observed in our study between AB and BB sows. In addition, the B allele was highly frequent in both populations, with 0.46 and 0.41 in Serão et al. (2014) and in our study, respectively, indicating that selection for increased frequency of this favorable allele may be performed with regards to S/P ratio. These results bring new possibilities for marker-assisted selection for greater antibody response in PRRSV-infected sows.

4.4 Effects of selected SNPs associated with S/P ratio on reproductive traits

Given the hypothesis of S/P ratio being an indicator trait for reproductive performance in PRRSV-infected (Serão et al., 2014) and healthy sows (Sanglard et al., 2020), we evaluated the effects of the

five selected SNPs associated with S/P ratio from Serão et al. (2014) and from the current study on reproductive performance before, during, and after the PRRS outbreak. Although the MHC region was not associated with any of the reproductive traits evaluated in a study using the same animals (Hickmann et al., 2021), the genetic variation in the MHC region has been associated with reproductive performance in other studies (Vaiman et al., 1998; Laplana et al., 2020; Sanglard et al., 2020). Sanglard et al. (2020) reported a SNP associated with S/P ratio in PRRSV-vaccinated gilts that was also associated with reproductive performance in the absence of PRRSV infection, even if this SNP was not detected in the univariate GWAS for reproductive traits.

In Duroc sows, only the MARC0089437 and MARC0058875 SNPs were associated with S/P ratio. However, they were associated with reproductive traits only outside the PRRS phase. At the MARC0089437 SNP, a greater S/P ratio was obtained for the AB and BB genotypes. For reproductive traits, AB sows had greater NBA pre-PRRS and TNB, NBA, and NW post-PRRS for this SNP. These results indicate that selection for heterozygotes at the MARC0089437 SNP may increase not only S/P ratio but also TNB, NBA, and NW in sows not facing a PRRS outbreak. At the MARC0058875 SNP, AA and AB animals had greater S/P ratio than AB animals. Although there was under-dominance for this SNP for S/P ratio, AA animals had greater TNB and NW post-PRRS, indicating that selection for fixation of the A allele would result in animals with greater post-PRRS reproductive performance and S/P ratio. Although not significantly associated with TNB and NW in the pre-PRRS phase, the AA genotype showed numerically greater performance than the other genotypes, suggesting that fixation of the favorable allele for this SNP might increase performance even in PRRSV-naïve animals. This is important as it is expected that purebred animals in the nucleus will not go through a PRRS outbreak. Hence, significant associations between the MARC0058875 SNP and pre-PRRS performance would further suggest that this SNP might be important in explaining variation in reproductive performance of purebred sows even in the absence of a PRRS outbreak. Interestingly, the only selected SNP

associated with reproductive performance during the PRRS phase was ASGA0031860. Although this SNP was not associated with S/P ratio in Duroc pigs, greater NBD was obtained in BB animals.

It is worth noting that, based on estimates of genetic correlations, we suggested that S/P ratio might not be an indicator trait for reproductive performance in Duroc pigs. However, the two SNPs associated with S/P ratio in Duroc sows (MARC0089437 and MARC0058875) were also associated with some reproductive traits for this breed, with all favorable genotypes being overall the same for S/P ratio and reproductive traits. Thus, although we could not find strong genetic correlations between S/P ratio and reproductive traits, it could be that these SNPs are capturing pleiotropic QTL(s) for these traits, similar to what Sanglard et al. (2020) reported. In contrast, the ASGA0031860 SNP identified by Serão et al. (2014) was not associated with S/P ratio in Duroc, but it was associated with NBD during the PRRS phase in our study. For this association, it could be that a reproduction-specific QTL in the MHC region is captured by this SNP, as this region has been associated with reproduction in other studies using healthy pigs (Vaiman et al., 1998). Nonetheless, it could also be that these associations are spurious as the sample size of this study is relatively small for obtaining accurate estimates for the genetic correlation of S/P ratio with reproductive traits. Hence, it could also be that S/P ratio and reproductive traits share a common genomic basis, such as observed in Landrace sows, which would indicate that these associations between selected SNPs for S/P ratio and reproductive traits in Duroc pigs are real. However, the statistical power to obtain these estimates was low, resulting in weak estimates of genetic correlations between S/P ratio and reproductive traits in Duroc pigs in our study, given the large standard errors. Nonetheless, additional studies are needed to better investigate the effect of these SNPs on reproductive traits in Duroc sows.

For Landrace, the three SNPs associated with S/P ratio were ASGA0032063, ASGA0032151, and MARC0089437. However, these SNPs were only associated with reproductive performance in the absence of PRRS. At the ASGA0032063 SNP, AB animals had a greater S/P ratio, followed by AA

525 and then by BB animals. For pre-PRRS NBD and NBS, BB sows also had lower performance but not
526 different than AB sows. Thus, these results suggest that greater reproductive performance might be
527 obtained by increasing the frequency of the AA genotype at this SNP in the population. For S/P ratio,
528 the ASGA0032151 SNP, BB sows had a greater S/P ratio than AA sows in our study, similar to the
529 results of Serão et al. (2014), who first reported the association between this SNP and S/P ratio.
530 Following what we found for S/P ratio, AA animals had better performance in post-PRRS NSB and
531 NW than BB animals, indicating that selection for increased frequency of the A allele at this SNP
532 would result in overall better improved reproductive performance. On the other hand, a greater S/P
533 ratio was obtained in AB animals at the MARC0089437 SNP. Interestingly, although sows with this
534 genotype had lower pre-PRRS NW (9.1 ± 0.33) than BB sows (9.7 ± 0.19), the same direction of effects
535 for S/P ratio was observed in post-PRRS TNB, in which AB animals had greater performance than BB
536 animals. Finally, although the ASGA0031860 SNP was not associated with S/P ratio in Landrace sows
537 in our study, AA animals had greater post-PRRS NW than BB animals, bringing the possibility of
538 selection for increased NW based on this SNP regardless of S/P ratio.

539 The lack of associations between these selected SNPs for S/P ratio and reproductive performance
540 during the PRRS outbreak in this study was unexpected. Moreover, the fact that associations of S/P
541 ratio SNPs with reproductive performance were only found in the pre-PRRS and post-PRRS phases
542 could be considered contradictory to the proposed use of S/P ratio as an indicator trait during a PRRS
543 outbreak. Therefore, these issues must be addressed. To begin with, previous studies have associated
544 polymorphisms in the MHC region with reproductive performance in healthy animals (Vaiman et al.,
545 1998; Laplana et al., 2020; Sanglard et al., 2020). Given that S/P ratio had moderate-high heritability
546 estimates in our study and that this trait is not under selection, we expect to find key SNPs for this trait
547 more easily than for reproductive traits, which are lowly heritable and under selection for decades.
548 Therefore, assuming that the MHC has a true effect on reproductive performance, even if the MHC

549 was not identified for these traits in this population (Hickmann et al., 2021), and these traits are
550 genetically correlated with S/P ratio, we could expect to find associations between S/P ratio in the
551 MHC with reproductive traits regardless of PRRS challenge. This could be even more evident for
552 Duroc sows, in which the MARC0089437 SNP accounted for by 9.2% of TGVM for S/P ratio and
553 associations between this SNP were found for reproductive traits in the pre-PRRS and post-PRRS
554 phases, even if we did not observe evidence for S/P ratio to be used as an indicator trait for this breed.

555 The statistical power to detect these associations during the PRRS outbreak could be lower than in the
556 absence of infection. The residual variance of traits under selections measured during challenge
557 conditions is expected to be greater than in the lack of challenge (Berghof et al., 2019). In fact, the
558 residual variances of the reproductive traits evaluated in this study were generally greater in the PRRS
559 phase than in the other phases (Hickmann et al., 2021). Therefore, the power to detect SNP associations
560 is expected to be lower in the PRRS phase than in the other phases, which could explain the lack of
561 associations during the PRRS outbreak period.

562 The greater number of associations in the post-PRRS phase than in the others could be due to two
563 factors. First, a greater number of sows and litters were used for analyses in the post-PRRS phase than
564 the others (details in Hickmann et al., 2021), which could have increased the statistical power to detect
565 significant associations between S/P ratio SNPs and reproductive performance. Second, these
566 associations might be more powerful to be detected once animals have been challenged. This is in
567 accordance with Sanglard et al. (2020). They reported significant associations between S/P ratio SNP
568 and reproductive performance in sows that were not under a PRRS outbreak but had been PRRSV
569 vaccinated when they were gilts. Hence, we hypothesize that the immune system of these animals must
570 be activated at some level to identify associations between S/P ratio SNPs and reproductive
571 performance with greater power.

572 Finally, the proposed use of S/P ratio as an indicator trait for reproductive performance during a PRRS
573 outbreak is based on the moderate-high heritability of this trait and its genetic correlation with
574 reproductive performance during PRRS. More importantly, these results validate the original proposal
575 by Serão et al. (2014). The lack of S/P ratio SNP associations with reproductive performance under
576 PRRS does not impact the novelty of S/P ratio due to the previous points raised in this section. This
577 illustrates some of the challenges of performing genomic analyses for complex lowly heritable traits
578 such as reproductive traits. Nonetheless, these results bring new possibilities for marker-assisted
579 selection for greater antibody response and improved reproductive performance based on the selected
580 SNPs reported in this study. However, a larger and independent dataset might be needed to identify
581 significant associations between S/P ratio SNPs and reproductive performance across PRRS phases.

582 **4.5 Genomic prediction accuracies**

583 Studies on genomic prediction of antibody response to PRRSV are scarce in the literature. To the best
584 of our knowledge, Serão et al. (2016) is the only study that performed genomic prediction analyses for
585 S/P ratio in sows during a PRRS outbreak. These authors reported GPAs using two strategies: using
586 crossbred F1 gilts during acclimation for training and validation or using crossbred F1 gilts during
587 acclimation for training and a purebred population under a PRRS outbreak (Serão et al., 2014) for
588 validation. The same SNP set strategies used by Serão et al. (2016) (SNP_{All}, SNP_{MHC}, and SNP_{Rest})
589 were used in our study. For their first strategy, the GPAs were 0.33, 0.24, and 0.09 for SNP_{All}, SNP_{MHC},
590 and SNP_{Rest}, respectively. For their second strategy, these were 0.45, 0.40, and 0.10, respectively.
591 These GPAs reported by Serão et al. (2016) were much lower than those from our within-breed
592 genomic prediction analyses. This major discrepancy between results could be because Serão et al.
593 (2016) performed analyses using data from seven breeding companies, where animals from the same
594 breeding company were not simultaneously used in the training and validation dataset. In contrast, we
595 used data from closely related animals, which took advantage of genetic similarities between the

training and validation datasets, which is expected to increase GPAs. Sanglard et al. (2020) also used genetically related animals for the genomic prediction of S/P ratio in PRRSV-vaccinated F1 gilts that shared genetic relationships with the animals used in our study. These authors reported GPAs of 0.67, 0.59, and 0.34 for SNP_{All}, SNP_{MHC}, and SNP_{Rest}, respectively, similar to those obtained in our study.

With regard to the between-breed scenario, our results were much worse than those in Serão et al. (2016) for SNP_{All} and SNP_{MHC}, whereas the one for SNP_{Rest} when training in Duroc and validating in Landrace (GPA = 0.09) was very similar to the result found in Serão et al. (2016). In general, between-breed GPAs indicate that this strategy should not be used in genomic selection for S/P ratio. The only sizeable GPA was obtained for SNP_{MHC} when training in Duroc and validating in Landrace. Interestingly, we obtained a negative GPA (-0.32). However, we observed a small positive GPA for this SNP set when Landrace was used for training and Duroc for validation (GPA = 0.09). These two contrasting results could suggest a combination of events. For example, it could be that the LD between SNPs and a major QTL in the MHC for Duroc and Landrace are in opposite phases between the two breeds. Also, it could be that some of the QTL effects captured by SNPs using Duroc sows are not segregating in Landrace sows. Finally, when Landrace is used for training, SNPs could be capturing few small effects of QTL on the same phase in both breeds, explaining the small and positive GPA for this scenario, whereas this was not observed when training using Duroc pigs. Nonetheless, the between-breed results show that genomic selection for S/P ratio should not be performed across breeds based on our results. The high within-breed genomic prediction accuracies for S/P ratio indicate that genomic selection within a breed is an efficient strategy to change S/P ratio within Landrace and Duroc populations. However, the sample size used in this study was still limited to obtain very accurate estimates for the measures reported. Therefore, a larger sample size would be needed to validate these results.

5. Conclusions

Antibody response to PRRSV infection, measured as S/P ratio, was shown to be moderately heritable in Landrace and Duroc sows following a PRRS outbreak. In combination with a high estimated genetic correlation of S/P ratio with NBA (0.61) in Landrace sows, our results validate and further support the use of S/P ratio as an indicator trait for improved reproductive performance during a PRRS outbreak. However, this seems to work only for Landrace populations. In Duroc, the weak estimates of genetic correlations of S/P ratio with reproductive performance and their large standard errors do not allow us to propose using S/P ratio as an indicator trait in this breed. Our genomic analyses further validated the major histocompatibility region as the major QTL for S/P ratio during a PRRS outbreak in Landrace, showing that this QTL also plays a major role for S/P ratio in Duroc pigs. In addition, we identified novel small-effect QTL on SSC7 (108–109 Mb) in Landrace and on SSC8 (25 Mb) in Duroc sows. We also provided information on specific SNPs within the major histocompatibility region in both populations, providing the opportunity of marker-assisted selection for increased S/P ratio and reproductive performance. Finally, the high genomic prediction accuracies for S/P ratio indicate that genomic selection within a breed is an efficient strategy to change S/P ratio in Landrace and Duroc populations.

6. Conflict of Interest

The authors declare that this study received funding from Smithfield Premium Genetics, NC, United States. The funder had the following involvement with the study: providing performance and genotype data and collection of blood samples. In addition, YH and KG are employed by the company Smithfield Premium Genetics, NC, United States. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7. Author Contributions

FH performed statistical analyses, interpreted results, prepared figures and tables, and drafted the manuscript. JB, LK, and JD were involved in the interpretation and discussion of results. YH and KG provided the data, led the collection of blood samples, and interpreted results. LS provided help and guidance for statistical analyses, being involved in the discussion of results as well. NS assisted with data analysis, interpretation of results, and drafted the manuscript. All authors read and approved the final version of the manuscript.

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9. Abbreviations

Chr, chromosome; ELISA, enzyme-linked immunosorbent assay; GRM, genomic relationship matrix; GEBV, genomic estimated breeding value; GPA, genomic prediction accuracy; GWAS, genome-wide association studies; LD, linkage disequilibrium; Mb, megabases; MCMC, Markov Chain Monte Carlo; MHC, major histocompatibility complex; MLV, modified live PRRSV vaccine; NBA, number of piglets born alive; NBD, number of piglets born dead; NBM, number of mummified piglets; NSB, number of stillborn piglets; NW, number of piglets weaned; PRRS, porcine reproductive and respiratory syndrome; PRRSV, porcine reproductive and respiratory syndrome virus; QTL, quantitative trait loci; S/P ratio, sample-to-positive ratio; SNP, single nucleotide polymorphisms; SNP_{All}, all SNPs across the genome; SNP_{MHC}, only SNPs in the QTL that harbors the MHC region;

664 SNP_{Rest}, all SNPs across the genome, excluding those in the MHC region; SSC, *Sus scrofa*
665 chromosome; TGVM, total genetic variance accounted for by markers; TNB, total number of piglets
666 born.

667 **10. Acknowledgments**

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671 **11. Data Availability Statement**

672 The datasets presented in this article are not readily available because the data that support the findings
673 of this study are not publicly available. Data may be available from authors upon reasonable request
674 and authorization from the company that generated the data.

675 **12. Ethics Statement**

676 The animal study was reviewed and approved by the Institutional Animal Care and Use Committee
677 (IACUC) at Iowa State University (protocol number 6-17-8551-S). Written informed consent was
678 obtained from the owners for the participation of their animals in this study.

679 **13. References**

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14. Figures

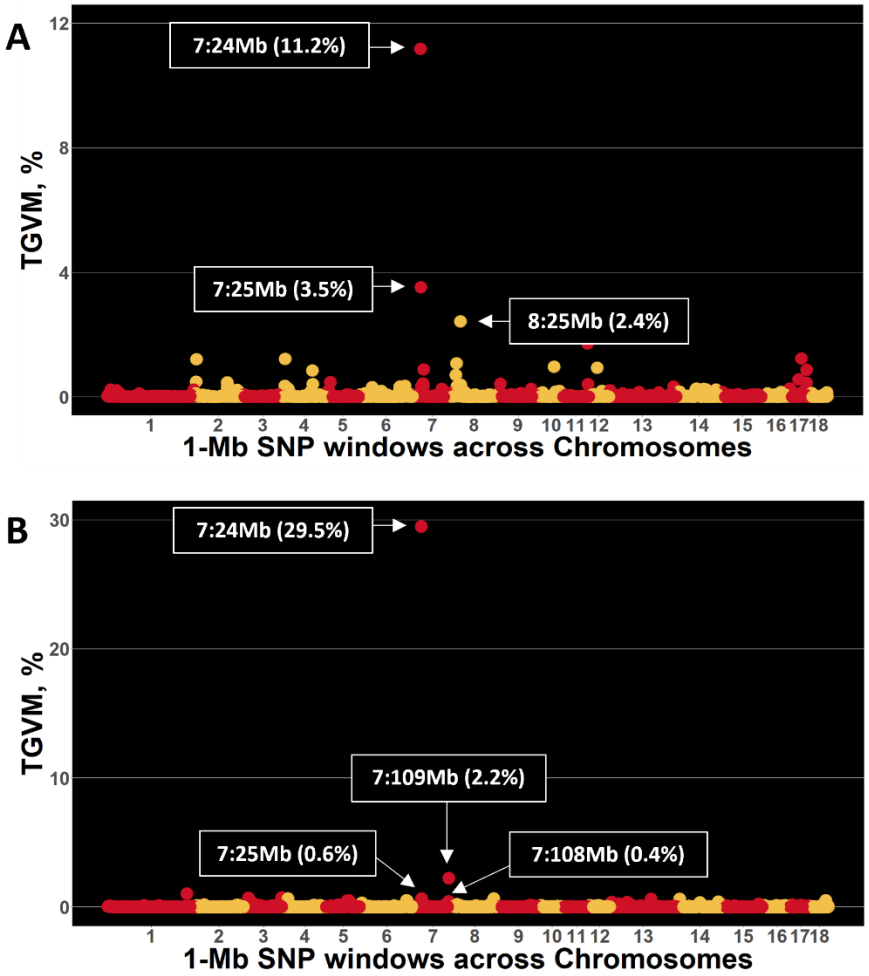

Figure 1. Manhattan plot for sample-to-positive (S/P) ratio during the porcine reproductive and respiratory syndrome (PRRS) outbreak in Duroc and Landrace sows. Each point represents a 1-Mb SNP window (x-axis) plotted against the percentage of total genetic variance accounted for by markers (TGVM; y-axis). **(A,B)** Results for Duroc and Landrace sows, respectively.

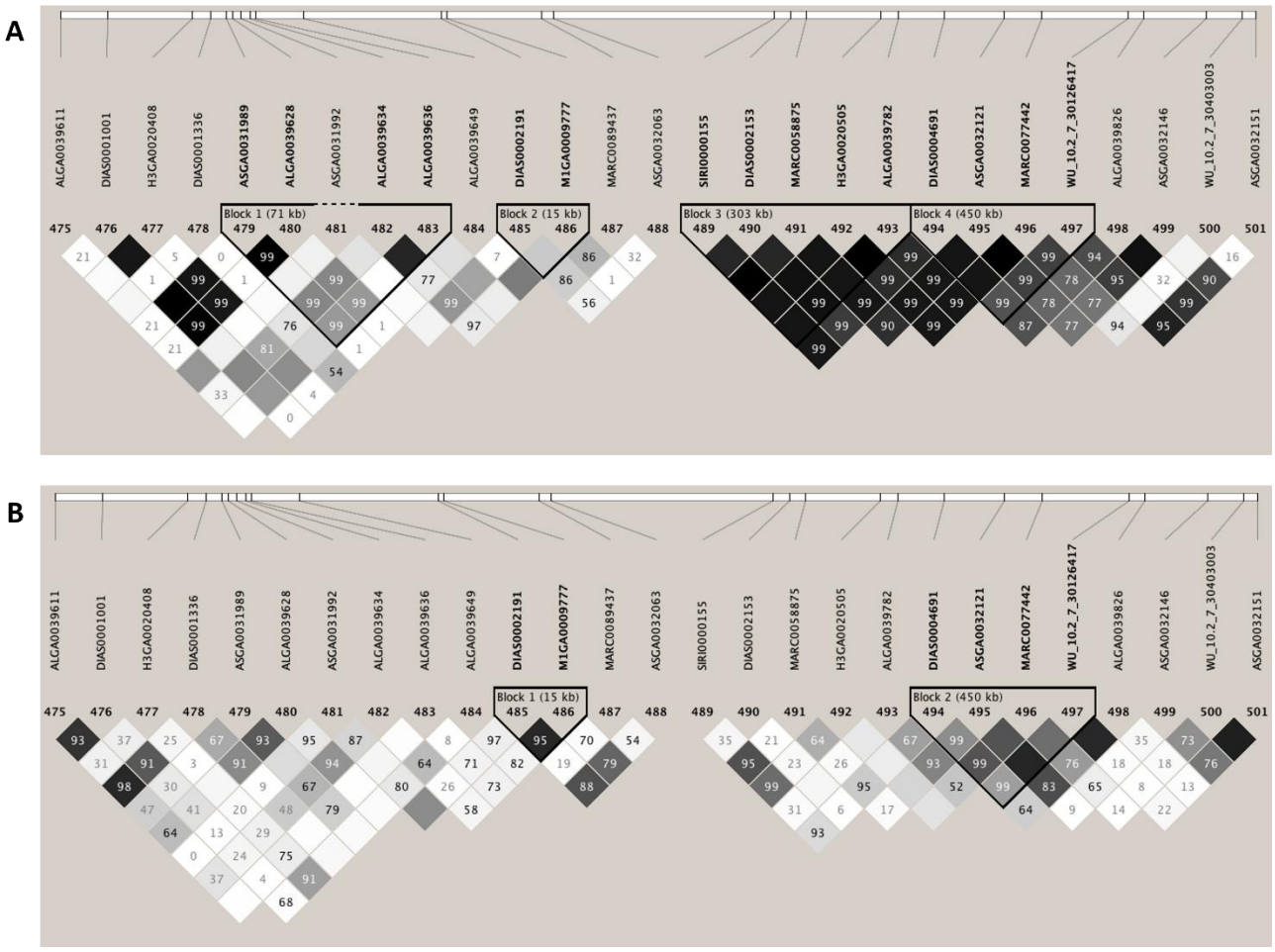

Figure 2. Linkage disequilibrium (LD) plots of the genotype data for the 3-Mb SNP window that harbors the major histocompatibility complex (MHC) on *Sus Scrofa* chromosome 7 (SSC 7: 24–25 Mb) associated with sample-to-positive (S/P) ratio. **(A,B)** Results for Duroc and Landrace sows, respectively. LD is expressed as r^2. The darker diamonds indicate greater LD. These plots indicate lower LD in Landrace sows than Duroc sows within this region.

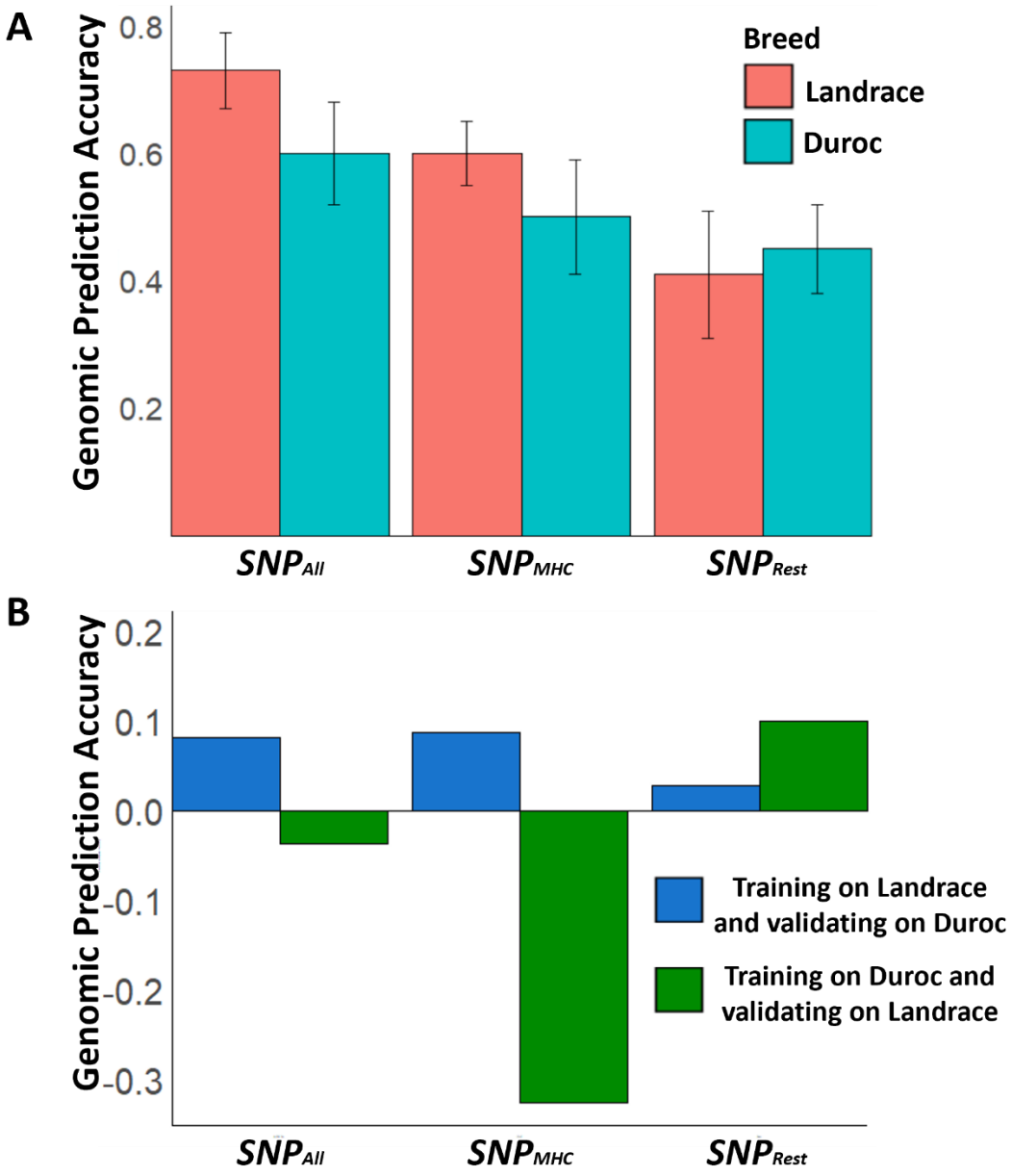

Figure 3. Genomic prediction accuracies of sample-to-positive (S/P) ratio across different SNP sets. **(A,B)** Genomic prediction accuracies for the within-breed and between-breed genomic prediction, respectively. SNP_{All} represents the set of SNPs using all 29,799 SNPs across the genome, while SNP_{MHC} accounts for only SNPs in the QTL that harbors the major histocompatibility complex (MHC) region. For SNP_{Rest}, all SNPs across the genome were used excluding those in the MHC region and a 2-Mb window surrounding the QTL in the MHC region to avoid having any SNPs in linkage disequilibrium with this QTL. The error bars in panel **(A)** represent the standard deviations across the 5-fold used to calculate genomic prediction accuracies.

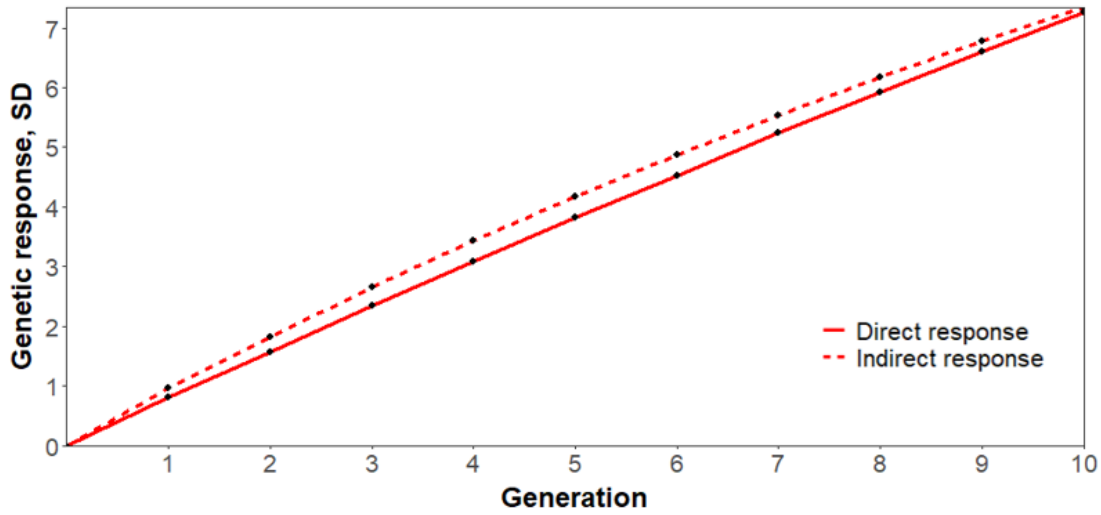

Figure 4. Simulated response to selection for increased number of piglets born alive (NBA) in Landrace sows after 10 generations based on (indirect) or not (direct) antibody response to porcine reproductive and respiratory syndrome virus infection, measured as sample-to-positive (S/P) ratio. The y- and x-axis represent the response to selection in genetic standard deviations and generations, respectively. Direct and indirect response to selection are represented by solid and dashed lines, respectively, assuming 5% selection intensity, using the genetic parameters obtained in this study.

15. Tables

Table 1. Heritability estimates (SE) and variance components of traits and their genetic correlation (r_g) with sample-to-positive (S/P) ratio for each PRRS phase and breed.

	Duroc				Landrace			
	Pre-PRRS							
Trait[1]	h^2 (SE)	σ_a^2	σ_e^2	r_g (SE)	h^2 (SE)	σ_a^2	σ_e^2	r_g (SE)
TNB	0.14 (0.04)	1.08	6.51	0.04 (0.19)	0.11 (0.03)	1.64	13.36	0.12 (0.21)
NBA	0.19 (0.04)	1.35	5.68	-0.04 (0.18)	0.13 (0.03)	1.42	9.86	0.15 (0.20)
NBD	0.01 (0.02)	0.01	1.47	NC[2]	0.06 (0.03)	0.02	0.35	-0.18 (0.25)
NSB	0.05 (0.03)	0.01	0.21	0.48 (0.24)	0.10 (0.03)	0.03	0.26	-0.13 (0.21)
NBM	0.03 (0.02)	<0.01	0.13	-0.38 (0.31)	0.01 (0.02)	<0.01	0.18	0.01 (0.47)
NW	0.09 (0.03)	0.34	3.60	-0.34 (0.22)	0.07 (0.03)	0.46	5.83	0.05 (0.25)
	PRRS							
	h^2 (SE)	σ_a^2	σ_e^2	r_g (SE)	h^2 (SE)	σ_a^2	σ_e^2	r_g (SE)
S/P ratio	0.35 (0.08)	0.032	0.059	-	0.34 (0.09)	0.033	0.063	-
TNB	0.12 (0.07)	1.15	8.27	0.23 (0.27)	0.01 (0.05)	0.14	15.25	0.47 (1.47)
NBA	0.11 (0.07)	1.20	9.67	-0.24 (0.30)	0.08 (0.07)	1.77	20.53	0.61 (0.34)
NBD	0.08 (0.06)	0.05	0.54	NC[2]	0.12 (0.07)	0.10	0.71	-0.33 (0.32)
NSB	0.02 (0.05)	0.01	0.30	0.01 (0.54)	0.14 (0.08)	0.06	0.35	-0.27 (0.31)
NBM	0.03 (0.05)	<0.01	0.53	-0.08 (0.41)	0.08 (0.07)	0.07	0.84	-0.11 (0.37)
NW	0.12 (0.06)	1.28	9.00	0.30 (0.25)	0.08 (0.07)	1.40	15.86	0.10 (0.37)
	Post-PRRS							
	h^2 (SE)	σ_a^2	σ_e^2	r_g (SE)	h^2 (SE)	σ_a^2	σ_e^2	r_g (SE)
TNB	0.15 (0.04)	1.37	7.58	-0.22 (0.17)	0.20 (0.04)	2.71	10.95	-0.06 (0.17)
NBA	0.13 (0.04)	0.98	6.79	-0.17 (0.18)	0.16 (0.04)	1.87	9.98	0.06 (0.18)
NBD	0.12 (0.04)	0.17	1.17	NC[2]	0.10 (0.03)	0.04	0.33	-0.26 (0.20)
NSB	0.07 (0.03)	0.01	0.18	-0.04 (0.22)	0.12 (0.03)	0.03	0.23	-0.20 (0.19)
NBM	0.06 (0.03)	0.01	0.11	-0.17 (0.23)	0.01 (0.02)	<0.01	0.19	-0.33 (0.54)
NW	0.14 (0.04)	1.12	6.77	-0.11 (0.18)	0.14 (0.04)	1.45	8.78	-0.09 (0.20)

[1]S/P ratio, sample-to-positive ratio; TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NBM, number of mummified piglets; NW, number of piglets weaned;
[2]NC, not converged.

Table 2. Effect[1] of selected SNPs[2] associated with sample-to-positive (S/P) ratio during the PRRS[3] outbreak for each breed.

		Genotype				
SNP name	%TGVM[4]	AA	AB	BB	MAF	*P*-value
Duroc						
ASGA0031860	<0.1	1.03 (0.07)	1.09 (0.04)	1.04 (0.03)	0.19 (A)	0.202
MARC0089437	9.2	0.86[b] (0.07)	1.10[a] (0.05)	1.21[a] (0.06)	0.41 (A)	0.002
ASGA0032063	<0.1	1.04 (0.03)	1.07 (0.05)	-	0.05 (B)	0.519
MARC0058875	0.2	1.04[a] (0.07)	0.97[b] (0.05)	1.15[a] (0.06)	0.41 (B)	0.018
ASGA0032151	<0.1	1.08 (0.06)	1.06 (0.04)	1.02 (0.04)	0.36 (A)	0.517
Landrace						
ASGA0031860	<0.1	1.51 (0.11)	1.47 (0.10)	1.44 (0.10)	0.35 (A)	0.511
MARC0089437	<0.1	-	1.39[a] (0.05)	1.28[b] (0.02)	0.04 (A)	0.034
ASGA0032063	29.1	1.48[b] (0.12)	1.55[a] (0.10)	1.39[c] (0.10)	0.31 (A)	0.002
MARC0058875	<0.1	1.48 (0.10)	1.45 (0.10)	1.49 (0.11)	0.40 (A)	0.617
ASGA0032151	0.6	1.40[b] (0.10)	1.48[ab] (0.10)	1.53[a] (0.10)	0.41 (B)	0.054

%TGVM, percentage of the total genetic variance of S/P ratio explained by the marker;
MAF, minor allele frequency (minor allele in parenthesis);
[1]Results for each genotype expressed as expected values for S/P ratio (standard errors within parenthesis), measurement of antibody response to PRRSV;
[2]SNPs are located on *Sus scrofa* chromosome 7 according to the *Sscrofa11.1* as follow: (GCA_000003025.6) assembly: ASGA0031860/rs80959936 (7:22,075,114), MARC0089437/rs80900036 (7:24,217,931), ASGA0032063/rs80940999 (7:24,247,099), MARC0058875/rs80986722 (7:24,865,378), and ASGA0032151/rs80947467 (7:25,967,157). SNP markers MARC0089437 and ASGA0032063 were associated with S/P ratio in this study, in Duroc and Landrace populations, respectively. The other markers were associated with S/P ratio in Landrace sows in Serão et al. (2014);
[3]PRRS, Porcine Reproductive and Respiratory Syndrome;
[4]The remaining of the TGVM of the S/P ratio QTL after accounting for the %TGVM of these SNPs were 1.5% and <0.1%, for Duroc and Landrace, respectively;
[a-c] Expected values within row lacking the same superscript indicate differences at *P*-value < 0.05.

Table 3. Effect[1] of selected SNPs[2] associated with sample-to-positive (S/P) ratio on reproductive traits[3] across PRRS[4] phases.

		Pre-PRRS					
SNP	Genotypes	TNB	NBA	NBD	NSB	NBM	NW
Duroc							
ASGA0031860	AA	9.74 (0.68)	8.45 (0.67)	0.78 (0.12)	0.54 (0.11)	0.28 (0.09)	7.29 (0.48)
	AB	9.22 (0.34)	8.25 (0.34)	0.64 (0.06)	0.46 (0.06)	0.18 (0.04)	7.21 (0.25)
	BB	9.26 (0.27)	8.13 (0.27)	0.74 (0.05)	0.50 (0.04)	0.23 (0.04)	7.11 (0.21)
	P-value	0.698	0.822	0.301	0.713	0.310	0.816
MARC0089437	AA	9.40 (0.64)	8.31^{B} (0.63)	0.68 (0.12)	0.42 (0.11)	0.27 (0.08)	7.56 (0.46)
	AB	9.92 (0.47)	8.79^{A} (0.46)	0.72 (0.08)	0.52 (0.08)	0.20 (0.06)	7.34 (0.34)
	BB	8.90 (0.61)	7.73^{B} (0.60)	0.75 (0.11)	0.57 (0.10)	0.21 (0.08)	6.71 (0.43)
	P-value	0.107	0.089	0.967	0.803	0.866	0.195
ASGA0032063	AA	9.45 (0.31)	8.26 (0.30)	0.77 (0.06)	0.52 (0.05)	0.25 (0.04)	7.13 (0.23)
	AB	9.37 (0.47)	8.29 (0.46)	0.67 (0.08)	0.48 (0.08)	0.20 (0.06)	7.28 (0.34)
	P-value	0.823	0.931	0.344	0.687	0.349	0.544
MARC0058875	AA	9.83 (0.55)	8.75 (0.55)	0.68 (0.10)	0.50 (0.09)	0.19 (0.07)	7.57 (0.40)
	AB	9.27 (0.47)	8.20 (0.46)	0.69 (0.09)	0.46 (0.08)	0.24 (0.06)	7.25 (0.34)
	BB	9.11 (0.70)	7.88 (0.69)	0.79 (0.12)	0.55 (0.11)	0.26 (0.09)	6.80 (0.50)
	P-value	0.523	0.514	0.931	0.842	0.750	0.491
ASGA0032151	AA	9.51 (0.53)	8.61 (0.52)	0.57 (0.09)	0.45 (0.08)	0.14 (0.07)	7.35 (0.38)
	AB	9.27 (0.39)	8.02 (0.38)	0.81 (0.07)	0.57 (0.06)	0.25 (0.05)	7.09 (0.28)
	BB	9.44 (0.37)	8.20 (0.36)	0.79 (0.07)	0.49 (0.06)	0.29 (0.05)	7.17 (0.27)
	P-value	0.736	0.302	0.132	0.313	0.152	0.624
Landrace							
ASGA0031860	AA	13.35 (0.62)	11.91 (0.54)	1.03 (0.09)	0.68 (0.08)	0.28 (0.06)	9.00 (0.39)
	AB	13.78 (0.39)	12.18 (0.34)	1.09 (0.05)	0.69 (0.05)	0.34 (0.04)	9.54 (0.25)
	BB	13.31 (0.34)	11.91 (0.30)	0.99 (0.05)	0.65 (0.04)	0.29 (0.03)	9.54 (0.23)
	P-value	0.332	0.604	0.623	0.877	0.438	0.305
MARC0089437	AB	13.33 (0.53)	11.76 (0.46)	1.12 (0.08)	0.70 (0.07)	0.35 (0.05)	9.08^{B} (0.34)
	BB	13.61 (0.29)	12.24 (0.26)	0.96 (0.04)	0.65 (0.04)	0.26 (0.03)	9.65^{A} (0.20)
	P-value	0.587	0.256	0.291	0.699	0.200	0.063
ASGA0032063	AA	13.65 (0.77)	12.63 (0.67)	0.66^{B} (0.11)	0.39^{B} (0.10)	0.20 (0.08)	9.54 (0.49)
	AB	13.49 (0.45)	11.79 (0.39)	1.25^{A} (0.06)	0.84^{A} (0.06)	0.34 (0.04)	9.34 (0.29)

	BB	13.30 (0.54)	11.58 (0.47)	1.26^{A} (0.08)	0.85^{A} (0.07)	0.38 (0.05)	9.20 (0.34)
	P-value	0.925	0.512	0.067	0.061	0.386	0.865
MARC0058875	AA	13.24 (0.51)	11.49 (0.44)	1.28 (0.07)	0.84 (0.07)	0.38 (0.05)	9.34 (0.33)
	AB	13.50 (0.43)	12.25 (0.38)	0.88 (0.06)	0.57 (0.06)	0.27 (0.04)	9.50 (0.28)
	BB	13.70 (0.58)	12.26 (0.51)	0.97 (0.09)	0.63 (0.08)	0.27 (0.06)	9.25 (0.37)
	P-value	0.843	0.383	0.110	0.138	0.416	0.648
ASGA0032151	AA	13.30 (0.50)	11.87 (0.44)	0.97 (0.07)	0.64 (0.07)	0.29 (0.05)	9.47 (0.32)
	AB	13.69 (0.41)	12.22 (0.36)	1.01 (0.06)	0.70 (0.05)	0.26 (0.04)	9.29 (0.27)
	BB	13.45 (0.45)	11.91 (0.40)	1.13 (0.06)	0.69 (0.06)	0.37 (0.04)	9.32 (0.29)
	P-value	0.586	0.504	0.693	0.767	0.191	0.782

		PRRS					
SNP	Genotypes	TNB	NBA	NBD	NSB	NBM	NW
Duroc							
ASGA0031860	AA	7.91 (0.85)	5.27 (0.86)	1.62^{B} (0.19)	0.41 (0.15)	1.19 (0.18)	2.97 (0.83)
	AB	8.86 (0.43)	5.91 (0.43)	1.75^{B} (0.10)	0.70 (0.07)	0.93 (0.09)	3.81 (0.44)
	BB	8.90 (0.35)	5.43 (0.36)	2.26^{A} (0.08)	0.80 (0.06)	1.24 (0.08)	3.41 (0.37)
	P-value	0.458	0.300	0.058	0.175	0.120	0.317
MARC0089437	AA	8.35 (0.84)	5.36 (0.85)	1.92 (0.19)	0.40 (0.14)	1.42 (0.18)	3.70 (0.83)
	AB	8.19 (0.59)	5.36 (0.59)	1.62 (0.14)	0.69 (0.10)	0.83 (0.13)	3.52 (0.59)
	BB	9.12 (0.81)	5.89 (0.82)	2.07 (0.18)	0.84 (0.14)	1.14 (0.18)	2.97 (0.81)
	P-value	0.505	0.805	0.625	0.471	0.312	0.778
ASGA0032063	AA	8.34 (0.38)	5.44 (0.38)	1.74 (0.09)	0.62 (0.07)	1.09 (0.08)	3.61 (0.40)
	AB	8.77 (0.60)	5.63 (0.61)	2.00 (0.13)	0.64 (0.10)	1.14 (0.13)	3.18 (0.60)
	P-value	0.389	0.704	0.418	0.851	0.829	0.377
MARC0058875	AA	8.71 (0.77)	5.70 (0.77)	1.72 (0.17)	0.40 (0.13)	1.20 (0.16)	3.75 (0.77)
	AB	9.09 (0.62)	5.92 (0.63)	2.18 (0.14)	0.53 (0.11)	1.56 (0.14)	3.47 (0.62)
	BB	7.87 (0.85)	5.00 (0.86)	1.72 (0.19)	1.02 (0.15)	0.69 (0.19)	2.96 (0.84)
	P-value	0.425	0.638	0.558	0.239	0.131	0.825
ASGA0032151	AA	9.36 (0.72)	6.26 (0.73)	1.73 (0.16)	0.51 (0.12)	1.13 (0.15)	3.74 (0.71)
	AB	8.43 (0.50)	5.50 (0.51)	1.76 (0.11)	0.60 (0.09)	1.07 (0.11)	3.18 (0.52)
	BB	7.88 (0.51)	4.85 (0.51)	2.12 (0.12)	0.79 (0.09)	1.15 (0.11)	3.27 (0.52)
	P-value	0.209	0.232	0.567	0.387	0.924	0.675
Landrace							

ASGA0031860	AA	13.54 (0.77)	7.69 (0.89)	3.86 (0.16)	1.07 (0.12)	2.64 (0.17)	4.68 (0.72)
	AB	13.18 (0.49)	7.79 (0.56)	3.68 (0.10)	1.19 (0.08)	2.09 (0.11)	5.06 (0.46)
	BB	13.31 (0.47)	7.22 (0.54)	4.01 (0.10)	1.16 (0.08)	2.31 (0.10)	4.98 (0.45)
	P-value	0.853	0.622	0.793	0.860	0.457	0.834
MARC0089437	AB	13.69 (0.75)	7.78 (0.86)	3.74 (0.16)	1.18 (0.12)	2.20 (0.16)	5.16 (0.70)
	BB	13.00 (0.33)	7.35 (0.38)	3.96 (0.07)	1.10 (0.05)	2.48 (0.07)	4.65 (0.33)
	P-value	0.370	0.625	0.777	0.759	0.624	0.465
ASGA0032063	AA	14.30 (0.94)	8.09 (1.09)	4.74 (0.20)	1.18 (0.15)	2.86 (0.21)	4.88 (0.87)
	AB	12.98 (0.56)	7.26 (0.63)	3.73 (0.11)	1.16 (0.09)	2.41 (0.12)	4.86 (0.53)
	BB	12.76 (0.71)	7.35 (0.82)	3.20 (0.15)	1.09 (0.11)	1.82 (0.15)	4.98 (0.67)
	P-value	0.465	0.790	0.523	0.959	0.410	0.979
MARC0058875	AA	12.62 (0.63)	7.07 (0.73)	3.79 (0.13)	1.22 (0.10)	2.17 (0.14)	4.76 (0.60)
	AB	13.59 (0.52)	7.60 (0.60)	4.03 (0.11)	1.07 (0.08)	2.48 (0.11)	4.99 (0.49)
	BB	13.83 (0.73)	8.04 (0.85)	3.72 (0.15)	1.14 (0.12)	2.37 (0.16)	4.97 (0.69)
	P-value	0.402	0.700	0.838	0.793	0.816	0.943
ASGA0032151	AA	13.02 (0.63)	7.90 (0.73)	3.55 (0.13)	1.12 (0.10)	2.23 (0.14)	4.79 (0.59)
	AB	13.40 (0.53)	7.72 (0.61)	3.82 (0.11)	1.11 (0.08)	2.26 (0.12)	4.97 (0.51)
	BB	13.62 (0.62)	7.08 (0.72)	4.19 (0.13)	1.20 (0.10)	2.53 (0.14)	4.95 (0.59)
	P-value	0.736	0.691	0.766	0.928	0.866	0.944

		Post-PRRS					
SNP	Genotypes	TNB	NBA	NBD	NSB	NBM	NW
Duroc							
ASGA0031860	AA	9.36 (0.64)	8.26 (0.59)	0.73 (0.11)	0.59 (0.09)	0.16 (0.07)	7.87^{A} (0.60)
	AB	8.91 (0.30)	7.88 (0.28)	0.72 (0.05)	0.49 (0.04)	0.20 (0.03)	6.89^{B} (0.31)
	BB	8.94 (0.23)	7.89 (0.22)	0.68 (0.04)	0.44 (0.03)	0.23 (0.02)	6.67^{B} (0.25)
	P-value	0.741	0.777	0.822	0.378	0.599	0.090
MARC0089437	AA	10.03^{a} (0.62)	8.43^{A} (0.57)	1.02 (0.10)	0.58 (0.09)	0.44^{a} (0.07)	7.80^{A} (0.58)
	AB	9.32^{a} (0.43)	8.43^{A} (0.40)	0.60 (0.07)	0.46 (0.06)	0.12^{b} (0.05)	7.46^{A} (0.42)
	BB	7.85^{b} (0.57)	7.17^{B} (0.51)	0.55 (0.09)	0.48 (0.08)	0.05^{b} (0.06)	6.17^{B} (0.53)
	P-value	0.041	0.068	0.126	0.675	0.004	0.063
ASGA0032063	AA	8.77 (0.26)	7.78 (0.24)	0.68 (0.04)	0.51 (0.04)	0.16 (0.03)	6.88 (0.27)
	AB	9.36 (0.44)	8.23 (0.41)	0.74 (0.07)	0.49 (0.06)	0.23 (0.05)	7.40 (0.43)
	P-value	0.109	0.179	0.585	0.783	0.115	0.124

MARC0058875	AA	10.29^{a} (0.62)	8.82 (0.56)	0.89 (0.10)	0.56 (0.08)	0.33^{a} (0.07)	8.14^{A} (0.57)
	AB	8.89^{ab} (0.41)	7.81 (0.38)	0.72 (0.07)	0.46 (0.06)	0.26^{a} (0.04)	7.01^{AB} (0.40)
	BB	8.02^{b} (0.57)	7.40 (0.52)	0.54 (0.09)	0.49 (0.08)	0.02^{b} (0.06)	6.28^{B} (0.53)
	P-value	0.037	0.149	0.452	0.720	0.013	0.069
ASGA0032151	AA	8.92 (0.53)	7.95 (0.49)	0.69 (0.09)	0.49 (0.07)	0.19 (0.06)	7.22 (0.50)
	AB	9.14 (0.36)	7.98 (0.34)	0.76 (0.06)	0.55 (0.05)	0.18 (0.04)	7.09 (0.36)
	BB	9.15 (0.35)	8.10 (0.32)	0.69 (0.06)	0.47 (0.05)	0.22 (0.04)	7.12 (0.35)
	P-value	0.904	0.934	0.713	0.423	0.623	0.950
Landrace							
ASGA0031860	AA	14.61 (0.53)	13.16 (0.49)	0.97 (0.08)	0.53 (0.07)	0.39 (0.06)	10.48^{a} (0.45)
	AB	14.02 (0.35)	12.71 (0.33)	0.84 (0.05)	0.55 (0.05)	0.26 (0.04)	10.14^{a} (0.32)
	BB	13.58 (0.37)	12.35 (0.34)	0.84 (0.06)	0.49 (0.05)	0.32 (0.04)	9.45^{b} (0.33)
	P-value	0.221	0.320	0.676	0.657	0.133	0.050
MARC0089437	AB	14.54^{A} (0.53)	13.12 (0.49)	0.96 (0.08)	0.54 (0.07)	0.35 (0.06)	10.36 (0.46)
	BB	13.60^{B} (0.24)	12.35 (0.23)	0.82 (0.04)	0.50 (0.03)	0.30 (0.03)	9.69 (0.23)
	P-value	0.081	0.117	0.380	0.668	0.487	0.138
ASGA0032063	AA	14.13 (0.73)	13.14 (0.67)	0.65 (0.12)	0.34 (0.11)	0.29 (0.08)	10.21 (0.62)
	AB	14.06 (0.41)	12.53 (0.38)	0.98 (0.06)	0.60 (0.06)	0.32 (0.04)	9.78 (0.37)
	BB	14.03 (0.47)	12.55 (0.43)	1.05 (0.07)	0.63 (0.07)	0.36 (0.05)	10.09 (0.41)
	P-value	0.995	0.714	0.311	0.254	0.865	0.626
MARC0058875	AA	13.78 (0.47)	12.46 (0.44)	0.90 (0.07)	0.52 (0.07)	0.35 (0.05)	9.86 (0.41)
	AB	14.28 (0.37)	13.03 (0.35)	0.85 (0.06)	0.51 (0.06)	0.31 (0.04)	10.33 (0.33)
	BB	14.15 (0.54)	12.73 (0.49)	0.94 (0.08)	0.53 (0.08)	0.32 (0.06)	9.88 (0.46)
	P-value	0.626	0.398	0.840	0.974	0.883	0.269
ASGA0032151	AA	14.39 (0.47)	13.09 (0.44)	0.86 (0.07)	0.49^{AB} (0.07)	0.32 (0.05)	10.67^{A} (0.41)
	AB	14.07 (0.38)	12.82 (0.35)	0.85 (0.06)	0.43^{B} (0.06)	0.40 (0.04)	9.88^{B} (0.34)
	BB	13.74 (0.49)	12.30 (0.45)	0.94 (0.08)	0.65^{A} (0.07)	0.26 (0.05)	9.53^{B} (0.42)
	P-value	0.623	0.448	0.852	0.089	0.129	0.057

[1]Results for each genotype expressed as number of piglets (standard errors within parenthesis);

[2]SNPs are located on *Sus scrofa* chromosome 7 according to the *Sscrofa11.1* as follow: (GCA_000003025.6) assembly: ASGA0031860/rs80959936 (7:22,075,114), MARC0089437/rs80900036 (7:24,217,931), ASGA0032063/rs80940999 (7:24,247,099), MARC0058875/rs80986722 (7:24,865,378), and ASGA0032151/rs80947467 (7:25,967,157). SNP markers MARC0089437 and

ASGA0032063 were associated with S/P ratio in this study, in Duroc and Landrace populations, respectively. The other markers were associated with S/P ratio in Landrace sows in Serão et al. (2014);
[3]TNB, total number of piglets born; NBA, number of piglets born alive; NBD, number of piglets born dead; NSB, number of stillborn piglets; NBM, number of mummified piglets; NW, number of piglets weaned. Results for NBD, NSB, and NBM were back-transformed from ln(phenotype+1);
[4]PRRS, Porcine Reproductive and Respiratory Syndrome (PRRS);
[a-b] Expected values within row lacking the same superscript indicate differences at *P*-value < 0.05;
[A-B] Expected values within row lacking the same superscript indicate differences at *P*-value < 0.10.

Chapter IV. General discussion

General discussion

The main takeaways from this thesis are that reproductive traits are lowly heritable during a PRRS outbreak with few QTL identified in Duroc and Landrace sows. Thus, there is a need for an indicator trait that is heritable and favorably genetically correlated with traits of interest, such as total antibody response to PRRSV. Our study validate the previous suggestion by Serão et al. (2014) for the use of S/P ratio in sows during a PRRS outbreak as this indicator trait, since S/P ratio showed to have a sizable heritability and to be favorably genetically correlated with NBA in PRRSV-infected Landrace sows. Also, our results indicate that genomic selection for S/P ratio has high accuracy within breed. In addition, we have provided novel findings for S/P ratio and reproductive traits for Duroc, which has not yet been reported in the literature.

This research, however, has some limitations that are inherent of this kind of study. Waiting for PRRS outbreaks to occur to collect data is a limitation when working with purebred herds. It is much easier and cheaper to collect data in commercial herds that are more frequently exposed to the PRRS virus. PRRS is a costly disease, which makes large-scale studies difficult to implement, especially in purebred herds. Thus, there may be some insufficient sample size for statistical analyses and data collection restrains when dealing with this kind of research.

This study though is also subject to some limitations that could potentially be addressed in future research. Total antibody response to PRRSV was analyzed because of the commercial ELISA test available. However, the use of total antibody response does not represent, biologically, the neutralization of the virus. A test that analyzes only neutralizing antibodies would be desirable. These antibodies would effectively neutralize

antigens and infectious agents, contributing to long-lived protection against viral infections. Genetic and genomic studies with this characteristic of extreme biological importance have not yet been carried out. Thus, the identification of genetic and genomic components associated with neutralizing antibodies would bring new information about the animal's genetic response to PRRSV.

Some studies have reported new and more accurate methods to quantify PRRSV neutralizing antibodies as well as phenotypic correlations between total and neutralizing antibodies (Brown et al., 2009; Ellingson, 2013; Popescu et al., 2017). However, genetic correlations between these two measures of the immune system against PRRSV have not been reported in the literature, yet. The identification of a favorable genetic correlation between total and neutralizing antibody response would support the use of S/P ratio as an indicator trait for improved reproductive performance in PRRSV-infected sows. Additionally, it is also necessary to evaluate the genetic, genomic, and phenotypic relationships between these two traits with the reproductive performance of healthy and diseased sows.

Novel and efficient strategies that would allow the genetic selection for improved reproductive performance in PRRSV-infected sows are needed. Since direct selection for farrowing traits is limited, we are constantly searching for potential proxies that could result in increased response to selection. However, a point to consider is the measurement of these proxies. It is far easier and cheaper to measure litter size traits than proxies such as uterine capacity, microbiome, etc. Therefore, we need to find heritable traits that are more predictive of farrowing traits than themselves, while cheap, easy to measure, and collected in younger animals. The identification of novel traits that

are heritable and have an additive genetic component that can predict performance is extremely relevant to the swine industry since genetic selection for improved reproductive performance in PRRSV-infected sows is still not a reality, mostly due to the fact that selection occurs in the nucleus, where a PRRSV infection is not expected.

There is also a need for further research to validate the use of S/P ratio after a modified live virus (MLV) vaccination to decide whether animals can be selected based on their response to vaccines. Sanglard et al. (2020b) has shown that this would be feasible. Nonetheless, additional research is needed to evaluate the genetic correlation between the antibody response against PRRSV of vaccinated and naturally infected animals. This will indicate, for the first time, the real possibility of selecting animals that have better reproductive performance after vaccination, without the need to wait for a PRRSV infection. It is also worth mentioning that time plays a significant role in this kind of analysis. Antibody response is a trait that is time sensitive. Time constraints may negatively affect any study. Therefore, researchers must be aware of this when comparing results. Advances in technology are also expected. Genomic selection, gene editing, cloning, among other technologies will continue to advance. These technologies will improve not only the reproductive performance of PRRSV-infected sows, but also increase productivity, welfare, and food security.

In conclusion, this study was able to characterize the genetic basis of reproductive performance and antibody response to PRRSV in pigs during a PRRS outbreak despite the limitations listed. The rationale behind this study can be applied to other species and diseases as well. This research field holds much promise for the future.

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Appendices – Recent publications

Appendix A – Abstracts published at scientific meetings as first author

1. **Hickmann, F**; Braccini Neto, J; Kramer, L; Sanglard, L. M. P; Gray, K. A; Huang, Y; Dekkers, J. C. M; Serão, N. V. L. Genomic basis of reproductive performance in PRRSV-infected sows. ASAS Midwest meeting, Omaha, 2020 (submitted).

2. **Hickmann, F**; Braccini Neto, J; Kramer, L; Sanglard, L. M. P; Gray, K. A; Huang, Y; Dekkers, J. C. M; Serão, N. V. L. Accuracies of genomic prediction for reproductive traits in PRRSV-infected sows. ASAS Midwest meeting, Omaha, 2020 (submitted).

3. **Hickmann, F**; Braccini Neto, J; Kramer, L; Sanglard, L. M. P; Gray, K. A; Huang, Y; Dekkers, J. C. M; Serão, N. V. L. Host-genomic scan for total antibody response during a PRRSV outbreak in purebred sows. 2019 North American PRRS Symposium, Chicago, 2019.

4. **Hickmann, F**; Braccini Neto, J; Kramer, L; Sanglard, L. M. P; Gray, K. A; Huang, Y; Dekkers, J. C. M; Serão, N. V. L. Accuracy of genomic prediction for total antibody response in purebred sows during a PRRS outbreak. 2019 North American PRRS Symposium, Chicago, 2019.

5. **Hickmann, F**; Braccini Neto, J; Linhares, D. C. L; Gray, K. A; Dekkers, J. C. M; Niederwerder, M. C; Serão, N. V. L. Genomic analysis of total antibody response to Porcine Reproductive and Respiratory Syndrome (PRRS) Modified Live Virus (MLV) vaccination in commercial replacement gilts. 2018 North American PRRS Symposium, Chicago, 2018.

Felipe Mathias Weber Hickmann

VITA

Universidade Federal do Rio Grande do Sul (UFRGS), *Porto Alegre, RS, Brazil*
Master of Science, May 2020
Major: Animal Breeding and Genetics
Mentor: Dr. José Braccini Neto
Thesis: Genetic basis of reproductive performance and antibody response in pigs during a porcine reproductive and respiratory syndrome (PRRS) outbreak

Bachelor of Science, February 2018

Iowa State University (ISU), *Ames, IA, United States*
Visiting Scholar, March 2019 - January 2020
Research field: Animal Breeding and Genetics
Mentor: Dr. Nick Serão

University of Technology Sydney (UTS), *Sydney, NSW, Australia*
Exchange student, September 2015 - November 2016
Sustainable agricultural production

Felipe Mathias Weber Hickmann, son of Tamaro Luiz Hickmann and Marlene Maria Weber Hickmann, was born on February 10th, 1993, in Venâncio Aires-RS. Born and raised in a pig farm, he wanted to study agriculture at college. He started his academic journey at the Universidade Federal do Rio Grande do Sul (UFRGS). Meanwhile, he got a scholarship to study at the University of Technology Sydney, Australia (2015-2016). He joined different research groups, such as Animal Science, Agribusiness and Rural Development research programs as an undergraduate research assistant. After graduation, he joined the Animal Science Research Program at UFRGS as a master's student, under the guidance of Dr. José Braccini Neto and Dr. Nick Serão as his co-adviser. He did part of his master's degree research at Iowa State University, United States. His master's thesis defense took place in May 2020.