Genetic analysis of reproductive traits and antibody response in a PRRS outbreak herd
N. V. L. Serão, O. Matika, R. A. Kemp, J. C. S. Harding, S. C. Bishop, G. S. Plastow and J. C. M. Dekkers

*J ANIM SCI* 2014, 92:2905-2921.
doi: 10.2527/jas.2014-7821 originally published online May 30, 2014

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.journalofanimalscience.org/content/92/7/2905
Porcine reproductive and respiratory syndrome (PRRS) is the most economically significant disease impacting pig production in North America, Europe, and Asia (Rowland et al., 2012). The effects of PRRS on pigs occur at all stages of production, causing respiratory and reproductive losses, such as pneumonia and...
increased rates of abortions, stillbirth, and mummies (Lunney et al., 2011). It has been estimated that productivity losses due to PRRS costs U.S. herds $664 million, with losses in breeding herds accounting for over $300 million of this total and an average cost of $3.08 per pig marketed (Holtkamp et al., 2013).

Although vaccination is considered to be one of the main strategies to control the PRRS virus (PRRSV; Karniychuk and Nauwynck, 2013), to date, this method has shown limited success under field conditions (Geldhof et al., 2013). Recent reports suggest that the exploitation of host genetics using SNP data may be another strategy to use against the PRRSV. Boddicker et al. (2012) found a major QTL on SSC 4 associated with PRRSV response, measured as the area under the curve of log viremia in blood up to 21 dpi, and weight gain (42 dpi) in growing pigs. The effects of the SNP marker that accounted for most of the genetic variation for these traits, WUR10000125 SNP, has been validated in independent data sets (Boddicker et al., 2014a,b).

Fewer data are available from genetic studies on the impacts of PRRS on reproductive traits; although indications of significant SNP are given by Lewis et al. (2009b) and Orrett et al. (2013), neither study is precise on the location of the SNP. Therefore, information about QTL controlling responses to PRRSV infections in reproductive sows remains a gap in our knowledge. The objective of this work was to study the genetic basis of antibody response and reproductive traits in a commercial sow herd before and after a spontaneous PRRS outbreak.

MATERIALS AND METHODS

Animals used in this study were cared for according to Canadian Council on Animal Care (1993) guidelines under industry standard conditions.

Source of Data

The data set available for analysis was obtained from a commercial multiplication herd that experienced a PRRS outbreak during the winter of 2011/2012. Available data for each litter included dam identification, dam parity, sire of litter, breed of sire of litter, farrowing location and date, weaning date, and the numbers of piglets born alive, stillborn, mummified, alive at 24 h, weaned, and fostered. The farrowing data included a total of 5,227 litters from 1,967 purebred Landrace sows from a commercial maternal line from January of 2010 through March of 2012. A 3-generation pedigree with 2,995 individuals was available for the analysis.

Following the appearance of typical clinical signs of PRRS, such as changes in the number of piglets born alive and mummified/stillbirths, premature farrowing, and delayed return to service, all sows on the farm were bled on January 5, 2012, and tested for anti-PRRSV antibody (Ab) by ELISA (IDEXX PRRS X3, IDEXX Laboratories Inc., Westbrook, Maine), which quantifies the antibody response in the serum of PRRS-infected pigs to the PRRSV nucleocapsid protein (Langenhorst et al., 2012). The ELISA results confirmed the outbreak and allowed semiquantification of PRRSV IgG levels, reported as sample-to-positive ratio (S/P ratio). In addition to S/P ratio, the phenotypic traits included in the data set were number piglets born alive (NBA), number of piglets alive at 24 h (NA24), number of stillborn piglets (NSB), number of piglets born mummified (NBM), number of piglets born dead (NBD; calculated as the sum of NBM and NSB), percentage of piglets born dead (PBD; calculated as NBD/[NBA + NBD]), number of piglets weaned (NW), and mortality from birth to weaning (MW; calculated as the difference between NW and the sum of NBA and number fostered). Before statistical analysis, NSB, NBA, NBM, and NBD were transformed as ln(trait + 1) because of the heavy right skewness observed in the data.

Partition of the Data into Pre-PRRS and PRRS Phases

Initial exploratory analyses of the data aimed to describe the dynamics of the epidemic and hence determine a suitable cutoff date for separating the pre-PRRS phase from the PRRS phase. The 30-d rolling average method outlined by Lewis et al. (2009a) was used for this purpose. This method smoothed the noise inherent in the data and allowed different traits to be used to define when the outbreak occurred. In this study, NBA, NA24, NSB, and NBM were used as separate indicator traits for this purpose.

Genetic Parameters

Genetic parameters for the measured traits were estimated separately for each PRRS phase. Since not all sows were included in both phases and different sources of variation influenced the data in the 2 phases, different models were used in these analyses. Sows in the pre-PRRS phase had from 1 to 5 records (farrowings), whereas the PRRS phase comprised only 1 record per sow. For all analyses, the fixed effects of parity and breed of sire (Yorkshire or Landrace) were included, along with a random animal genetic effect. In addition, the fixed effect of contemporary group (CG; combination of breeding month and farrowing year) was included, as well as a random permanent environment effect for dam for the pre-PRRS phase analyses. For the PRRS phase analyses, fitted covariates were the number fostered (for NW and MW) and the 30-d rolling average of the trait being analyzed. The latter was used to better account for the
epidemic severity and dynamics during the PRRS disease phase compared to including CG. For NBD, the 30-d rolling averages of NSB and NBM were used as covariates. Before the final analyses of the PRRS phase data, we compared models with the 30-d rolling average vs. CG. In general, the P-values for the 30-d rolling average covariate were much lower than P-values for the effect of CG. In addition, estimates of genetic parameters derived from the model with CG had generally larger SE than those derived from the model with the 30-d rolling average as a covariate. Thus, we decided to fit the covariate 30-d rolling average instead of CG in the final model for the PRRS phase. All genetic parameter analyses were performed using ASReml 3.0 (Gilmour et al., 2009).

Genotype Data

All sows in the PRRS phase were sampled for DNA and then genotyped using the Illumina PorcineSNP60 BeadChip (Illumina Inc., San Diego, CA). Of the 641 sows present in the herd, 600 individuals were genotyped using version 1 of the platform (GeneSeek, Lincoln, NE), and 41 were genotyped using version 2 (University of Alberta, Edmonton, AB, Canada). One individual was genotyped using both versions of the platform, and these results were used to assess genotyping quality and consistency between the 2 versions. Less than 0.03% (18 SNP) of the genotypes were inconsistent between the 2 platforms. Since version 2 of the SNP platform was created using the version 1 specification (Illumina, 2012) and only 0.03% of the SNP genotypes were inconsistent for the individual, the data sets from the 2 versions were combined. After removing SNP not present in 1 of the platforms, 61,177 SNP remained in the initial data set and were used for quality control, which was performed in 2 steps. First, genotypes with GenCall scores lower than 0.2 were set as missing (Illumina, 2005; Serão et al., 2013). In the second step, SNP were excluded from the data set when missing in more than 5% of individuals or when the frequency of the minor allele was less than 1%. After edits, 46,163 SNP were included in the data set, with a total genotyping call rate of 99.61%.

Effect of the WUR Genotype

The SNP WUR10000125 (WUR), which has been associated with response to PRRSV in growing pigs (Boddicker et al., 2012), was extracted from the genotype data and used to evaluate the association of its genotype with traits in both PRRS phases. Since only 1 animal had the BB genotype for this SNP and previous studies indicate that the favorable B allele has a complete dominance effect over the unfavorable allele A (Boddicker et al., 2012, 2014b), this genotype was switched to AB. The WUR SNP genotype was then fitted in the model as a fixed effect with 2 levels (AB and AA). The other effects in the model were the same as used for estimation of genetic parameters.

Genome-wide Association Study

Bayesian genomic selection methods that fit the effects of all SNP simultaneously as random effects were used to associate SNP with phenotypes. Bayesian method Cπ (Habier et al., 2011) was used to estimate the proportion of SNP with zero effects (π) and then Bayes B (Meuwissen et al., 2001) was used for the association analyses. Since these methods do not allow for missing genotypes, these were replaced with the mean genotype for that SNP (Boddicker et al., 2012). The value of π used in the Bayes B analysis was chosen on the basis of sample size and the estimate obtained from Bayes Cπ. Initially, π was set to 1 minus the proportion of SNP that could be simultaneously fitted in the model according to the number of degrees of freedom available after accounting for all effects in the model (including the mean). This initial value of π was used as the starting value in the Bayes Cπ analysis, and if the resulting estimate of π was greater than the initial π (i.e., fewer SNP would be simultaneously fitted in the model), the estimated π was used in the Bayes B analysis. However, when the estimated π would result in more SNP included in the model than the number of degrees of freedom available, the initial π was used. All SNP association analyses were performed using GenSel version 4.4 (Fernando and Garrick, 2009). GenSel provides estimates of the genetic variance that are explained by each nonoverlapping 1-Mb window across the genome (Wolc et al., 2012). Windows that explained more than 0.5% of the total genetic variance explained by the markers were further investigated.

Pre-PRRS Phase. To account for repeated records during the pre-PRRS phase, each observation was pre-adjusted for the fixed effects of breed of sire, parity, contemporary group, and number fostered (for NW and MW) and then averaged across the number of observations on the individual. The SNP association analysis was then performed using the following model:

\[
\bar{y}_i = \mu + \sum_{m} z_i \alpha_m + \delta_i + \epsilon_i, \quad [1]
\]

where is the vector of the averaged preadjusted phenotypic values of \( n \) observations, \( \mu \) is the general mean, \( z_i \) is the vector of genotype covariates for SNP \( i \), \( a_i \) is the allele substitution effect for SNP \( i \), \( \delta_i \) is an indicator for whether SNP \( i \) was included (\( \delta_i = 1 \)), with prior probability of \( 1 - \pi \) or excluded (\( \delta_i = 0 \), with prior probability of \( \pi \)) in the model for a given iteration of the Markov chain Monte Carlo (MCMC), and \( \epsilon_i \) is the vector of residuals associat-
Serão et al.

The 30-d rolling average for NSB, NBM, NBA, and NA24 per litter across time are shown in Fig. 1. The sudden drop in NBA and NA24 and the increase in NSB and NBM indicated that the PRRS outbreak occurred at the end of November 2011. Following inspection of the raw data and the rolling averages, November 20, 2011, was chosen as the cutoff date to define pre-PRRS and PRRS outbreak data sets. In total, 4,702 litters and 1,815 sows fell into the pre-PRRS phase data set, and 525 litters and 641 sows fell into the PRRS phase data set.

**Genetic Parameters**

Estimates of the heritability of traits by phase are presented in Table 1. The reproductive traits generally showed low heritability estimates in both phases. During the pre-PRRS phase, the highest and lowest heritability estimates were for NSB and NBM, with estimates of 0.12 ± 0.03 and 0.01 ± 0.01, respectively. NBM also had the lowest repeatability estimate (0.05 ± 0.02),
whereas NBA had the highest estimate of repeatability (0.18 ± 0.02). With the exception of NSB, NBD, and PBD, repeatability estimates were at least 2-fold greater than their corresponding estimates of heritability for all reproductive traits. For the reproductive traits, the lowest and highest heritability estimates in the PRRS phase were for MW and NBD, with 0.01 ± 0.01 and 0.12 ± 0.08, respectively. As expected, because of the smaller data set, all heritability estimates had greater SE in the PRRS phase than in the pre-PRRS phase. The only trait with a high heritability estimate in this data set was S/P ratio, with an estimate of 0.45 ± 0.13.

Estimates of genetic and phenotypic correlations between S/P ratio and the reproductive traits during the PRRS phase are shown in Table 2. Although S/P ratio had low phenotypic correlations with the reproductive traits, most genetic correlation estimates were high. Traits NBA and NA24 had the same positive genetic correlation estimate with S/P ratio (0.73 ± 0.23), whereas the other reproductive traits had strong negative genetic correlation estimates, ranging from -0.58 ± 0.29 (NW) to -0.72 ± 0.28 (NSB), with the exception of NBD, which had an estimate of -0.27 ± 0.44. Analyses were also conducted to estimate the genetic correlation between PRRS phases for the same trait, but this led to poor convergence for some traits and estimates greater than 1 for others, so these estimates are not reported here. The complexity of the models, which differed between phases, and the low number of sows in both phases (~400) may have contributed to these problems.

Table 1. Estimates and SE of heritability ($h^2$) for traits during the pre-PRRS and the PRRS phases and of repeatability ($t$) during the pre-PRRS phase

| Trait | Pre-PRRS phase | PRRS phase |
|-------|----------------|------------|
|       | $t$ | SE | $h^2$ | SE | $h^2$ | SE |
| NBA   | 0.18 | 0.02 | 0.08 | 0.03 | 0.09 | 0.07 |
| NA24  | 0.15 | 0.02 | 0.05 | 0.02 | 0.10 | 0.07 |
| NSB   | 0.14 | 0.02 | 0.12 | 0.03 | 0.06 | 0.07 |
| NBM   | 0.05 | 0.02 | 0.01 | 0.01 | 0.08 | 0.07 |
| NBD   | 0.12 | 0.02 | 0.11 | 0.02 | 0.12 | 0.08 |
| PBD   | 0.12 | 0.02 | 0.09 | 0.02 | 0.07 | 0.06 |
| NW    | 0.13 | 0.02 | 0.03 | 0.02 | 0.09 | 0.07 |
| MW    | 0.08 | 0.02 | 0.02 | 0.01 | 0.01 | 0.01 |
| S/P ratio | — | — | — | — | 0.45 | 0.13 |

1 For the pre-PRRS and PRRS phases, the numbers of litters used were 4,702 and 525, respectively, from 1,815 and 641 sows, respectively. PRRS, porcine reproductive and respiratory syndrome.

2 NBA, number of piglets born alive; NA24, number of piglets alive at 24 h; NSB, number of stillborn piglets; NBM, number of piglets born mummified; NBD, number of piglets born dead; PBD, percentage of piglets born dead; NW, number of piglets weaned; MW, mortality from birth through weaning; S/P ratio, sample-to-positive ratio.
Table 2. Estimates and SE of the phenotypic ($r_p$) and genetic ($r_g$) correlations between sample-to-positive (S/P) ratio and the reproductive traits during the porcine reproductive and respiratory syndrome (PRRS) phase

| Trait | $r_p$ | SE for $r_p$ | $r_g$ | SE for $r_g$ |
|-------|-------|--------------|-------|--------------|
| NBA   | 0.06  | 0.05         | 0.73  | 0.24         |
| NA24  | 0.10  | 0.05         | 0.73  | 0.23         |
| NSB   | -0.07 | 0.05         | -0.72 | 0.28         |
| NBM   | -0.04 | 0.05         | -0.66 | 0.28         |
| NBD   | 0.01  | 0.05         | -0.27 | 0.44         |
| PBD   | -0.04 | 0.05         | -0.70 | 0.27         |
| NW    | -0.04 | 0.05         | -0.58 | 0.29         |
| MW    | —     | —            | —     | —            |

1 NBA, number of piglets born alive; NA24, number of piglets alive at 24 h; NSB, number of stillborn piglets; NBM, number of piglets born mumified; NBD, number of piglets born dead; PBD, percentage of piglets born dead; NW, number of piglets weaned; MW, mortality from birth through weaning.

Associations with the WUR Genotype

The association between genotype at the WUR SNP and the traits analyzed is presented in Table 3. The WUR genotype was associated with NBA ($P$-value = 0.056) and NW ($P$-value = 0.039) during the pre-PRRS phase, with AB animals showing favorable performance for NBA and AA animals showing greater performance for NW. In contrast, the WUR genotype was not associated with any trait analyzed in the PRRS phase, although trends for the effect of this genotype on NBA and NA24 were in the expected direction.

Genomic Regions Associated with Traits

The genomic regions associated (TGVM > 0.5%) with the traits analyzed are presented in Table 4. For the pre-PRRS phase, 2 regions were associated with NSB and 1 with PBD. For NSB, the 1-Mb regions on SSC7 and SSC12 explained 1.0% and 0.6% of the TGVM, respectively. For PBD, 1 region with 51 SNP within positions 98 and 100 Mb on SSC12 accounted for 3.0% of the TGVM. These 3 associated windows in the pre-PRRS phase had moderate PPI, ranging from 0.33 to 0.58.

In the PRRS phase, genomic regions were found to be associated with NSB, NBD, and S/P ratio. A 1-Mb region on SSC1 was associated with NBD, explaining 0.8% of the TGVM (PPI = 0.29). This region was expanded to a 4-Mb window that was associated with NSB. This region on SSC1, encompassing positions 32 through 36 Mb, explained 11.0% of the TGVM and had high PPI (0.76). Six genomic regions were identified that were associated with S/P ratio, accounting for a total of 48.8% of the TGVM (Fig. 2). Three of these 6 regions were located on SSC7, at 24 through 31 Mb, at 40 Mb, and at 128 through 130 Mb, explaining 25.2%, 3.3%, and 15.7% of the TGVM, respectively. The 2 windows with the highest TGVM also had PPI = 1. The other 3 regions associated with S/P ratio were located on SS2, at position 2 Mb, and 2 were located on SSC14, at positions 39 Mb and 147 through 148 Mb, explaining 0.8% (PPI = 0.39), 0.7% (PPI = 0.15), and 3.1% (PPI = 0.82) of the TGVM, respectively.

The genomic regions found to be associated in this study (Table 4) were explored to identify SNP that could potentially explain a greater part of the TGVM from these SNP windows. The SNP that had high PPI in the associated windows (results not shown) were fitted separately from their associated SNP windows in the GWAS models (Eq. [1] and [3]), and their contribution to the TGVM was assessed. The results from these additional analyses are presented in Table 5 for traits PBD (pre-PRRS phase) and NSB (PRRS phase). The 2-Mb SNP window previously associated with pre-PRRS PBD had a drop in the TGVM from 3.0% to 0.2% when 3 of the 51 SNP located in this window were removed from the SNP window. The 3 selected SNP (Table 5) were located within 274 kb and showed high LD. Marker ALGA0043701 explained 0.5% (PPI = 0.06) of the TGVM and was in high LD ($r^2 = 0.77$) with the other 2 selected SNP, M1GA0010603 (PPI = 0.11) and ASGA0035348 (PPI = 0.12), which explained 1.0% and 1.2% of the TGVM, respectively, and were in perfect LD with each other ($r^2 = 1$) based on individuals that had genotypes for both SNP (2 individuals had missing genotypes for 1 SNP). In fact, after removing either of the 2 SNP that were in perfect LD, the remaining SNP and ALGA0043701 accounted for the same %TGVM as before, with approxi-

Table 3. Least squares means (SE) of the WUR genotypes for reproductive traits and antibody response during the pre-PRRS phase and the PRRS phase

| Trait  | Pre-PPRS phase | PRRS phase |
|-------|----------------|------------|
|       | AA             | AB         | P-value | AA             | AB         | P-value |
| NBA   | 12.58 (0.98)   | 13.20 (1.03) | 0.056   | 8.89 (1.31)   | 9.89 (1.36) | 0.127   |
| NA24  | 12.46 (1.02)   | 12.90 (1.06) | 0.179   | 7.71 (1.30)   | 8.73 (1.35) | 0.106   |
| NSB   | -0.06 (0.18)   | 0.73 (0.18)  | 0.206   | 1.08 (0.20)   | 0.98 (0.21) | 0.340   |
| NBM   | 0.13 (0.11)    | 0.12 (0.12)  | 0.635   | 0.90 (0.25)   | 0.86 (0.26) | 0.724   |
| NBD   | 0.76 (0.19)    | 0.83 (0.20)  | 0.253   | 1.22 (0.26)   | 1.12 (0.27) | 0.428   |
| PBD   | 0.10 (0.03)    | 0.10 (0.04)  | 0.768   | 0.19 (0.36)   | 0.17 (0.36) | 0.525   |
| NW    | 10.15 (0.49)   | 9.89 (0.50)  | 0.039   | 6.33 (1.14)   | 6.77 (0.17) | 0.436   |
| MW    | 1.65 (0.62)    | 1.91 (0.64)  | 0.105   | 2.93 (0.81)   | 2.51 (0.84) | 0.656   |
| S/P ratio | —             | —           | —       | 1.83 (0.06)   | 1.82 (0.08) | 0.883   |

1 The frequency of the B allele was 0.12 in both pre-PRRS and PRRS phases. PRRS, porcine reproductive and respiratory syndrome.
2 The numbers of genotyped sows used in the pre-PRRS and PRRS phases were 519 and 641, respectively.
3 NBA, number of piglets born alive; NA24, number of piglets alive at 24 h; NSB, number of stillborn piglets; NBM, number of piglets born mumified; NBD, number of piglets born dead; PBD, percentage of piglets born dead; NW, number of piglets weaned; MW, mortality from birth through weaning; S/P ratio, sample-to-positive ratio.
4 Expressed as ln(x + 1).
Table 4. Genomic regions explaining more than 0.5% of the total genetic variance explained by windows (%TGVM) for traits during the pre-PRRS and the PRRS phases

| Trait         | c    | π     | %TGVM | PPI | SSC | Mb | No. of SNP |
|---------------|------|-------|-------|-----|-----|----|------------|
| Pre-PRRS phase |      |       |       |     |     |    |            |
| NSB           | 0.20 | 0.9888| 0.95  | 0.44| 7   | 53 | 27         |
| PBD           | 0.21 | 0.9888| 3.01  | 0.58| 2   | 98 | 99         |
| PRRS phase    |      |       |       |     |     |    |            |
| NSB           | —    | 0.9917| 11.04 | 0.76| 1   | 32 | 35         |
| NBD           | —    | 0.9917| 0.81  | 0.29| 1   | 32 | 31         |
| S/P ratio     | —    | 0.9983| 25.15 | 1   | 7   | 24 | 30         |
|               | —    | 0.9983| 15.73 | 1   | 7   | 128| 129        |
|               | —    | 0.9983| 3.33  | 0.52| 7   | 40 | 26         |
|               | —    | 0.9983| 3.06  | 0.82| 14  | 145| 147        |
|               | —    | 0.9983| 0.83  | 0.39| 2   | 2  | 22         |
|               | —    | 0.9983| 0.67  | 0.15| 14  | 39 | 34         |

1 PRRS, porcine reproductive and respiratory syndrome; NSB, number of stillborn piglets; PBD, proportion born dead; S/P ratio, sample-to-positive ratio; π, proportion of SNP with zero effects in the model; c, percentage of the genetic variance not accounted for by the marker variance; PPI, posterior probability of inclusion of the SNP window.

mately 1.0% and 0.5%, respectively. As shown in Table 5, the PPI of the SNP window after removing these SNP was higher (PPI = 0.46) than for any of the 3 selected SNP, which ranged from 0.06 to 0.12.

For PRRS phase NSB, 5 SNP were fitted separately from their associated SNP window in the model (Eq. [3]), reducing the %TGVM of the 4-Mb SNP window on SSC1 from 11.0% to 2.4% (PPI = 0.67; Table 5). These selected SNP showed high average pairwise LD ($r^2 = 0.81$) and %TGVM ranging from 0.8% (MARC001988) to 3.6% (MARC0034894). Most of the variance was captured by the 3 SNP located within 238 kb on Mb 32 (7.9% of the TGVM), whereas the remaining 2 SNP located over 500 kb downstream jointly accounted for 1.9%. All 5 selected SNP had low PPI, ranging from 0.04 to 0.11. The previous SNP windows associated with pre-PRRS NSB and PRRS phase NBD (Table 4) did not show any SNP in these windows with PPI 1.5-fold greater than the average PPI of the SNP in the associated window, and thus, there were no selected SNP removed from the SNP windows in the GWAS models for these traits.

The drop in %TGVM of the SNP windows associated with S/P ratio after removing the selected SNP is presented in Table 6. A total of 11 SNP were removed from the SNP windows associated with S/P ratio, all from SSC7. Five SNP were removed from the 7-Mb region on SSC7 and resulted in a drop in the %TGVM of the window from 25.2% to 1.4%. This 7-Mb window included the SNP ASGA0032151, which accounted for the highest %TGVM in this study, at 10.9%. In addition, this SNP also had the highest PPI (0.57) among the selected SNP for this window and was in moderate LD ($r^2 = 0.50$) with ASGA0032161, which accounted for 0.8% of the TGVM (PPI = 0.06). The 1-Mb windows located 10 Mb downstream of the previous 1-Mb window had a drop in the %TGVM from 3.3% to 0.1% (PPI = 0.06) and had just 1 selected SNP removed from the SNP window. This SNP, M1GA0025482, had approximately the same %TGVM (3.4%; PPI = 0.55) as the window did before removing this SNP. The other genomic region on SSC7 that was associated with S/P ratio had 5 SNP removed from the SNP window and showed a sizable drop in the %TGVM from 15.7% to 2.1%. These 5 selected SNP were in high average LD ($r^2 = 0.97$), where ASGA0037093 and ALGA0045692 showed complete LD ($r^2 = 1$) and explained the highest %TGVM among these SNP, with 3.7% (PPI = 0.23) and 5.4% (PPI = 0.33), respectively. The 2 SNP windows located on SSC14 did not have any SNP with a high PPI, and thus, none of the SNP were removed from the associated SNP windows.

Analysis of the Selected SNP

Trait associations for the selected SNP (Tables 5 and 6) were further investigated by including them as fixed effects in the same models as used to estimate genetic parameters. Results are shown in Table 7. Of the 3 selected SNP for pre-PRRS PBD (Table 5), only ASGA0035348 was fitted in the model because of the high LD between this and the other 2 selected SNP, and it was significantly associated with PBD (P-value < 0.001), with BB sows showing better performance (0.08 ± 0.03) than AB (0.10 ± 0.03) and AA sows (0.12 ± 0.03). In fact, once this SNP was fitted in the model, ALGA0043701 was not significant, and M1GA0010603 was not estimable since it was in perfect LD with ASGA0035348. For PRRS phase NSB, MARC0034894 was the only SNP fitted in the model and had a significant association (P-value < 0.001). This SNP had the highest %TGVM among the 5 selected SNP (Table 5), and it was in high LD with the others. In addition, once MARC0034894 was fitted as a fixed effect in the model, none of the other SNP were significant. This SNP is located on a predicted locus for the histone H2A variant 3-like gene, with the B allele having a favorable additive effect on NSB, decreasing ln(NSB + 1) from 1.28 ± 0.22 (AA) to 0.80 ± 0.22 (BB).

A total of 7 SNP were simultaneously fitted for S/P ratio (Table 7). Four of the 7 SNP are located in the 7-Mb SNP window on SSC7 that explained 25.1% of the TGVM (Table 4). Of these, MARC0058875 and ASGA0032151 were significantly associated (P-value < 0.001) with S/P ratio, where BB sows had lower antibody response (1.7 ± 0.1 for both SNP) than the other genotypes. Although none of these 4 SNP are located in genic regions, they are located on the swine major histocompatibility complex (MHC), also known as the swine leukocyte antigen (SLA) region. Low LD was observed in this 7-Mb region (Fig. 3A). The
other 3 selected SNP fitted simultaneously in the model showed significant association ($P$-value < 0.001) with S/P ratio (Table 7). Two of the remaining selected SNP were also located on SSC7, with M1GA0025482 being positioned in an intergenic region and ALGA0045692 being in the intronic region of the Repressor element-1 silencing transcription corepressor 1 gene ($RCOR1$). Although ALGA0045692 was fitted in the model, this SNP showed high LD with other SNP in the window (data not shown) and is located in a genomic region displaying high LD (Fig. 3B) and many candidate genes.

DISCUSSION

Definition of the PRRS Outbreak Phases

We used the 30-d rolling average method as proposed by Lewis et al. (2009a) to smooth the underlying noise inherent in PRRS outbreak data to define when the outbreak occurred. Number born mummified and NSB were used as indicators of PRRSV infection in sows at different stages of gestation (Karniychuk and Nauwynck, 2013), whereas NBA and NA24 helped visualize how the non-random drop in these 2 traits occurred with the increase of NBM and NSB due to the PRRS outbreak. From our rolling average results, it can be considered that if pregnant sows were infected with PRRSV on the same day, those closer to parturition (later gestation) will have increased NSB, whereas those in early gestation will have higher NBM (Karniychuk and Nauwynck, 2013).

The difference in the number of sows (641) and litters (525) in the PRRS phase was because not all sows in the herd had farrowing information between the estimated date of the outbreak, November 20, 2011, and March 31, 2012, the last day of data provided by the commercial herd. For the 116 sows without farrowing data, it was unclear whether they aborted after the PRRS outbreak, failed to hold service, or farrowed after March 31, 2012, because of limited information on their pregnancy status. Nevertheless, these 116 sows had S/P ratio data and thus were kept in the data set for analyses for this trait.

Genetic Parameters

The genetic parameter estimates obtained for the pre-PRRS phase in our study are in general agreement with previously published estimates in disease-free herds using Landrace sows. The estimated heritabilities for NBA, NSB, NBD, PBD, NW, and MW were comparable to those in the literature, with reported estimates of 0.03 to 0.15, 0.03 to 0.12, 0.08 to 0.09, 0.04 to 0.08, 0.03 to 0.16, and 0.02 to 0.10, respectively (Robinson and Quinton, 2002; Chen et al., 2003; Holm et al., 2004; Serenius et al., 2004; Imboonta et al., 2007; Ziedina et al., 2011; Vidovic et al., 2012; Sevón-Aimonen and Uimari, 2013). Heritability estimates are scarce in the literature using our trait definition for NA24 and in pure-bred Landrace sows for NBM, but similar estimates for the latter have been reported using other breeds or crossbred animals, ranging from 0.01 to 0.06 (Lewis et al., 2009a; Oteru et al., 2012; Schneider et al., 2012a).

All traits had moderate to low estimates of repeatability in the pre-PRRS phase. Although the repeatability estimates for NSB, NBD, and PBD were mainly due to additive genetic variance, which contributed at least 75% of repeatability estimates, for the other traits a large
GWAS for reproduction and Ab response to PRRS

was highly heritable in this population. Reports of heritability estimates by Lewis et al. (2009a) are not significantly different when accounting for other factors such as permanent environmental effects or nonadditive genetic effects. Similar repeatability estimates for NBA have been reported by others (Fernández et al., 2008; Dube et al., 2012; Vidovic et al., 2012). In general, these results indicate that this data set well represents the genetic basis of farrowing traits in PRRS-free Landrace sows.

The heritability estimates were generally higher in the PRRS phase than in the pre-PRRS phase, similar to what was observed by Lewis et al. (2009a). The point estimates of heritabilities during the PRRS phase reported by Lewis et al. (2009a) were higher than those obtained in our study for NBA, NBM, NSB, and NW, with heritability estimates of 0.15, 0.13, 0.17, and 0.15, respectively, but were the same for NBD (0.12). It is worth pointing out that heritability estimates reported in this study and by Lewis et al. (2009a) are not significantly different when accounting for the SE associated with the estimates.

Although the PRRS phase heritability estimates for the reproductive traits were moderate to low, S/P ratio was highly heritable in this population. Reports of heritability estimates for ELISA S/P ratio are scarce in the literature. Hess et al. (2013) estimated a heritability of 0.13 ± 0.13 for serum levels of IgG, measured with fluorescent microsphere immunoassays, in nursery pigs 42 d after an experimental infection with PRRSV. The S/P ratio data used in this study was derived from serum samples collected 46 d after the estimated day of the outbreak. Antibody titer to the PRRSV nucleocapsid protein that results in seropositive animals (ELISA S/P ratio ≥ 0.4) can be first detected at 9 to 13 dpi, with levels peaking at 30 to 50 dpi and slowly decreasing up to 4 mo postinfection (Collins et al., 1996; Brown et al., 2009; Kim et al., 2011). Therefore, the ELISA S/P ratio data used in this study may be representing the peak antibody response to the PRRSV in these animals. Because the samples were collected at 1 time only, we were not able to verify if the high genetic correlation obtained between S/P ratio and the reproductive traits would also be high at other time points, especially before the peak levels.

Since reproductive traits had low estimates of heritability following the PRRS outbreak, the highly heritable component associated with S/P ratio and its high genetic correlations with reproductive traits in the PRRS phase suggest that ELISA S/P ratio measured ~46 d after the estimated PRRS infection day has the potential to be used as a genetic indicator trait for reproductive performance following a PRRS outbreak. For instance, using the genetic parameters, indirect selection of PRRS phase NBA using the phenotype for S/P ratio could potentially be implemented in 2 ways. First, following a PRRS outbreak at a commercial level, S/P ratio data should be collected from sows following PRRS exposure. These data could be used to estimate breeding values for the sires of the commercial sows and used for selection of sires for increased S/P ratio. Second, if S/P ratio following

---

### Table 5. Percentage of the total genetic variance explained by the markers (TGVM) and locations for the SNP windows previously associated and selected SNP fitted separately for reproductive traits during the pre-PRRS and the PRRS phases

| Trait       | SSC (Mb) | %TGVM-i | %TGVM-f | PPI  |
|-------------|----------|---------|---------|------|
| **Pre-PRRS phase** |          |         |         |      |
| PBD         | 7 (98–99)| 3.01    | 0.22    | 0.46 |
| **PRRS phase** |         |         |         |      |
| NSB         | 1 (32–35)| 11.04   | 2.39    | 0.67 |

| Trait       | SSC (Mb) | %TGVM-i | %TGVM-f | PPI  |
|-------------|----------|---------|---------|------|
| **Pre-PRRS phase** |          |         |         |      |
| PBD         | 7 (98–99)| 3.01    | 0.22    | 0.46 |
| **PRRS phase** |         |         |         |      |
| NSB         | 1 (32–35)| 11.04   | 2.39    | 0.67 |

**Note:**

1. PRRS, porcine reproductive and respiratory syndrome; TGVM-i, initial TGVM of the SNP window (Table 4); TGVM-f, final TGVM of the SNP window after removing SNP with a higher frequency of Markov chain Monte Carlo samples with nonzero effect in the model; PPI, posterior probability of inclusion of the SNP window or selected SNP; PBD, proportion born dead; NSB, number of stillborn piglets.
vaccination is a genetic trait similar to S/P ratio following an actual PRRSV infection, sires could be selected on the basis of data from commercial sows that are vaccinated against the PRRSV. PRRSV-infected and PRRS-vaccinated animals have similar S/P ratios (Ellingson et al., 2010), suggesting that S/P ratio data from commercial herds that vaccinate sows against PRRSV can be used to select superior sires. However, before proceeding, these results must be validated on other data sets and at other time points for ELISA S/P ratio. In particular, the antibody response must be assessed at different times to better define the genetic relationship between this trait and the reproductive performance of sows under PRRS infection.

In this study we used a multiplier herd with multiparous sows that had not been previously exposed to PRRSV. Therefore, different situations, in addition to those mentioned above, should also be investigated to better understand the relationship between S/P ratio and reproductive traits in PRRSV-infected sows. Examples are use of sows at the commercial level, sows vaccinated against PRRSV, sows previously exposed to PRRSV, replacement gilts, and the relationship between S/P ratio and reproductive traits across different parities, although no significant effect of parity was found in our analysis for S/P ratio (data not shown).

### Effect of the WUR Genotype

The WUR SNP on SSC4 has previously been associated with PRRS tolerance in growing pigs, in which AB animals had favorable performance (greater weight gain and lower PRRS viral load) compared to AA animals (Boddicker et al., 2012). In our study we found associations (P-value < 0.10) before the PRRS outbreak in reproductive sows. Interestingly, the favorable genotype AB in growing pigs was favorable for NBA but unfavorable for NW in our study, as well as for MW but with an even weaker association than NBA and NW. The 2 significant associations for WUR found in this study did not show high levels of significance, probably because of the lower statistical power expected when using field data (Gordon et al., 2004). This low power may also explain the lack of statistical association between the WUR SNP and the traits evaluated in the PRRS phase. However, the trend of the association of the WUR SNP with PRRS phase NBA and NA24 suggests that this SNP could indeed be associated with these traits, but a greater sample size would be required to increase the statistical power to detect these effects.

### Genome-wide Associated Study and Candidate Genes

As described above for the WUR genotype, previous GWAS reported a major QTL on SSC4, accounting for 15.7% and 11.2% of the TGVM for viral load and weight gain up to 42 dpi, respectively, in growing pigs that were experimentally infected with PRRSV (Boddicker et al., 2012, 2014a,b). With the same experimental animals, Hess et al. (2013) found that approximately 50% of the TGVM for serum levels of IgG, measured with fluorescent microsphere immunoassays, was accounted for by a region harboring MHC class I antigen genes. For reproductive sows infected with PRRSV, Lewis et al. (2009b) identified 6 SNP associated with the traits NBA, NBD, and NBM, whereas Orrett et al. (2013) reported an association between NBD and a region on SSC4 but did not report the specific genomic locations. In our study, the WUR SNP was previously associated with performance in growing pigs infected with PRRSV (Boddicker et al., 2012), in our study we found associations (P-value < 0.10) before the PRRS outbreak in reproductive sows. Interestingly, the favorable genotype AB in growing pigs was favorable for NBA but unfavorable for NW in our study, as well as for MW but with an even weaker association than NBA and NW. The 2 significant associations for WUR found in this study did not show high levels of significance, probably because of the lower statistical power expected when using field data (Gordon et al., 2004). This low power may also explain the lack of statistical association between the WUR SNP and the traits evaluated in the PRRS phase. However, the trend of the association of the WUR SNP with PRRS phase NBA and NA24 suggests that this SNP could indeed be associated with these traits, but a greater sample size would be required to increase the statistical power to detect these effects.

### Table 6. Percentage of the total genetic variance explained by the markers (TGVM) and locations for the SNP windows associated and selected SNP fitted separately for sample-to-positive (S/P) ratio

| SNP window | %TGVM-i | %TGVM-f | PPI | SNP name   | SSC (kb) | %TGVM | PPI |
|------------|---------|---------|-----|------------|----------|-------|-----|
| 7 (24–30)  | 25.15   | 1.41    | 0.32| ASGA0031860| 7 (24,018)| 2.39  | 0.19|
|            |         |         |     | H3GA0020425| 7 (27,301)| 1.63  | 0.20|
|            |         |         |     | MARC0058875| 7 (29,077)| 4.17  | 0.21|
|            |         |         |     | ASGA0032151| 7 (30,435)| 10.88 | 0.57|
|            |         |         |     | ASGA0032161| 7 (30,521)| 0.81  | 0.06|
| 7 (40)     | 3.33    | 0.07    | 0.06| M1GA0025482| 7 (40,726)| 3.39  | 0.55|
| 7 (128–129)| 15.73   | 2.06    | 0.19| MARC0037274| 7 (128,892)| 0.34  | 0.03|
|            |         |         |     | ASGA0037093| 7 (129,119)| 3.68  | 0.23|
|            |         |         |     | ALGA0045692| 7 (129,184)| 5.42  | 0.33|
|            |         |         |     | ALGA0045737| 7 (129,340)| 1.82  | 0.11|
|            |         |         |     | BGIS0000745| 7 (129,389)| 2.53  | 0.16|

1TGVM-i, initial TGVM of the SNP window (Table 4); TGVM-f, final TGVM of the SNP window after removing SNP with a higher frequency of Markov chain Monte Carlo samples with nonzero effect in the model; PPI, posterior probability of inclusion of the SNP window or selected SNP.
we identified novel genomic regions associated with pre-
PRRS NSB and PBD and with PRRS phase NSB, NBD, 
and S/P ratio. The identified regions were compared to 
those reported in the literature, and candidate genes up
to 2 Mb outside the associated window were investigated 
to account for the resolution of the association analysis 
methods used in this study (Garrick and Fernando, 2013).

**Pre-PRRS Phase.** A large number of QTL for re-
productive traits (such as NBA, NSB, NBM, and NW) 
in PRRS-free sows have been reported in the literature, 
and these are summarized in the PigQTLdb (Hu et al., 
2013). Associations between SNP and PBD are scarce 
in the literature, but results for NBD have been previ-
ously reported. Rempel et al. (2010) reported SNP as-
associated with NBD on SSC1 and on SSC18 (P-value < 
0.1), whereas Schneider et al. (2012b) found an asso-
ciation with NBD on SSC11 for a SNP harboring the 
dachshund homolog 1 gene (*DACH1*). Although we 
did not find SNP associations for NBD in our study, we 
report a novel 2-Mb region on SSC7 associated with 
PBD. The 2-Mb windows had sizeable %TGVM (3.0%) 
and moderate PPI (0.58). However, the PPI of the se-
lected SNP were also too low to affirm that those SNP 
account for all of the TGVM. It is important to note 
that 1 selected SNP (ASGA0035348) had a significant 
association with PBD. Among the genes located along 
the associated region, the mediator of RNA polymerase 
II transcription subunit 6 gene (*MED6*) encodes for a 
subunit of the Thyroid Hormone Receptor-Associated 
Proteins (TRAP) complex, a transcriptional coactivator 
that has been shown to interact with estrogen receptors 
(Kang et al., 2002). Estrogen is important for implanta-
tion and establishment of pregnancy in sows (Spencer et 
al., 2004) and is mediated in the uterus by the estrogen 
receptors α gene (*ESR1*; Knapczyk-Stwora et al., 2011). 
Polymorphisms on *ESR1* have been associated with re-
productive performance traits (Rothschild et al., 1996; 
Rempel et al., 2010), and its expression is controlled by 
components of the TRAP complex (Kang et al., 2002; 
Zhang et al., 2005). In this manner, the transcriptional 
activity of estrogen receptor genes might be mediated by 
*MED6*, which then affects the reproductive performance 
of the sows.

Although NSB was the only trait with SNP identified 
in both pre-PRRS and PRRS phases, these genomic re-

gions differed between phases. Our 2 regions associated 
with pre-PRRS NSB were located in previously reported 
QTL regions, with Li et al. (2009) reporting a sugge-

tive QTL at 59 cM for NSB, whereas ours was at 53 Mb. 
Two genes potentially involved in reproductive processes 
from this region are the progestin and adipocyte receptor 
family member VIII gene (*PAQR8*), which encodes for 
a steroidal membrane receptor involved in oocyte maturation 
(Gioacchini et al., 2010), and the B-cell lymphoma 2-
related protein A1 gene (*BCL2A1*), which is an apop-
tosis suppressor (Craig, 1995) and has been shown to 
support bovine placental functions throughout gestation. 
On SSC12, Holl et al. (2004) found a QTL peaking at 
47.2 cM, whereas Oenteru et al. (2012) reported a QTL 
region from 42.6 to 43.5 Mb (P-value < 0.01) with NSB. 
In our study, a 1-Mb SNP window located at 10 Mb on 
SSC12 was associated with pre-PRRS NSB, where many 
genes associated with NBD on SSC12 were also reported. 
Previously associated with embryo development (Asou 
et al., 2002), the sex determining region Y box 9 gene 
(*SOX9*) causes severe bone defects and perinatal death in 
heterozygous mutant mice (Bi et al., 2001). The general 
but important activity of the ABC gene superfamily and 
the role of *SOX9* on prenatal development make these

---

**Table 7.** Least squares means (SE) of traits for the genotypes and minor allele frequency (MAF) of the selected SNP during the pre-PRRS and the PRRS phases.  

| Trait | SNP name | Genotype | MAF (allele) | P-value |
|-------|----------|----------|--------------|---------|
| PBD   | ASGA0035348 | AA 0.12 (0.03) | AB 0.10 (0.03) | BB 0.08 (0.03) | 0.42 (A) | <0.001 |
| NSB   | MARC0034894 | AA 1.28 (0.22) | AB 1.09 (0.21) | BB 0.80 (0.22) | 0.42 (A) | <0.001 |
| S/P ratio | ASGA0031860 | AA 1.87 (0.08) | AB 1.88 (0.06) | BB 1.81 (0.05) | 0.26 (A) | 0.194 |
|       | HGGA0020425 | AA 1.84 (0.07) | AB 1.83 (0.06) | BB 1.89 (0.06) | 0.45 (B) | 0.309 |
|       | MARC0058875 | AA 1.70 (0.05) | AB 1.90 (0.06) | BB 2.00 (0.07) | 0.32 (B) | <0.001 |
|       | ASGA0032151 | AA 1.75 (0.06) | AB 1.88 (0.06) | BB 1.93 (0.06) | 0.46 (B) | <0.001 |
|       | M1GA0025482 | AA 1.90 (0.08) | AB 1.89 (0.06) | BB 1.77 (0.05) | 0.20 (A) | <0.001 |
|       | ALGA0045692 | AA 1.70 (0.06) | AB 1.83 (0.06) | BB 2.04 (0.06) | 0.44 (A) | <0.001 |

1. PRRS, porcine reproductive and respiratory syndrome; PBD, proportion born dead; NSB, number of stillborn piglets; S/P ratio, ratio-to-positive ratio.
2. Different letters within SNP denote significant at P-value < 0.01.
3. Expressed as ln(x+1).
genes interesting candidates for controlling variation in NSB in pigs.

**PRRS Phase.** The 4-Mb region on SSC1 associated with PRRS phase NSB included the 1-Mb window associated with PRRS phase NBD. This region has not previously been associated with reproductive traits in sows. Although the region associated with PRRS phase NSB encompassed 4 Mb, the 5 selected SNP were located within 1.1 Mb and removed most of the %TGVM accounted for by the 4-Mb window. Interestingly, 2 genes in this 1.1-Mb interval are related to reproductive and survival processes. The solute carrier family 2, facilitated glucose transporter member 1 gene (*SLC2A1*, also known as *GLUT1*) encodes for a glucose transporter upregulated in the ovine placenta (Currie et al., 1997) and during oocyte maturation in mice (J. Zhou et al., 2000; Y. Zhou et al., 2004). This gene is responsible for the GLUT1 deficiency syndrome, which has been shown to confer embryonic lethality in mice (Wang et al., 2006). The serine/threonine-protein kinase encoded by the serum/glucocorticoid regulated kinase 1 gene (*SGK1*) is involved in cellular homeostasis (Luca et al., 2009). In mice, deregulated functions of *SGK1* have been associated with reproductive failure (Salker et al., 2011). Outside this 1.1 Mb, but approximately 2 Mb upstream of the 4-Mb SNP window associated with NSB, is the interferon γ receptor 1 gene (*IFNGR1*). The protein encoded by this gene is responsible for binding interferon γ (*IFNγ*), a well-known cytokine produced by T cells that regulates the expression of genes associated in the immune response, such as those located in the MHC region on SSC7 (Boehm et al., 1997; Batista et al., 2004). Associations between IFNγ and PRRSV levels have been extensively reported in the literature (Piras et al., 2005; Wesley et al., 2006; Lunney et al., 2010; Zhou et al., 2012). In contrast, little is known about the relationship between *IFNGR1* and PRRS, with Xing et al. (2010) reporting that *IFNGR1* is upregulated in spleen and downregulated in the lymph node of PRRSV-infected animals compared to uninfected ones. Although this region on SSC1 harbors genes showing different functions, with *SGK1* and *SLC2A1/GLUT1* involved in reproductive and survival processes and *IFNGR1* associated with immune response, these genes show complimentary functions that may explain the variation of NSB in sows infected with PRRSV.

We found more genomic regions associated with S/P ratio than with any other trait in our study. These are the first reported GWAS results for PRRSV ELISA S/P ratio. Of the 6 genomic regions associated in this study, the 7-Mb window that encompassed the MHC region account-
ed for more %TGVM than any other region in this study. The MHC region harbors genes associated with immune response to infectious diseases and vaccines and can be separated into class I, II, and III genes in the pig (Lunney et al., 2009). Our selected SNP that accounted for the highest %TGVM is located in the MHC class II region. This SNP (ASGA0032151) also had a significant association with S/P ratio, with BB and AB sows having a greater PRRSV Ab response than AA sows. Genes involved in the antigen presentation pathway are located in the MHC class I molecules (Kitamura et al., 2011), this region harbors genes from the ABC transporters superfamily, such as the transporter associated with antigen processing 1 and 2 genes (TAP1 and TAP2, respectively). In pigs, TAP1 has previously been associated with response to swine fever (Feng et al., 2012) and Salmonella (Uthe et al., 2011), whereas Sun et al. (2012) reported a SNP in exon 3 of this gene that was significantly associated (P-value < 0.05) with PRRSV Ab response in 17-d-old PRRSV-infected pigs. Although associated with immune response activity, TAP1 has been shown to be expressed in the blastocyst stage in mice, indicating that this gene may also play a role in embryo preimplantation (Cooper et al., 1998). In general, associations between the MHC region/gene and reproductive processes have been extensively reported in the literature, with spontaneous abortion and infertility in humans (Jin et al., 2009), in reproductive success in mice (Warner, 1986; Liljander et al., 2006), and in reproductive traits in the pig, such as piglet mortality (Kristensen, 1985), ovulation rate (Rothschild et al., 1984), and fetus survival (Joyce et al., 2008), supporting the results that ELISA S/P ratio may be used as an indicator trait for reproductive traits.

Reports in the literature indicate the presence of high LD (reviewed by Lunney et al., 2009), but the LD plot of the SSC7 region (24 through 31 Mb) associated with S/P ratio in this study showed little LD for the population studied. In fact, this whole 7-Mb region had a low average and median r² of 0.14 and 0.05, respectively. Others have reported haplotypes for this region across genes within the same MHC class, indicating that LD exists at short distances (Chardon et al., 1985; Rogel-Gaillard et al., 1999; Horton et al., 2004; Cho et al., 2010). The 5 selected SNP in this region are spread along these 7 Mb, with the exception of ASGA0032151 and ASGA0032161, which are located ~100 kb apart, and were in moderate LD (r² = 0.50). It has been shown that the interaction between MHC genes is associated with diseases in humans (Blackwell et al., 2009; Lincoln et al., 2009; Zhang et al., 2011), which could in turn explain why these 5 selected SNP were spread across this region. We further investigated the interaction between the selected SNP for S/P ratio and only 2 SNP had a significant interaction (P-value = 0.03). These 2 SNP were MARC0058875 and ASGA0032151, and although their interaction was significant, the results from including the interaction in the analysis were not drastically different than those without this interaction (results not shown), and therefore, the interaction term was excluded from the final analysis.

The SSC7 region associated with S/P ratio that had the second highest %TGVM (15.7%) was in high LD in this study, which may hinder identification of causative mutations. This region is located at positions 128 through 130 Mb, 100 Mb downstream of the MHC region. Many genes are located within the 500-kb region encompassed by the 5 selected SNP. In addition to RCR1, which is involved in the pathogenesis of Huntington’s disease (Shapshak, 2013), this region harbors the tumor necrosis factor (TNF) receptor-associated factor 3 gene (TRAF3). This gene is a member of the TNF receptor superfamily, a group of proteins important for the activation of the immune response (Lin et al., 2013). The protein encoded by TRAF3 has been associated with immune response regulators, such as the nuclear factor κB (NF-κB; He et al., 2006), activator protein 1 (AP1), cluster of differentiation 40 (CD40), the B cell-activating factor (BAFF), and IFNγ through the interaction with members of the interleukin-1 receptor family (Hacker et al., 2011). This gene has been shown to be upregulated in Zaire ebolavirus–infected pigs (Nfon et al., 2013). Also, a QTL in this region for PRRSV Ab titer in miniature pigs vaccinated for PRRSV, Mycoplasma hyopneumoniae, and Aujeszky’s disease virus has previously been reported (Wimmers et al., 2009). In addition to these reports, the function of TRAF3 and the strong association observed for this region in this study (with PPI = 1) indicate that this region may in fact play an important role in controlling variation in S/P ratio following PRRSV infection.

The remaining 4 regions associated with S/P ratio accounted for a lower %TGVM than the other 2 regions on SSC7, located at positions 24 through 31 Mb and 128 through 130 Mb. The third and last region on SSC7 associated with S/P ratio is relatively close to the 7-Mb window that had the greatest %TGVM. Interestingly, the SNP M1GA00025482 accounted for virtually all the %TGVM of the window. This SNP was included as a fixed effect in the model, and AB animals had greater S/P ratio values than BB sows. This SNP is less than 2 Mb upstream of the cyclin D3 gene (CCND3), which regulates androgen receptor (Zong et al., 2007) and is upregulated in the uterus during blastocyst implantation (Das et al., 1999). On SSC14, the 3-Mb window at the end of the chromosome had a high PPI (PPI = 0.82), whereas the 1-Mb window at Mb 39 had a low PPI of 0.15. These regions include genes associated with immune response
function, such as interleukin 28B (*IL28B*) and interferon lambda 4 (*IFNL4*), which have been associated with clearance of the hepatitis C virus (Prokunina-Olsson et al., 2013), and with embryonic development, such as T-box transcription factors 2 (*TBX2*) and 5 (*TBX5*; Douglas et al., 2012) and budding uninhibited by benzimidazoles 3 (*BUB3*; Kalitsis et al., 2000). On SSC2, the 1-Mb window had low evidence of association (PPI = 0.39). This region has, however, been associated with NSB (Oneteru et al., 2012), NBM (Holl et al., 2004), and NBA (Stinckens et al., 2010) in pigs. In addition, this region harbors genes showing reproductive functions, such as deformed epidermal autoregulatory factor-1 (*DEAF1*) and pleckstrin homology-like domain family A member 2 (*PHLDA2*), which have been associated with embryo development (Barker et al., 2008) and extraembryonic energy storage (Tunster et al., 2010), respectively, as well as genes showing immune response function, such as the interferon regulatory factor 7 gene (*IRF7*), which regulates type-I interferon (Honda et al., 2005).

**Conclusions**

Following a PRRS outbreak, ELISA S/P ratio measured approximately 46 d after PRRSV infection proved to be highly heritable and genetically correlated with farrowing traits in the PRRS phase, using a multiplier Landrace sow herd for a commercial maternal line. These findings indicate that S/P ratio has the potential to be used as an indicator trait to select for farrowing traits under PRRS infection. Genomic regions were associated with NSB and PBD in the pre-PRRS phase and with NSB, NBD, and S/P ratio in the PRRS phase. For S/P ratio, a region encompassing the MHC region on SSC7 explained over 25% of the TGVM. Two other regions on SSC7 and SSC14 and 1 region on SSC2 were also associated with S/P ratio, explaining almost 50% of the TGVM. All genomic regions associated with NSB, PBD, and S/P ratio in this study harbor genes that can be associated with reproductive performance, and regions associated with S/P ratio also harbor genes associated with immune response activity. The genetic correlation between S/P ratio and reproductive traits must be validated in additional populations and disease outbreaks. Also, greater sample sizes are required to further refine the regions found to be associated with these traits in order to find the genes or SNP controlling these traits before and after a PRRS outbreak.

**LITERATURE CITED**

Asou, Y., A. Nifuji, K. Tsuji, K. Shinomiya, E. N. Olson, P. Koopman, and M. Noda. 2002. Coordinated expression of *scleraxis* and *Sox9* genes during embryonic development of tendons and cartilage. J. Orthop. Res. 20:827–833.

Barker, H. E., G. K. Smyth, J. Wettenhall, T. A. Ward, M. L. Bath, G. J. Lindeman, and J. E. Vissader. 2008. Defa-1 regulates epithelial cell proliferation and side-branching in the mammary gland. BMC Dev. Biol. 8:94.

Barrett, J. C. 2009. Haploview: Visualization and analysis of SNP genotype data. Cold Spring Harb. Protoc. 2009:pdb.ip71. doi:10.1101/pdb.ip71.

Batista, L., C. Pijoan, S. Dee, M. Olin, T. Molitor, H. S. Joo, Z. Xiao, and M. Murtaugh. 2004. Virological and immunological responses to porcine reproductive and respiratory syndrome virus in a large population of gilts. Can. J. Vet. Res. 68:267–273.

Bi, W., W. Huang, D. J. Whitworth, J. M. Deng, R. R. Behringer, and B. de Crombrugghe. 2001. Haploinsufficiency of Sox9 results in defective cartilage primordia and premature skeletal mineralization. Proc. Natl. Acad. Sci. USA 98:6698–6703.

Blackwell, J. M., S. E. Jamieson, and D. Burgher. 2009. HLA and infectious diseases. Clin. Microbiol. Rev. 22:370–385.

Bodicker, N. J., A. Bjorquist, R. R. R. Rowland, J. K. Lunney, J. M. Reece, and J. C. M. Dekkers. 2014b. Genome-wide association and genomic prediction for host response to porcine reproductive and respiratory syndrome infection. Genet. Sel. Evol. 46:18.

Bodicker, N. J., D. J. Garrick, R. R. R. Rowland, J. K. Lunney, J. M. Reece, and J. C. M. Dekkers. 2014a. Validation and further characterization of a major quantitative trait locus associated with host response to experimental infection with porcine reproductive and respiratory syndrome virus. Anim. Genet. 45:48–58.

Bodicker, N. J., E. H. Waide, R. R. R. Rowland, J. K. Lunney, D. J. Garrick, J. M. Reece, and J. C. M. Dekkers. 2012. Evidence for a major QTL associated with host response to porcine reproductive and respiratory syndrome virus challenge. J. Anim. Sci. 90:1733–1746.

Boehm, U., T. Klamp, M. Groot, and J. C. Howard. 1997. Cellular responses to interferon-gamma. Annu. Rev. Immunol. 15:749–795.

Brown, E., S. Lawson, C. Welbon, J. Cnannotarajah, J. Li, M. P. Murtaugh, E. A. Nelson, R. M. Molina, J. J. Zimmerman, R. R. Rowland, and Y. Fang. 2009. Antibody response to porcine reproductive and respiratory syndrome virus (PRRSV) nonstructural proteins and implications for diagnostic detection and differentiation of PRRSV types I and II. Clin. Vaccine Immunol. 16:628–635.

Canadian Council on Animal Care. 1993. E. D. Rolfert, B. M. Cross, and A. McCWilliam, editors, Guide to the care and use of experimental animals. 2nd ed. Vol. 1. Can. Counc. Animal Care, Ottawa.

Chardon, P., M. Vaiman, M. Kirszenbaum, C. Geffrotin, C. Renard, and D. Cohen. 1985. Restriction fragment length polymorphism of the major histocompatibility complex of the pig. Immunogenetics 21:161–171.

Chen, P., T. J. Baas, J. W. Mabry, K. J. Koehler, and J. C. Dekkers. 2003. Genetic parameters and trends for litter traits in U.S. Yorkshire, Duroc, Hampshire, and Landrace pigs. J. Anim. Sci. 81:46–53.

Cho, H. O., C. S. Ho, Y. J. Lee, I. C. Cho, S. S. Lee, M. S. Ko, C. Park, D. M. Smith, T. J. Jeon, and J. H. Lee. 2010. Establishment of a resource population of SLA haplotype-defined Korean native pigs. Mol. Cells 29:493–499.

Collins, J. E., S. Dee, P. Halbur, K. Keffaber, B. Lautner, M. McCaw, M. Rodilbaugh, E. Sanford, and P. Yeske. 1996. Laboratory diagnosis of porcine reproductive and respiratory syndrome (PRRS) virus infection. J. Swine Health Prod. 4:33–35.

Cooper, J. C., N. Fernandez, E. Joly, and G. B. Dealtry. 1998. Regulation of major histocompatibility complex and TAP gene products in preimplantation mouse stage embryos. Am. J. Reprod. Immunol. 40:165–171.

Craig, R. W. 1995. The hcl-2 gene family. Semin. Cancer Biol. 6:35–43.

Currie, M. J., N. S. Bassett, and P. D. Gluckman. 1997. Ovine glucose transporter-1 and -3: CDNA partial sequences and developmental gene expression in the placenta. Placenta 18:393–401.
Das, S. K., H. Lim, B. C. Paria, and S. K. Dey. 1999. Cyclin D3 in the mouse uterus is associated with the decidualization process during early pregnancy. J. Mol. Endocrinol. 22:91–101.

Dean, M., A. Rzhetsky, and R. Allikmets. 2001. The human ATP-binding cassette (ABC) transporter superfamily. Genome Res. 11:1156–1166.

Douglas, N. C., K. Heng, M. V. Sauer, and V. E. Papaioannou. 2012. Dynamic expression of Tbx2 subfamily genes in development of the mouse reproductive system. Dev. Dyn. 241:365–375.

Dube, B., S. D. Mulugeta, and K. Dzama. 2012. Estimation of genetic and phenotypic parameters for sow productivity traits in South African Large White pigs. S. Afr. J. Anim. Sci. 42:389–397.

Ellingson, J. S., Y. Weng, S. Layton, J. Ciacci-Zanella, M. B. Roof, Holm, B., M. Bakken, G. Klemetsdal, and O. Vangen. 2004. Genetic

Holl, J. W., J. P. Cassady, D. Pomp, and R. K. Johnson. 2004. A genetic

Hess, A. S., B. R. Trible, Y. Wang, N. K. Boddicker, R. R. Rowland, He, J. Q., B. Zarnegar, G. Oganesyan, S. K. Saha, S. Yamazaki, S. E.

Hacker, H., P. H. Tseng, and M. Karin. 2011. Expanding TRAF function: TRAF3 as a tri-faced immune regulator. Nat. Rev. Immunol. 13:109–121.

Habier, D., R. L. Fernando, and D. J. Garrick. 2011. GenSel manual v3. www.beadchip.com/downloads/technote_gencall_faq_porcine_snp60v2.pdf. (Accessed 2 April 2014.)

Garrick, D. J., and R. L. Fernando. 2013. Implementing a QTL detection study (GWAS) using genomic prediction methodology. Methods Mol. Biol. Vol. 1019. p. 275–298.

Garrick, D. J., J. F. Taylor, and R. L. Fernando. 2009. Deregressing estimated breeding values and weighting information for genomic regression analyses. Genet. Sel. Ecol. 41:55.

Geldhof, M. F., W. van Breedam, E. de Jong, A. L. Rodriguez, U. U.

Asagiri, M. Sato, T. Mizutani, Honda, K., H. Yanai, H. Negishi, M. Asagiri, M. Sato, T. Mizutani, N. Shimada, Y. Ohba, A. Takaoka, N. Yoshida, and T. Taniguchi. 2005. IRF-7 is the master regulator of type-I interferon-dependent immune responses. Nature 434:772–777.

Horton, R., L. Wilmng, V. Rand, R. C. Lovering, E. A. Bruford, V. K. Khodiyar, M. J. Lush, S. Povey, C. C. Talbot Jr., M. W. Wright, H. M. Wain, J. Trowsdale, A. Ziegler, and S. Beck. 2004. Gene map of the extended human MHC. Nat. Rev. Genet. 5:889–899.

Hu, Z. L., C. A. Park, X. L. Wu, and J. M. Reecey. 2013. Animal QTLdb: An improved database tool for livestock animal QTL/association data dissemination in the post-genome era. Nucleic Acids Res. 41:D871–D879.

Illumina. 2005. Illumina GenCall data analysis software. http://res.illumina.com/documents/products/technotes/technote_gencall_data_analysis_software.pdf. (Accessed 2 April 2014.)

Illumina. 2012. Frequently asked questions: PorcineSNP60 v2 BeadChiper. http://res.illumina.com/documents/products/other/faq_porcine_sn60v2.pdf. (Accessed 2 April 2014.)

Imboonta, N., L. Rydhammer, and S. Tumwason. 2007. Genetic parameters for reproduction and production traits of Landrace sows in Thailand. J. Anim. Sci. 85:53–59.

Jin, K., H. N. Ho, T. P. Speed, and T. J. Gill III. 1995. Reproductive failure and the major histocompatibility complex. Annu. Rev. Genet. 29:155–168.

Joyce, M. M., J. R. Burghardt, R. C. Burghardt, R. N. Hooper, F. B. Bazer, and G. A. Johnson. 2008. Uterine MHC class I molecules and beta 2-microglobulin are regulated by progesterone and conceptus interferons during pig pregnancy. J. Immunol. 181:2494–2505.

Kalitsis, P., E. Earle, J. K. Fowler, and K. H. Choo. 2000. Bub3 gene disruption in mice reveals essential mitotic spindle checkpoint function during early embryogenesis. Genes Dev. 14:2277–2282.

Kang, Y. K., M. Guermah, C. X. Yuan, and R. G. Roeder. 2002. The TRAP/mediator coactivator complex interacts directly with estrogen receptors alpha and beta through the TRAP220 subunit and directly enhances estrogen receptor function in vitro. Proc. Natl. Acad. Sci. USA 99:2642–2647.

Karniychuk, U. U., and H. J. Nauwync. 2013. Pathogenesis and prevention of placental and transplacental porcine reproductive and respiratory syndrome virus infection. Vet. Res. 44:95–104.

Kim, H., H. K. Kim, J. H. Jung, Y. J. Choi, J. Kim, C. G. Um, S. B. Hyun, S. Shin, B. Lee, G. Jang, B. K. Kang, H. J. Moon, and D. S. Song. 2011. The assessment of efficacy of porcine reproductive respiratory syndrome virus inactivated vaccine based on the viral quantity and inactivation methods. Virol. J. 8:323.

Kitamura, A., Y. Maekawa, H. Uehara, K. Izumi, I. Kawachi, M. Nishizawa, Y. Toyoshima, H. Takahashi, D. M. Standley, K. Tanaka, J. Hamazaki, S. Murata, K. Obara, I. Toyoshima, and K. Yasutomo. 2011. A mutation in the immunoproteasome subunit PSMB8 causes autoinflammation and lipodystrophy in humans. J. Clin. Invest. 121:4150–4160.

Knapczyk-Stwora, K., M. Durlej, M. Duda, K. Czernichowska-Ferreira, A. Tabecka-Lonczynska, and M. Slomczynska. 2011. Expression studies in the common Swiss and Danish swine breeds. Anim. Genet. 42:298–300.
Langenhorst, R. J., L. Lawson, A. Kittaworarat, J. J. Zimmerman, Z. Sun, J. Christopher-Hennings, E. A. Nelson, and Y. Fang. 2012. Development of a fluorescent microsphere immunoassay for detection of antibodies against porcine reproductive and respiratory syndrome virus using oral fluid samples as an alternative to serum-based assays. Clin. Vaccine Immunol. 19:180–189.

Lewis, C. R. G., M. Torremorell, L. Galina-Pantoja, and S. C. Bishop. 2009a. Genetic parameters for performance traits in commercial sows estimated before and after an outbreak of porcine reproductive and respiratory syndrome. J. Anim. Sci. 87:867–886.

Lewis, C. R. G., M. Torremorell, L. Galina-Pantoja, N. Deeb, M. A. Mellencamp, A. L. Archibald, and S. C. Bishop. 2009b. A genome-wide association analysis identifying SNPs for PRRS tolerance on a commercial pig farm. Proc. Assoc. Adv. Anim. Breed. Genet. 18:187–190.

Li, K., J. Ren, Y. Xing, Z. Zhang, J. Ma, Y. Guo, and L. Huang. 2009. Quantitative trait loci for litter size and prenatal loss in a White Duroc × Chinese Erhualian resource population. Anim. Genet. 40:963–966.

Liljander, M., M.-A. Sällström, S. Andersson, P. Wernhoff, Å. Andersson, R. Holmdahl, and R. Mattsson. 2006. Identification of genetic regions of importance for reproductive performance in female mice. Genetics 173:901–909.

Lin, W. W., J. M. Hildebrand, and G. A. Bishop. 2013. A complex relationship between TRAF3 and non-canonical NF-κB2 activation in B lymphocytes. Front. Immunol. 4:477.

Lincoln, M. R., S. V. Ramagopalan, M. J. Chao, B. M. Herrera, G. C. Deluca, S. M. Orton, D. A. Dyment, A. D. Sadovnick, and G. C. Ebers. 2009. Epistasis among HLA-DRB1, HLA-DQA1, and HLA-DQB1 loci determines multiple sclerosis susceptibility. Proc. Natl. Acad. Sci. USA 106:7542–7547.

Luca, F., S. Kashyap, C. Southard, M. Zou, D. Witonsky, A. Di Rienzo, and S. D. Conzen. 2009. Adaptive variation regulates the expression of the human SGK1 gene in response to stress. PLoS Genet. 5:e1000489.

Lunney, J. K., E. R. Fritz, J. M. Reecy, D. Kuhr, E. Prucnal, R. Molina, J. Christopher-Hennings, J. Zimmerman, and R. R. Rowland. 2010. Interleukin-8, interleukin-Ibetoa, and interferon-gamma levels are linked to PRRS virus clearance. Viral Immunol. 23:127–134.

Lunney, J. K., C. S. Ho, M. Wysocki, and D. M. Smith. 2009. Molecular genetics of the swine major histocompatibility complex, the SLA complex. Dev. Comp. Immunol. 33:362–374.

Lunney, J. K., J. P. Steibel, J. M. Reecy, E. Fritz, M. F. Rothschild, M. Kerrigan, B. Trible, and R. R. R. Rowland. 2011. Probing genetic control of swine responses to PRRSV infection: Current progress of the PRRS host genetics consortium. BMC Proc. 5(Suppl. 4):S30.

Meuwissen, T. H., B. J. Hayes, and M. E. Goddard. 2001. Prediction of total genetic value using genome-wide dense marker maps. Genetics 157:1819–1829.

Nfon, C. K., A. Leung, G. Smith, C. Embury-Hyatt, G. Kobering, and H. M. Weingart. 2013. Immunopathogenesis of severe acute respiratory disease in Zaire ebolavirus-infected pigs. PLoS ONE 8:e61904.

Ontera, S. K., B. Fan, Z.-Q. Du, D. J. Garrick, K. J. Stalder, and M. F. Rothschild. 2012. A whole-genome association study for pig reproductive traits. Anim. Genet. 43(1):18–26.

Orrett, C. M., O. Matika, A. Archibald, C. R. G. Lewis, D. McLaren, N. Deeb, and S. C. Bishop. 2013. Genetics of host response to infection with porcine reproductive and respiratory syndrome virus (PRRSV). Adv. Anim. Biosci. 4:81.

Piras, F., S. Bollard, F. Laval, F. Joisel, G. Reynaud, C. Charreyre, C. Andreoni, and V. Juillard. 2005. Porcine reproductive and respiratory syndrome (PRRS) virus-specific interferon-gamma(+) T-cell responses after PRRS virus infection or vaccination with an inactivated PRRS vaccine. Viral Immunol. 18:381–389.

Prokunina-Olsson, L., B. Muchmore, W. Tang, R. M. Pfeiffer, H. Park, H. Dickson, D. Hergott, P. Porter-Gill, A. Mummy, I. Kohara, S. Chen, N. Brand, M. Tarway, L. Liu, F. Sheik, J. Astemborski, H. L. Bonkovsky, B. R. Edlin, C. D. Howell, T. R. Morgan, D. L. Thomas, B. Rehermann, R. P. Donnelly, and T. R. O’Brien. 2013. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Nat. Genet. 45:164–171.

Rempel, L. A., D. J. Nonneman, T. H. Wise, T. Erkens, L. J. Peelman, and G. A. Rohrer. 2010. Association analyses of candidate single nucleotide polymorphisms on reproductive traits in swine. J. Anim. Sci. 88:1–15.

Robinson, J. A. B., and V. M. Quinton. 2002. Genetic parameters of early neonatal piglet survival and number of piglets born. Proc. 7th World Congr. Genet. Appl. Livest. Prod., Montpellier, France III:1–4.

Rogel-Gaillard, C., N. Bourgeaux, A. Billault, M. Vaiman, and P. Chardon. 1999. Construction of a swine BAC library: Application to the characterization and mapping of porcine type C endoviral elements. Cytogenet. Cell Genet. 85:205–211.

Rothschild, M., C. Jacobson, D. Vaske, C. Tuggle, L. Wang, T. Short, G. Eckardt, S. Sasaki, A. Vincent, D. McLaren, O. Southwood, H. van der Steen, A. Mileham, and G. Plastow. 1996. The estrogen receptor locus is associated with a major gene influencing litter size in pigs. Proc. Natl. Acad. Sci. USA 93:201–205.

Rothschild, M. F., D. R. Zimmerman, R. K. Johnson, L. Venier, and C. M. Warner. 1984. SLA haplotype differences in lines of pigs which differ in ovulation rate. Anim. Blood Groups Biochem. Genet. 15:155–158.

Rowland, R. R., J. Lunney, and J. Dekkers. 2012. Control of porcine reproductive and respiratory syndrome (PRRS) through genetic improvements in disease resistance and tolerance. Front. Genet. 3:260.

Salker, M. S., M. Christian, J. H. Steel, J. Nauytial, S. Lavery, G. Trew, Z. Webster, M. Al-Sabbagh, G. Puchchakayala, M. Föller, C. Landles, A. M. Sharkey, S. Quenby, J. D. Aplin, L. Regan, F. Lang, and J. J. Brosens. 2011. Deregulation of the serum- and glucocorticoid-inducible kinase SGK1 in the endometrium causes reproductive failure. Nat. Med. 17:1509–1513.

Schneider, J. F., L. A. Rempel, and G. A. Rohrer. 2012a. Genome-wide association study of swine farrowing traits. Part I: Genetic and genomic parameter estimates. J. Anim. Sci. 90:3353–3359.

Schneider, J. F., L. A. Rempel, W. M. Snelling, R. T. Wiedmann, D. J. Nonneman, and G. A. Rohrer. 2012b. Genome-wide association study of swine farrowing traits. Part II: Bayesian analysis of marker data. J. Anim. Sci. 90:3360–3367.

Serào, N. V. L., D. González-Peña, J. E. Beever, D. B. Faulkner, B. R. Southey, and S. L. Rodríguez-Zas. 2013. Single nucleotide polymorphisms and haplotypes associated with feed efficiency in beef cattle. BMC Genet. 14:94–114.

Serénsis, T., M.-I. Sevón-Aimonen, A. Kause, E. A. Mantysaari, and A. Mäki-Tanila. 2004. Selection potential of different prolificacy traits in the Finnish Landrace and Large White populations. Acta Agric. Scand. Anim. Sci. 54:36–43.

Sevón-Aimonen, M.-L., and P. Uimari. 2013. Heritability of sow longevity and lifetime prolificacy in Finnish Yorkshire and Landrace pigs. Agric. Food Sci. 22(3):325–330.

Shapshak, P. 2013. Molecule of the month: MiRNA and Huntington’s disease (HD). Bioinformation 9:549–550.

Spencer, T. E., R. C. Burghardt, G. A. Johnson, and F. W. Bazer. 2004. Conceptus signals for establishment and maintenance of pregnancy. Anim. Reprod. Sci. 82–83:537–550.

Stincken, A., P. Mathur, S. Janssens, V. Bruggeman, O. M. Ongabesam, M. Schroyen, G. Spincemaille, E. Decuypere, M. Georges, and N. Deeb. 2010. Indirect effect of IGF2 intron3 g.307G:A mutation on prolificacy in sows. Anim. Genet. 41:493–498.
Sun, N., D. Liu, H. Chen, X. Liu, F. Meng, X. Zhang, H. Chen, S. Xie, X. Li, and Z. Wu. 2012. Localization, expression change in PRRSV infection and association analysis of the porcine TAP1 gene. Int. J. Biol. Sci. 8:49–58.

Tunster, S. J., B. Tycko, and R. M. John. 2010. The imprinted Phlda2 gene regulates extraembryonic energy stores. Mol. Cell. Biol. 30:295–306.

Uthe, J. J., S. M. Bearson, L. Qu, J. C. M. Dekkers, D. Nettleton, Y. Rodriguez Torres, A. M. O’Connor, J. D. McKeen, and C. K. Tuggle. 2011. Integrating comparative expression profiling data and association of SNPs with Salmonella shedding for improved food safety and porcine disease resistance. Anim. Genet. 42:521–534.

Vidovic, V., D. Lukac, M. Stupar, V. Višnjic, and J. Krnjaic. 2012. Heritability and repeatability estimates of reproduction traits in purebred pigs. Biotechnol. Anim. Husb. 28:455–462.

Wang, D., J. M. Pascual, H. Yang, K. Engelstad, X. Mao, J. Cheng, J. Yoo, J. L. Noebels, and D. C. de Vivo. 2006. A mouse model for Glut-1 haploinsufficiency. Hum. Mol. Genet. 15:1169–1179.

Warner, C. M. 1986. Genetic manipulation of the major histocompatibility complex. J. Anim. Sci. 63:279–287.

Wesley, R. D., K. M. Lager, and M. E. Kehrli Jr. 2006. Infection with porcine reproductive and respiratory syndrome virus stimulates an early gamma interferon response in the serum of pigs. Can. J. Vet. Res. 70:176–182.

Wimmers, K., E. Murani, K. Schellander, and S. Ponsuksili. 2009. QTL for traits related to humoral immune response estimated from data of a porcine F2 resource population. Int. J. Immunogenet. 36:141–151.

Wolc, A., J. Arango, P. Settar, J. E. Fulton, N. P. O’Sullivan, R. Preisinger, D. Habier, R. L. Fernando, D. J. Garrick, W. G. Hill, and J. C. M. Dekkers. 2012. Genome-wide association analysis and genetic architecture of egg weight and egg uniformity in layer chickens. Anim. Genet. 43(Suppl. 1):87–96.

Xing, F., C. Jiang, S. Liang, L. Kang, and Y. Jiang. 2010. Genomic structure and characterization of mRNA expression pattern of porcine interferon gamma receptor 1 gene. Int. J. Immunogenet. 37:477–485.

Zhang, X., A. Krutchinsky, A. Fukuda, W. Chen, S. Yamamura, B. T. Chait, and R. G. Roeder. 2005. MEDI/TRAP220 exists predominantly in a TRAP/mediator subpopulation enriched in RNA polymerase II and is required for ER-mediated transcription. Mol. Cell 19:89–100.

Zhang, B. Y., J. Zhang, and J. S. Liu. 2011. Block-based Bayesian epistasis association mapping with application to Wtccc type 1 diabetes data. Ann. Appl. Stat. 5:2052–2077.

Zhou, Y., J. Bai, Y. Li, X. Wang, X. Wang, and P. Jiang. 2012. Suppression of immune responses in pigs by nonstructural protein 1 of porcine reproductive and respiratory syndrome virus. Can. J. Vet. Res. 76:255–260.

Zhou, J., M. Bievre, and C. A. Bondy. 2000. Reduced GLUT1 expression in Igf1—/— null oocytes and follicles. Growth Horm. IGF Res. 10:111–117.

Zhou, Y., P. L. Kaye, and M. Pantaleon. 2004. Identification of the facilitative glucose transporter 12 gene Glut12 in mouse preimplantation embryos. Gene Expr. Patterns 4:621–631.

Ziedina, I., D. Jonkus, and L. Paur. 2011. Genetic and phenotypic parameters for reproduction traits of Landrace sows in Latvia. Agric. Conspectus Sci. 76:219–222.

Zong, H., Y. Chi, Y. Wang, Y. Yang, L. Zhang, H. Chen, J. Jiang, Z. Li, Y. Hong, H. Wang, X. Yun, and J. Gu. 2007. Cyclin D3/CDK11p58 complex is involved in the repression of androgen receptor. Mol. Cell. Biol. 27:7125–7142.
References

This article cites 96 articles, 28 of which you can access for free at:
http://www.journalofanimalscience.org/content/92/7/2905#BIBL