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Evidence for recombination variability in purebred swine populations

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Abstract

This study aimed to investigate interpopulation variation due to sex, breed and age, and the intrapopulation variation in the form of genetic variance for recombination in swine. Genome-wide recombination rate and recombination occurrences (RO) were traits studied in Landrace (LR) and Large White (LW) male and female populations. Differences were found for sex, breed, sex-breed interaction, and age effects for genome-wide recombination rate and RO at one or more chromosomes. Dams were found to have a higher genome-wide recombination rate and RO at all chromosomes than sires. LW animals had higher genome-wide recombination rate and RO at seven chromosomes but lower at two chromosomes than LR individuals. The sex-breed interaction effect did not show any pattern not already observable by sex. Recombination increased with increasing parity in females, while in males no effect of age was observed. We estimated heritabilities and repeatabilities for both investigated traits and obtained the genetic correlation between male and female genome-wide recombination rate within each of the two breeds studied. Estimates of heritability and repeatability were low (h^2 = 0.01–0.26; r = 0.18–0.42) for both traits in all populations. Genetic correlations were high and positive, with estimates of 0.98 and 0.94 for the LR and LW breeds, respectively. We performed a GWAS for genome-wide recombination rate independently in the four sex/breed populations. The results of the GWAS were inconsistent across the four populations with different significant genomic regions identified. The results of this study provide evidence of variability for recombination in purebred swine populations.

KEYWORDS

genetic variance, recombination rate, selection, swine

1 | INTRODUCTION

Meiotic recombination is a fundamental biological process in sexually reproducing organisms that introduces genetic variation in the population by the exchange of genetic material between homologous chromosomes during meiosis. The effects of recombination include the breakage of linkage blocks, the creation of new haplotypes and maintenance of adaptation level in the population (Bachtrog & Charlesworth, 2002; Feldmant et al., 1980). Recombination rate, quantified as the number of recombination events in the genome, has been recognized as an important parameter to understand the genetic

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TABLE 1 Summary of animals included in the analysis

	Landrace		Large white	
	Sires	**Dams**	**Sires**	**Dams**
Summary				
Number of animals	281	1,356	270	1755
Number of progeny	4,657	4,628	5,718	5,706
Average number of progeny per animal	16.57	3.41	21.18	3.25
Minimum number of progeny per animal	1	1	1	1
Maximum number of progeny per animal	121	11	138	13
Total number of animals in pedigree	291,137		391,159	

makeup of animal populations, although its effects have been historically studied mostly in humans, mice and other model organisms. Nonetheless, interest in this trait in livestock species has increased recently (Ma et al., 2015; Shen et al., 2018; Tortereau et al., 2012; Wang et al., 2016). Previous research has found that factors such as sex, population and age have a detectable effect on recombination parameters, which in turn has made it a research area of continuous and growing interest. In different species, males and females have been found to significantly differ on magnitude (Lenormand & Dutheil, 2005; Shen et al., 2018; Tortereau et al., 2012) and distribution (Ma et al., 2015; Tortereau et al., 2012) of recombination rate across the genome. Population differences for recombination have been found in humans (Evans & Cardon, 2005) as differences in recombination history and pairwise distances of LD, and in cattle as differences in the number of chromosomal crossovers between breeds (Shen et al., 2018). While not as heavily studied as sex and population, the effect of age on recombination has been documented in both males (Griffin et al., 1995) and females (Campbell et al., 2015; Hussin et al., 2011; Martin et al., 2015).

Genetic variation for recombination parameters has been observed in sheep (Johnston et al., 2016) and human (Fledel-Alon et al., 2011; Kong et al., 2004), with the additive genetic variance explaining anywhere from 14% to 30% of the total phenotypic variance for recombination rate, with heritability estimates differing between sexes. Despite the advantages of increasing recombination rate and the evidence of sizeable additive variance for this trait, recombination rate is currently not considered as a target of selection in swine. Nevertheless, multiple studies have explored the benefits of positive selection for recombination rate on selection response of economically important traits. Using simulation studies and experiments on fruit flies, a positive effect on selection response has been found by selection for increased recombination rate (Battagin et al., 2016; McPhee & Robertson, 1970). Further simulations have found that manipulation of recombination hotspots using genomic technologies where the hotspot is shifted towards a QTL results in increased genetic gain (Gonen et al., 2017). These results are indicative of the need for further exploration of this trait, mainly as a way of introducing exploitable genetic variability. Therefore, the objectives of this study were to investigate the differences in meiotic recombination between classes of swine breed, sex and age, as well as to measure the additive genetic component of variance and identify important genomic regions underlying genome-wide recombination rate using a genome-wide association study (GWAS).

2 | MATERIALS AND METHODS

2.1 | Animals and recombination event estimation

To detect recombination events, family trios were created, consisting of sire, dam and their respective progeny. Animals belonged to either the Landrace (LR) or Large White (LW) breed and came from Smithfield Premium Genetics (SPG; Rose Hill, NC) nucleus lines. Birth years for the populations were from 2009 to 2016 for LR animals and from 2007 to 2016 for LW animals. Genotype data included individuals genotyped with porcine chips of 60K (PorcineSNP60K Bead Chip; Illumina Inc.) (n = 6,574) or 80K (GGP Porcine HD v1 80K; GeneSeek Inc., Neogen Co.) (n = 25,347) densities. All individuals were imputed to the 60K density using FImpute (Sargolzaei et al., 2014). FindhapV4 (VanRaden et al., 2011) was subsequently employed to obtain crossover events for all trios. The data for the trios consisted of the total number of crossovers for each progeny/chromosome/parent combination. A recombination event was detected as the appearance of a new haplotype(s) in the offspring of the trio. Phased genotype recombinations were then assigned to either the sire or the dam for the estimation of maternal and paternal

recombinations. Overall, recombination events were detected for 281 LR sires, 1,356 LR dams, 270 LW sires and 1,755 LW dams. A summary of the data can be found in Table 1.

Traits analysed in this study included genome-wide recombination rate (GWRR) which was obtained from the aggregation of observed recombination events across the genome and recombination occurrence (RO) at each of the 18 autosomal chromosomes (SSC1-SSC18). RO was analysed as a binary trait due to data structure, where for all chromosomes, the number of meiosis events where recombination occurred more than once was not enough to justify further categories. Therefore, the phenotypes for RO were the presence/absence of at least one recombination event at a particular chromosome.

To investigate potential environmental effects on recombination, age at meiosis was obtained for dams and sires. Due to the possible confounding between dam age at meiosis and parity, we opted for using only the latter in the subsequent analyses. For sires, the age at meiosis was calculated starting from progeny birth date by subtracting 113 days for gestation and another 35 days to account for the time to spermatogenesis (Zeng et al., 2006). Age at meiosis in sires was further classified into 4 groups based on the quartiles of the distribution for ease of interpretation of results, with the mean age at meiosis being 209.5, 267.5, 340.5 and 710 days for groups 1–4, respectively.

2.2 | Interpopulation variation

We estimated the effects of breed, sex and age for all traits using PROC GLIMMIX in SAS (v. 9.4, SAS Institute Inc.) with the following model (model I):

$$y_{ijklmn} = \mu + \text{Breed}_i + \text{Sex}_j + \text{Age}_{k(j)} + \text{Breed} \times \text{Sex}_{i:j} + p_{l\,(i:j)} + \text{cg}_m + e_{ijklmn} \quad (1)$$

where y_{ijklmn} is the phenotypic observation for the investigated trait; μ is the overall intercept; Breed_i is the fixed effect of the ith class of breed (i = LR, LW); Sex_j is the fixed effect of the jth class of sex (j = sire, dam); $\text{Age}_{k(j)}$ is the fixed effect of the kth class of parity (k = 1, 2, 3, ≥4) or sire age class at meiosis (k = 1, 2, 3, 4) nested within jth class of sex; $\text{Breed} \times \text{Sex}_{i:j}$ is the fixed effect of the interaction between the ith class of breed and jth class of sex; $p_{l(i:j)}$ is the random effect of the lth parent within ith class of breed and jth class of sex; cg_m is the random effect of the mth contemporary group calculated as the concatenation of year, season and farm at the time of recombination; and e_{ijklmn} is the random residual. All the random effects were assumed normally and independently distributed with mean equal to zero and variance equal to σ^2_{P} for the parent effect, σ^2_{CG} for the contemporary group effect and σ^2_{E} for the residual. For RO, the DIST and LINK options were used to specify a binary distribution underlying the data and a probit link, respectively. Least square means were estimated for all effects using the PROC GLIMMIX LSMEANS statement, and additionally, estimates for RO were transformed from the underlying liability scale to probability scale using PROC PLM in SAS (v. 9.4, SAS Institute Inc.) and stating the ILINK option, which applies the inverse link function. Statistical significance was considered at the $\alpha = .05$ level.

2.3 | Intrapopulation variation

Variance components, as well as heritability and repeatability estimates for GWRR and RO at 18 chromosomes (SSC1-SSC18), were estimated using the THRGIBBS1F90 software (v. 2.116) (Tsuruta & Misztal, 2006) for each of the four breed/sex combinations, where a single-trait threshold model was used for RO. The PREGSF90 software (v. 1.21) (Aguilar et al., 2014) was used for quality control of genotypes with default settings, including removal of monomorphic SNPs, and SNPs with minor allele frequency <0.05 and/or call rate <0.90. The model (model II) used for this analysis had the form:

$$y_{ijklm} = \text{CG}_i + \text{AGE}_j + a_k + pe_l + e_{ijlkm} \quad (2)$$

where y_{ijklm} is the investigated trait; CG_i is the fixed effect of ith class of contemporary group; AGE_j is the fixed effect for jth class of dam parity or sire age at meiosis depending on population modelled; a_k is the random additive effect k of the parent, following $a \sim N(0, \mathbf{H}\sigma^2_a)$, where $\mathbf{H}$ is the relationship matrix blending the numerator and realized relationship matrices using ssGBLUP methodology (Legarra et al., 2009), and σ^2_a is the additive genetic variance; pe_l is the random permanent environmental effect l of the parent, following $pe \sim N(0, \mathbf{I}\sigma^2_{pe})$, where $\mathbf{I}$ is an identity matrix, and σ^2_{pe} is the permanent environmental variance; and e_{ijklm} is the random residual, following $e \sim N(0, \mathbf{I}\sigma^2_e)$, σ^2_e is the residual variance and $\mathbf{I}$ is as described before. The residual variance was fixed at 1 for identifiability when analysing RO.

All analyses were run for 150,000 cycles with a burn-in of 50,000 and every 10th sample being stored, for a total of 10,000 samples for subsequent inference. Heritability (h^2) and repeatability (r) were calculated at every iteration using:

$$h^2 = \frac{\sigma^2_a}{\sigma^2_a + \sigma^2_{pe} + \sigma^2_e}; r = \frac{\sigma^2_a + \sigma^2_{pe}}{\sigma^2_a + \sigma^2_{pe} + \sigma^2_e}$$

Additionally, bivariate analyses were conducted by extending model II to fit multiple traits, so that the genetic correlation between the same trait measured in different sexes within breed (i.e. genetic correlation between GWRR of LR sires and dams)

could be obtained. Bivariate analyses were run for 300,00 cycles with a burn-in of 100,000 and every 10th sample being stored, for a total of 20,000 samples for subsequent inference. Convergence for both the single-trait and multiple trait analyses was assessed using the geweke.diag function of the "coda" package (v. 0.19-2) (Plummer et al., 2006) in R (v. 3.5.1), where a *Z*-score within −2 and 2 was taken as evidence of convergence. Posterior means, standard deviations and highest posterior densities were obtained for all the parameters of interest. The posterior mean and standard deviation of the parameters calculated at every iteration was used as estimates of the trait parameter (heritability, repeatability or genetic correlation) and standard error, respectively.

2.4 | GWAS for genome-wide recombination

A GWAS was conducted on each breed/sex combination for genome-wide recombination using a single-step approach (Legarra et al., 2009) with the same model as the variance component estimation analysis (model II). Variance explained by 10 SNP overlapping windows was calculated using previously published methods (Bergamaschi et al., 2020; Tiezzi et al., 2020). Two thresholds were arbitrarily set for calling relevant windows for subsequent analysis, a low threshold (window explained at least 0.3% variance) and a high threshold (window explained at least 0.5% variance). For the selected regions of interest, a bootstrapping analysis with 1,000 iterations was performed, where an empirical $\alpha = .05$ was used to establish significance similarly to what is previously reported in (Howard et al., 2015). Overlapping windows that were declared significant after the bootstrapping analysis were merged into a larger window of interest. These windows were then used for identifying potential candidate genes for GWRR in the four sex/breed combination populations. Annotation of genes was performed in R with the "*biomaRt*" package (v. 2.40.4) (Durinck et al., 2009) using the "org.Ss.eg.db" database. ENTREZ gene ID's for the genes of interest were obtained and passed to the enrichGO function of "*clusterProfiler*" package (v. 3.12.0) (Yu et al., 2012) in R for gene ontology (GO) enrichment, with special focus on enriched terms of the biological process classification.

3 | RESULTS

3.1 | Descriptive statistics

A summary of the animals included in the analysis can be found in Table 1, including the number of animals, the number of progeny per sex/breed combination, and the average, minimum and maximum number of progeny per animal per sex/breed combination. The distribution of GWRR and incidence of RO at each chromosome in each sex/breed combination are presented in Figures 1 and 2, respectively.

3.2 | Differences between breeds, sexes and age groups

Results for this analysis, reported as least square means, can be found in Tables 2 and 3. Significant differences among breeds were found for GWRR, and RO at SSC1, SSC2, SSC3, SSC10, SSC11, SSC12, SSC15, SSC16 and SSC18. LW showed higher GWRR and RO at SSC2, SSC3, SSC10, SSC11, SSC12, SSC16 and SSC18, but lower than SSC1 and SSC15 of LR. Differences between sires and dams were found for both traits. Females had higher rates of meiotic recombination, with GWRR and RO at all chromosomes being higher in sows. The interaction between breed and sex was also fitted in the model and was significant for both traits. For GWRR and RO at all chromosomes except SSC1, both groups of dams had higher lsmeans than LR and LW sires. For RO at SSC1, LW sires had significantly lower recombination incidence than LR sires and both groups of dams. LW and LR sires also differed for RO at SSC2 and SSC16, where LW sires had significantly higher recombination incidence than LR sires. Differences between LR and LW dams were found for RO at SSC10, SSC11, SSC12 and SSC18, where LW dams had higher recombination incidence than LR dams. All four groups differed from each other for RO at SSC3, where LW dams had the highest recombination incidence and LR sires had the lowest.

The effect of age was also investigated since it has been previously linked to differences in recombination rate (Campbell et al., 2015; Wang et al., 2016). For GWRR and RO at all chromosomes except SSC3 and SSC14, no significant difference was found between the sire age groups. Sires in age groups 1 and 2 had higher RO at SSC3 than sires in age group 4 and lower at SSC14 than sires in age group 3. For dams, four age groups were created according to parity (1, 2, 3 and ≥4 parities). Significant differences between dams in different parity groups were found for GWRR and RO at SSC1, SSC5, SSC7, SSC14 and SSC15. Dams that had four or more parities had higher GWRR than parities 1 and 2 dams, higher RO at SSC1, SSC7 and SSC14 than parity 1 dams, higher RO at SSC5 than parity 3 dams and higher RO at SSC15 than parity 2 dams.

3.3 | Heritability, repeatability and genetic correlations of recombination traits

Heritability of each trait for all breed/sex combinations can be found in Figure 3a. All heritability estimates in this study were low, ranging from 0.01 to 0.26. For GWRR, heritability

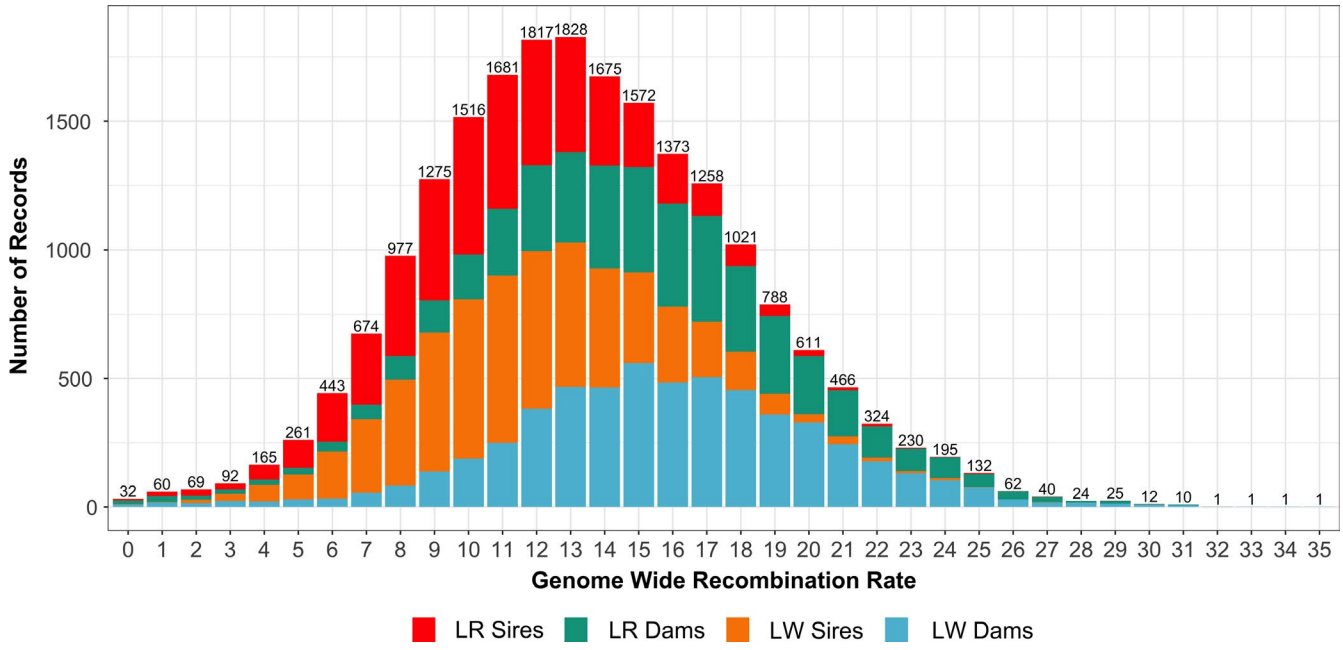


FIGURE 1 Distribution of phenotypes for genome-wide recombination rate in the four populations. The *y*-axis represents the number of records for each value of genome-wide recombination rate represented in the *x*-axis. The colours represent the four populations: Landrace sires (red), Landrace dams (green), Large White sires (orange) and Large white dams (light blue)

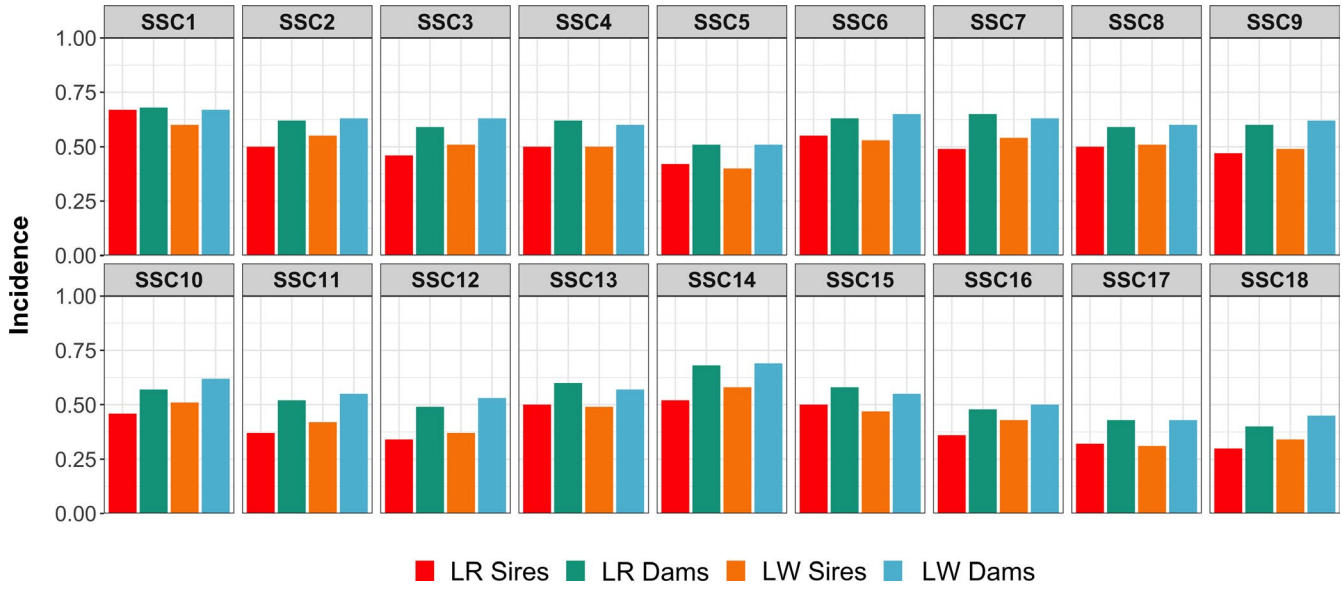


FIGURE 2 Incidence of recombination occurrence at 18 pig (*Sus scrofa*) chromosomes (SSC) for each population. Each bar plot represents an individual chromosome, starting from chromosome 1 (SSC1) up to chromosome 18 (SSC18). The *y*-axis represents the incidence of recombination which can range from 0 to 1. The *x*-axis represents each population: Landrace sires (red), Landrace dams (green), Large White sires (orange) and Large white dams (light blue)

estimates were noticeably higher for dams, ranging from 0.23 ($SE = 0.03$) to 0.26 ($SE = 0.03$), than sires, which ranged from 0.05 ($SE = 0.04$) to 0.08 ($SE = 0.04$). For RO, LR sires had the highest heritability at SSC10 (0.12, $SE = 0.06$), and estimates ranging from 0.03 ($SE = 0.02$) to 0.11 ($SE = 0.05$) for RO at the remaining chromosomes; LR dams had the highest estimate for RO at SSC7 (0.09, $SE = 0.03$), and estimates ranging from 0.02 ($SE = 0.02$) to 0.08 ($SE = 0.03$) for RO at the remaining chromosomes; LW sires had the highest estimate for RO at SSC10, SSC14 and SSC17, all three with estimates of 0.11 ($SE = 0.05$, 0.05 and 0.06 for SSC10, SSC14 and SSC17, respectively) and estimates ranging from

TABLE 2 Least Squares Means (*SE* within parenthesis) results for the effects of breed, sex, and breed×sex in model I

	Least Square Means*							
	Breed		Sex		Breed×Sex			
Trait	LR	LW	Sire	Dam	LR sire	LW sire	LR dam	LW dam
GWRR	13.14^{a} (0.14)	13.55^{b} (0.13)	11.10^{a} (0.16)	15.59^{b} (0.14)	10.82^{a} (0.22)	11.38^{a} (0.22)	15.45^{b} (0.16)	15.72^{b} (0.15)
RO								
SSC1	0.69^{a} (0.01)	0.66^{b} (0.01)	0.65^{a} (0.01)	0.70^{b} (0.01)	0.67^{ab} (0.02)	0.62^{a} (0.02)	0.70^{b} (0.01)	0.69^{b} (0.01)
SSC2	0.57^{a} (0.01)	0.61^{b} (0.01)	0.54^{a} (0.01)	0.64^{b} (0.01)	0.50^{a} (0.02)	0.58^{b} (0.02)	0.64^{c} (0.01)	0.64^{c} (0.01)
SSC3	0.53^{a} (0.01)	0.58^{b} (0.01)	0.48^{a} (0.01)	0.63^{b} (0.01)	0.45^{a} (0.02)	0.52^{b} (0.02)	0.61^{c} (0.01)	0.64^{d} (0.01)
SSC4	0.56^{a} (0.01)	0.55^{a} (0.01)	0.49^{a} (0.01)	0.62^{b} (0.01)	0.48^{a} (0.02)	0.50^{a} (0.02)	0.63^{b} (0.01)	0.61^{b} (0.01)
SSC5	0.45^{a} (0.01)	0.44^{a} (0.01)	0.38^{a} (0.01)	0.51^{b} (0.01)	0.39^{a} (0.02)	0.37^{a} (0.02)	0.51^{b} (0.01)	0.51^{b} (0.01)
SSC6	0.59^{a} (0.01)	0.58^{a} (0.01)	0.52^{a} (0.01)	0.65^{b} (0.01)	0.54^{a} (0.02)	0.51^{a} (0.02)	0.63^{b} (0.01)	0.65^{b} (0.01)
SSC7	0.60^{a} (0.01)	0.59^{a} (0.01)	0.51^{a} (0.01)	0.68^{b} (0.01)	0.50^{a} (0.02)	0.51^{a} (0.02)	0.69^{b} (0.01)	0.66^{b} (0.01)
SSC8	0.54^{a} (0.01)	0.54^{a} (0.01)	0.48^{a} (0.01)	0.60^{b} (0.01)	0.49^{a} (0.02)	0.48^{a} (0.02)	0.59^{b} (0.01)	0.60^{b} (0.01)
SSC9	0.55^{a} (0.01)	0.56^{a} (0.01)	0.47^{a} (0.01)	0.64^{b} (0.01)	0.47^{a} (0.02)	0.48^{a} (0.02)	0.63^{b} (0.01)	0.64^{b} (0.01)
SSC10	0.52^{a} (0.01)	0.57^{b} (0.01)	0.48^{a} (0.01)	0.61^{b} (0.01)	0.46^{a} (0.02)	0.50^{a} (0.02)	0.59^{b} (0.01)	0.64^{c} (0.01)
SSC11	0.45^{a} (0.01)	0.49^{b} (0.01)	0.39^{a} (0.01)	0.55^{b} (0.01)	0.38^{a} (0.02)	0.41^{a} (0.02)	0.53^{b} (0.01)	0.57^{c} (0.01)
SSC12	0.40^{a} (0.01)	0.44^{b} (0.01)	0.34^{a} (0.01)	0.51^{b} (0.01)	0.33^{a} (0.02)	0.36^{a} (0.02)	0.48^{b} (0.01)	0.53^{c} (0.01)
SSC13	0.55^{a} (0.01)	0.54^{a} (0.01)	0.49^{a} (0.01)	0.60^{b} (0.01)	0.49^{a} (0.02)	0.50^{a} (0.02)	0.62^{b} (0.01)	0.58^{b} (0.01)
SSC14	0.63^{a} (0.01)	0.65^{a} (0.01)	0.56^{a} (0.01)	0.72^{b} (0.01)	0.54^{a} (0.02)	0.57^{a} (0.02)	0.71^{b} (0.01)	0.72^{b} (0.01)
SSC15	0.55^{a} (0.01)	0.52^{b} (0.01)	0.49^{a} (0.01)	0.58^{b} (0.01)	0.50^{a} (0.02)	0.47^{a} (0.02)	0.59^{b} (0.01)	0.56^{b} (0.01)
SSC16	0.41^{a} (0.01)	0.46^{b} (0.01)	0.36^{a} (0.01)	0.51^{b} (0.01)	0.32^{a} (0.02)	0.39^{b} (0.02)	0.50^{c} (0.01)	0.53^{c} (0.01)
SSC17	0.35^{a} (0.01)	0.35^{a} (0.01)	0.29^{a} (0.01)	0.42^{b} (0.01)	0.29^{a} (0.02)	0.28^{a} (0.01)	0.42^{b} (0.01)	0.41^{b} (0.01)
SSC18	0.33^{a} (0.01)	0.38^{b} (0.01)	0.30^{a} (0.01)	0.41^{b} (0.01)	0.29^{a} (0.01)	0.32^{a} (0.02)	0.39^{b} (0.01)	0.44^{c} (0.01)

Abbreviations: GWRR, genome-wide recombination rate; LR, Landrace; LW, Large White; RO, recombination occurrence; SSC, *Sus scrofa* chromosome.

*Estimates followed by different letters are significantly different ($\alpha = .05$).

0.03 (*SE* = 0.03) to 0.10 (*SE* = 0.05) for RO at the remaining chromosomes; LW dams had the highest estimate for RO at SSC8 (0.07, *SE* = 0.02), and estimates ranging from 0.01 (*SE* = 0.01) to 0.06 (*SE* = 0.02) for RO at the remaining chromosomes. The estimates for additive genetic variance for RO at SSC1, SSC2 and SSC13 for LR dams, SSC4 and SSC8 for LW sires, SSC12 for LR sires and dams as well as LW sires did not converge; therefore, heritability estimates are not presented for these traits.

The estimates of repeatability of each trait are presented in Figure 3b. The repeatability of GWRR was low in all four populations, with estimates of 0.28 (*SE* = 0.03) for LR sires, 0.39 (*SE* = 0.02) for LR dams, 0.27 (*SE* = 0.03) for LW sires and 0.42 (*SE* = 0.02) for LW dams. The repeatability of RO traits was also low for all populations, with estimates ranging from 0.18 (SSC5, *SE* = 0.02) to 0.26 (SSC15, *SE* = 0.03) for LR sires, from 0.20 (SSC10, *SE* = 0.02) to 0.28 (SSC14, *SE* = 0.03; SSC16, *SE* = 0.02) for LR dams, from 0.18 (SSC3, *SE* = 0.03) to 0.26 (SSC11, *SE* = 0.03) for LW sires and from 0.17 (SSC13, *SE* = 0.02) to 0.33 (SSC1, *SE* = 0.02) for LW dams. The estimate(s) of additive and/or permanent environmental variance for RO at SSC1, SSC2 and SSC9 for LR dams, SSC6 and SSC8 for LW sires, SSC4 and SSC13 for LR dams and LW sires, and SSC12 for LR sires and dams as well as LW sires did not converge; therefore, repeatability estimates are not presented for these traits.

The genetic correlation between male and female GWRR was positive and very high in both breeds, with estimates of 0.98 (*SE* = 0.05) and 0.94 (*SE* = 0.09) for the LR and LW breeds, respectively. The estimates of genetic correlation between male and female RO occurrence traits can be found in Appendix S5.

3.4 | Significant genome regions for genome-wide recombination rate

A GWAS was done for GWRR in each breed/sex population, where the primary focus was identifying significant genomic regions by estimating variance explained by overlapping 10 SNP windows. A Manhattan plot of variance explained by window can be found in Figure 4, with significance

TABLE 3 Least Squares Means (*SE* within parenthesis) results for the effect of age in model I

	Least square means*							
	Sire age†				Dam parity			
Trait	1 (209.5)	2 (267.5)	3 (340.5)	4 (710)	1	2	3	≥4
GWRR	11.05^{a} (0.19)	11.12^{a} (0.18)	11.06^{a} (0.18)	11.19^{a} (0.22)	15.12^{a} (0.13)	15.30^{a} (0.16)	15.76^{ab} (0.25)	16.17^{b} (0.25)
RO								
SSC1	0.66^{a} (0.02)	0.64^{a} (0.02)	0.65^{a} (0.02)	0.64^{a} (0.02)	0.68^{a} (0.01)	0.69^{ab} (0.01)	0.68^{ab} (0.03)	0.74^{b} (0.02)
SSC2	0.53^{a} (0.02)	0.55^{a} (0.02)	0.53^{a} (0.02)	0.53^{a} (0.02)	0.63^{a} (0.01)	0.62^{a} (0.01)	0.63^{a} (0.03)	0.68^{a} (0.02)
SSC3	0.50^{a} (0.02)	0.52^{a} (0.02)	0.48^{ab} (0.02)	0.43^{b} (0.02)	0.60^{a} (0.01)	0.62^{a} (0.01)	0.61^{a} (0.03)	0.66^{a} (0.02)
SSC4	0.49^{a} (0.02)	0.50^{a} (0.02)	0.47^{a} (0.02)	0.49^{a} (0.02)	0.62^{a} (0.01)	0.61^{a} (0.01)	0.64^{a} (0.03)	0.61^{a} (0.02)
SSC5	0.39^{a} (0.02)	0.38^{a} (0.02)	0.38^{a} (0.02)	0.36^{a} (0.02)	0.51^{ab} (0.01)	0.51^{ab} (0.01)	0.46^{a} (0.03)	0.56^{b} (0.02)
SSC6	0.52^{a} (0.02)	0.52^{a} (0.02)	0.51^{a} (0.02)	0.55^{a} (0.02)	0.65^{a} (0.01)	0.65^{a} (0.01)	0.63^{a} (0.03)	0.64^{a} (0.02)
SSC7	0.50^{a} (0.02)	0.51^{a} (0.02)	0.50^{a} (0.02)	0.52^{a} (0.02)	0.64^{a} (0.01)	0.67^{ab} (0.01)	0.67^{ab} (0.03)	0.73^{b} (0.02)
SSC8	0.48^{a} (0.02)	0.46^{a} (0.02)	0.48^{a} (0.02)	0.51^{a} (0.02)	0.60^{a} (0.01)	0.60^{a} (0.01)	0.58^{a} (0.03)	0.61^{a} (0.02)
SSC9	0.48^{a} (0.02)	0.46^{a} (0.02)	0.48^{a} (0.02)	0.48^{a} (0.02)	0.60^{a} (0.01)	0.64^{a} (0.01)	0.67^{a} (0.03)	0.64^{a} (0.02)
SSC10	0.48^{a} (0.02)	0.50^{a} (0.02)	0.48^{a} (0.02)	0.47^{a} (0.02)	0.59^{a} (0.01)	0.60^{a} (0.01)	0.65^{a} (0.03)	0.61^{a} (0.02)
SSC11	0.39^{a} (0.02)	0.38^{a} (0.02)	0.38^{a} (0.02)	0.41^{a} (0.02)	0.53^{a} (0.01)	0.55^{a} (0.01)	0.56^{a} (0.03)	0.58^{a} (0.02)
SSC12	0.34^{a} (0.02)	0.35^{a} (0.02)	0.34^{a} (0.02)	0.35^{a} (0.02)	0.51^{a} (0.01)	0.49^{a} (0.01)	0.48^{a} (0.03)	0.54^{a} (0.02)
SSC13	0.48^{a} (0.02)	0.49^{a} (0.02)	0.51^{a} (0.02)	0.49^{a} (0.02)	0.58^{a} (0.01)	0.59^{a} (0.01)	0.66^{a} (0.03)	0.57^{a} (0.02)
SSC14	0.53^{a} (0.02)	0.53^{a} (0.02)	0.60^{b} (0.02)	0.57^{ab} (0.02)	0.69^{a} (0.01)	0.69^{ab} (0.01)	0.73^{ab} (0.02)	0.75^{b} (0.02)
SSC15	0.51^{a} (0.02)	0.50^{a} (0.02)	0.46^{a} (0.02)	0.48^{a} (0.02)	0.56^{ab} (0.01)	0.55^{a} (0.01)	0.56^{ab} (0.03)	0.63^{b} (0.02)
SSC16	0.37^{a} (0.02)	0.37^{a} (0.02)	0.35^{a} (0.02)	0.35^{a} (0.02)	0.48^{a} (0.01)	0.49^{a} (0.01)	0.54^{a} (0.03)	0.54^{a} (0.02)
SSC17	0.29^{a} (0.01)	0.29^{a} (0.01)	0.29^{a} (0.02)	0.29^{a} (0.02)	0.43^{a} (0.01)	0.43^{a} (0.01)	0.39^{a} (0.03)	0.42^{a} (0.02)
SSC18	0.31^{a} (0.01)	0.32^{a} (0.01)	0.30^{a} (0.02)	0.30^{a} (0.02)	0.42^{a} (0.01)	0.41^{a} (0.01)	0.41^{a} (0.03)	0.41^{a} (0.02)

Abbreviations: GWRR, genome-wide recombination rate; RO, recombination occurrence; SSC, *Sus scrofa* chromosome.

*Estimates followed by different letters are significantly different ($\alpha = .05$).

†Average age in days for each group is presented under parenthesis.

considered at "low" (0.3%) and "high" (0.5%) variance explained thresholds, which have been previously used to establish significance (Medeiros de Oliveira Silva et al., 2017; Oliveira et al., 2019). Variance explained by the top five windows in each population can be found in Table 4, alongside genes mapped inside each window. In LR sires, the top five windows were located in chromosomes 4, 10 and 13 and explained from 1.24% to 1.49% of the total variance; in LR dams, the top five windows were all located in chromosome 14 and explained from 1.35% to 2.09% of the total variance; in LW sires, the top five windows were located in chromosomes 1 and 7 and explained from 1.82% to 3.58% of the total variance; in LW dams, the top five windows were located in chromosomes 8 and 12 and explained from 2.01% to 2.46% of the total variance.

Significant overlapping windows were merged, resulting in a total of 115 and 48 significant non-overlapping windows identified in LR sires, 92 and 37 in LR dams, 103 and 40 in LW sires and 83 and 37 in LW dams for the low and high variance thresholds, respectively. Genes in the non-overlapping genomic windows were identified. A Venn diagram of unique and shared genes between the populations studied at both variance explained thresholds is presented in Figure 5. The majority of genes identified were population-specific, with 401 and 155 genes solely identified in LR sires, 415 and 112 genes solely identified in LR dams, 420 and 147 genes solely identified in LW sires and 250 and 116 genes solely identified in LW dams, for the low and high thresholds, respectively. The number of genes shared exclusively between members of a breed, 48 (low threshold) and 17 (high threshold) between LR animals, and 33 (low threshold) and 6 (high threshold) between LW animals, was found to be generally higher than the number of genes shared exclusively between members of a given sex, 27 (low threshold) and 3 (high threshold) for sires, and 5 (low threshold) and 3 (high threshold) for dams. Overall, six genes were found to be shared across all four populations at the low threshold, ATF1, ENSSSCG00000051669, TMPRSS12, METRNL, B3GNTL1 and ENSSSCG00000017136. GO enrichment analysis was performed for genes identified in both thresholds

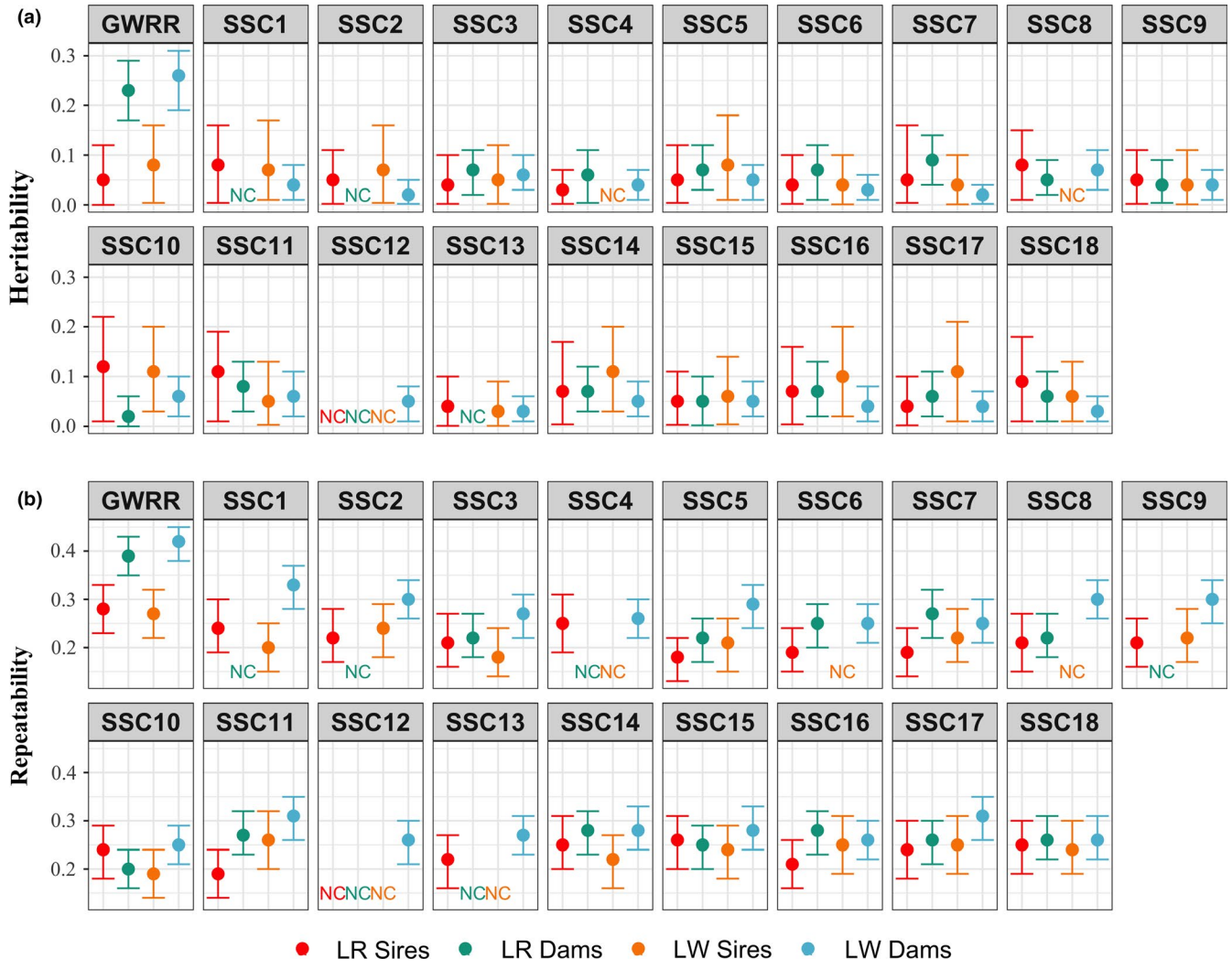


FIGURE 3 Heritability (a) and repeatability (b) estimates for genome-wide recombination rate and recombination occurrence at 18 pig (*Sus scrofa*) chromosomes (SSC) in the four populations: Landrace sires (red), Landrace dams (green), Large White sires (orange) and Large white dams (light blue). Estimates labelled as "NC" did not converge

to find significantly enriched GO terms relating to biological processes. The top 20 terms for adjusted *p*-value are presented in Figure 6 for both the low and high thresholds. No term was found to be significantly enriched for genes in either threshold.

4 | DISCUSSION

In the current work, we have explored differences in GWRR and RO in the porcine autosomes (SSC1-SSC18) across classes of breed, sex and age. The effect of breed on recombination was of special interest because of the scarcity of research that has been done to explore recombination features across populations in swine. Our results show that there exists variation in recombination between breeds of swine. For lsmeans results, when there was a significant difference between the two breeds, LW animals had higher means than LR, the exception being for RO at SSC1 and SSC15. Our results agree with previous studies done in swine and dairy cattle, where breed has been found to be an effect contributing to significant differences in recombination rate and related traits. In swine, breed differences for recombination rate have not been studied in depth. Nonetheless, evidence of linkage map differences between American, Swedish and European pig breeds has been previously found (Ollivier, 1995). In dairy cattle, a breed effect on recombination traits has been studied, with differences in the distribution of recombination rate and hotspot regions and similarity for global recombination patterns have been found between breeds (Shen et al., 2018). Meanwhile in sheep, the opposite phenomenon has been observed, where a high degree of similarity between the recombination maps of the distantly related Soay and Lacaune breeds has been found in males (Petit et al., 2017).

Heterochiasmy, which is the difference in recombination that exist between sexes of the same species, is a phenomenon

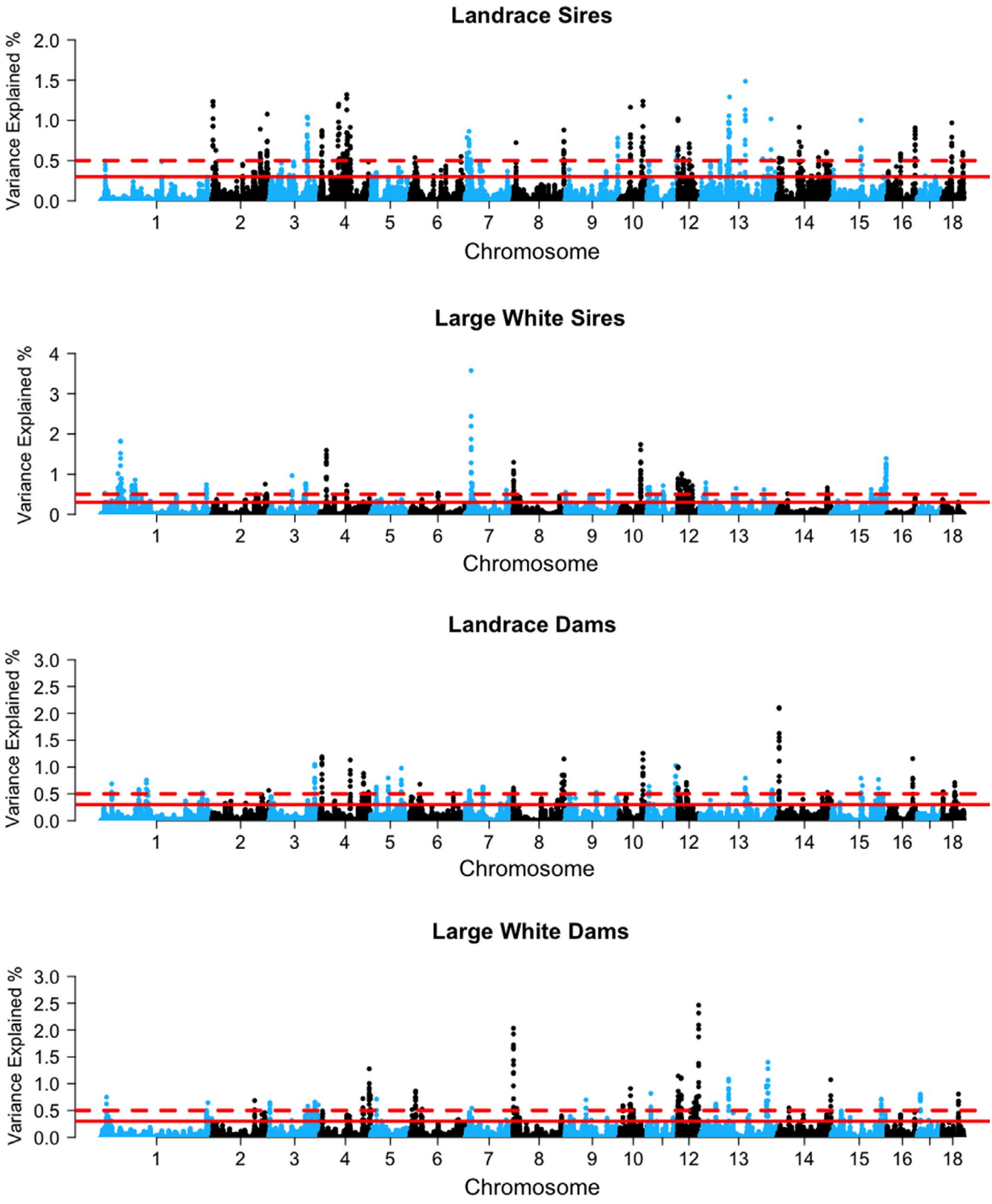


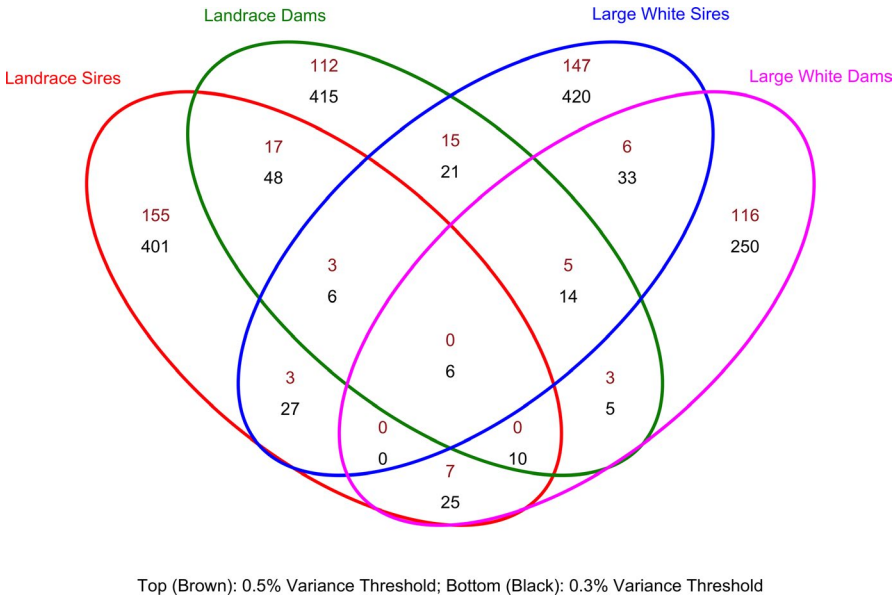
FIGURE 4 Manhattan plots for variance explained by 10 SNP windows. A Manhattan plot for each population is shown: Landrace sires (upper left), Landrace dams (lower left), Large White sires (upper right) and Large White dams (lower right). The *y*-axis represents the percentage of variance explained by each window. The *x*-axis represents the chromosome where each window is located. Thresholds to declare windows significant at the 0.3% (solid) and 0.5% (dashed) levels are shown in red

TABLE 4 Top 5 overlapping genomic windows for variance explained in each sex/breed combination and associated genes

Sex/Breed Combination	Chromosome	Start, Mb	Stop, Mb	σ^2, %	Genes
LR Sires	13	127.81	129.32	1.49	CLDN16, TMEM207, IL1RAP, GMNC, ENSSSCG00000031478, UTS2B, CCDC50, FGF12
	4	75.64	76.24	1.32	ENSSSCG00000032573, PLAG1, ENSSSCG00000006248, ENSSSCG00000040470, LYN, TGS1, TMEM68, XKR4
	13	83.04	83.46	1.29	XRN1, ATR, PLS1, TRPC1
	4	75.56	76.19	1.27	ENSSSCG00000036133, SDR16C5, ENSSSCG00000032573, PLAG1, ENSSSCG00000006248, ENSSSCG00000040470, LYN, TGS1, TMEM68, XKR4
	10	66.67	66.90	1.24	
LR Dams	14	5.10	5.28	2.09	
	14	5.15	5.39	1.63	
	14	5.14	5.38	1.55	
	14	5.25	5.45	1.37	
	14	5.19	5.44	1.35	
LW Sires	7	15.70	15.90	3.58	ENSSSCG00000045270, E2F3
	7	15.65	15.88	2.44	ENSSSCG00000045270, E2F3
	7	15.72	15.93	2.19	ENSSSCG00000045270, E2F3, CDKAL1
	7	15.63	15.85	1.87	MBOAT1, ENSSSCG00000045270, E2F3
	1	55.34	55.89	1.82	HTR1E, CGA, ZNF292, ENSSSCG00000042121, GJB7, SMIM8, C6orf163, SLC35A1, ENSSSCG00000004302
LW Dams	12	59.05	59.34	2.46	ZNF287, LRRC75A, TRPV2, UBB, ENSSSCG00000018034, PIGL, ENSSSCG00000050244
	12	58.99	59.21	2.32	ZNF624, ENSSSCG00000044615, ENSSSCG00000045078, ZNF287, LRRC75A, TRPV2, UBB, ENSSSCG00000018034, PIGL, ENSSSCG00000050244
	12	59.03	59.33	2.09	ZNF287, LRRC75A, TRPV2, UBB, ENSSSCG00000018034, ENSSSCG00000035103, ENSSSCG00000050244
	8	1.34	1.74	2.03	FAM193A, TNIP2, SH3BP2, ADD1, MFSD10, NOP14
	12	59.08	59.36	2.01	LRRC75A, TRPV2, UBB, ENSSSCG00000018034, ENSSSCG00000035103, ENSSSCG00000050244, ENSSSCG00000018039

Abbreviations: LR, Landrace; LW, Large White.

that has been heavily studied, with evidence found in many species including cattle (Ma et al., 2015; Shen et al., 2018; Wang et al., 2016), deer (Johnston et al., 2018), swine (Tortereau et al., 2012) and humans (Lynn et al., 2004). Our results agree with the existence of differences between sexes for recombination traits. Particularly, we found that sex was a significant effect for both traits studied, with dams having a higher genome-wide recombination rate and RO across all chromosomes. Our results are in general accordance with previous studies that have found higher estimates in females for recombination rate and autosomal crossover count (Johnston et al., 2018; Tortereau et al., 2012). On the contrary, in cattle, evidence has been found suggesting higher recombination rates in males than females in various breeds (Shen et al., 2018). Differences in recombination features between sexes in mice have been previously attributed to the



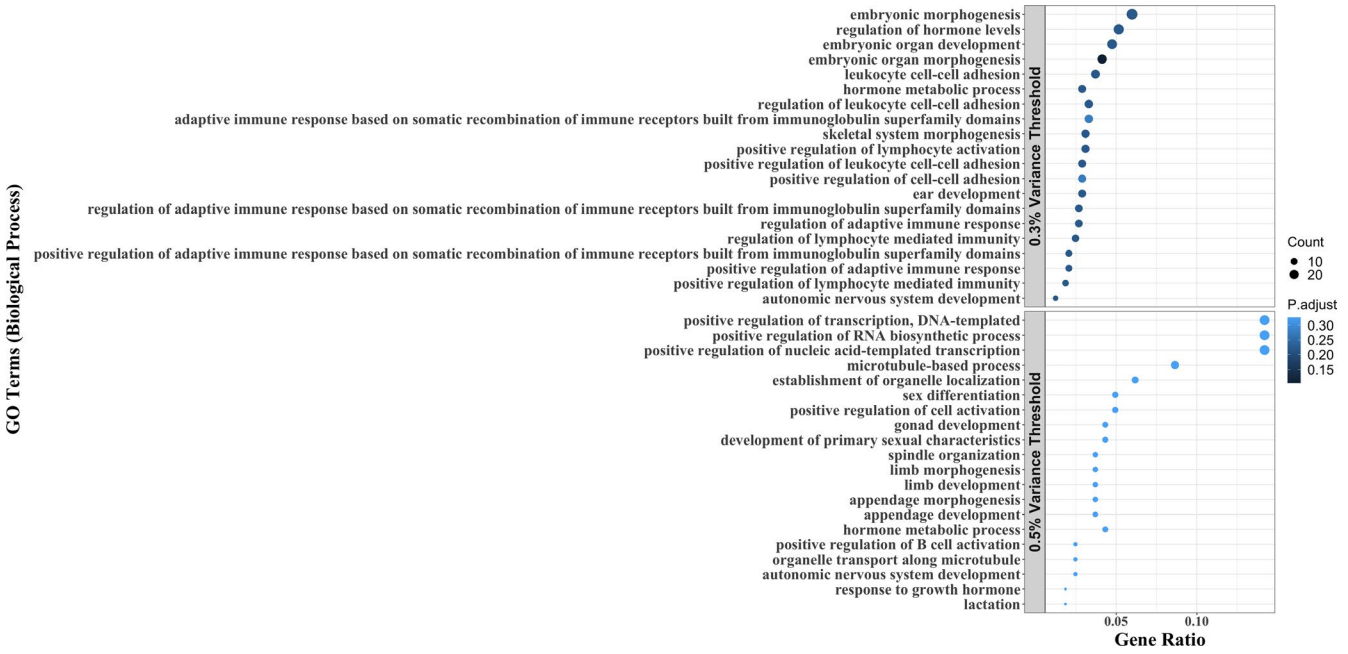


FIGURE 5 Venn diagram of the number of common and unique genes identified in the four populations

FIGURE 6 Biological process gene ontology (GO) terms. The top 20 GO terms for both the 0.3% and 0.5% variance explained thresholds are shown. The *x*-axis represents the gene ratio. The *y*-axis represents the GO terms. The adjusted *p*-value is shown by colour

formation of the synaptonemal complex during female meiosis (Lynn et al., 2005). Further research is needed to extend these findings in other mammalian species such as swine. To explore differences in recombination between our four populations, we fitted the interaction of sex and breed to model I. Significant differences were found between two or more populations for GWRR and RO, with the most consistent result being higher lsmeans for LR and LW dams compared to sires. This is indicative of sex being the predominant factor as opposed to breed for differences in GWRR and RO in the populations studied.

Evidence of recombination differences between classes of dam parity and classes of sire age at meiosis was found. Dams of the highest parity class (four or more parities) had significantly higher GWRR than parity 1 and 2 dams and higher RO than one or more age classes at SSC1, SSC5, SSC7, SSC14 and SSC15. The effect of maternal age on recombination has been well documented in humans, with direction and magnitude of effect varying between studies (Campbell et al., 2015; Hussin et al., 2011; Martin et al., 2015). While in cattle, when maternal age has been studied in relation to crossover interference, only a marginal

effect has been detected (Wang et al., 2016). The results of our study suggest a positive relationship between female age and recombination, one hypothesis that has been put forth to explain this is that high recombination rate increases the chance of a gamete successfully becoming a live birth (Kong et al., 2004), which becomes increasingly advantageous with age. Age did not affect recombination in sires for the most part, with only RO at SSC3 and SSC14 having a significant difference between sire age classes. Contrary to dams, increasing age did not influence sire recombination in a sole direction, with animals in sire age class 1 and 2 having a higher RO than sires in age class 4 at SSC3 and lower RO than sires in age class 3 at SSC14. Male age could potentially have an influential role in spermatogenesis, as higher male age is linked to non-disjunction, specifically disomy in humans (Griffin et al., 1995); however, most studies have found little to no effect of male age on recombination rate (Campbell et al., 2015; Hussin et al., 2011).

Heritability estimates in this study were low, which agrees with the low heritability consistently found for recombination traits across mammalian species (Johnston et al., 2016; Kadri et al., 2016; Kong et al., 2004; Sandor et al., 2012). Generally, there were no discernible differences between breeds with respect to heritability estimates for any trait studied. There was an apparent effect of sex on the heritabilities estimated, which is most evident for GWRR, with dams having significantly higher estimates than sires (0.23 for LR dams, 0.26 for LW dams, 0.05 for LR sires and 0.08 for LW sires). Differences in heritability estimates between males and females for recombination rate have been previously found in sheep (Johnston et al., 2016), red deer (Johnston et al., 2018) and dairy cattle (Kadri et al., 2016). The differences found are indicative that the phenotype for genome-wide recombination rate has greater environmental influences in the male sex. Repeatability estimates were low for all traits studied and in all four populations. Similarly to the heritability estimates, breed did not play a major role in differences between the populations for trait repeatability while sex contributed to significant differences in GWRR repeatability, with dams having higher repeatability than sires (0.39 for LR dams, 0.42 for LW dams, 0.28 for LR sires and 0.27 for LW sires). Similar studies done in layer chickens (Weng et al., 2019) and beef cattle (Weng et al., 2014) have found estimates of repeatability for genome-wide recombination in similar ranges as the present study. Genetic correlations were estimated within breed and between sexes for GWRR. Estimates were very high and positive in both breeds suggesting a shared genetic architecture for recombination between sexes. These results agree with a previous estimate (0.66) for the genetic correlation of male and female GWRR in dairy cattle reported by Kadri et al. (2016). However, a similar study done in humans found no correlation between sexes for recombination rate (Fledel-Alon et al., 2011), which is indicative of differences between swine and humans in the genetic architecture of sex-specific recombination rate. However, great caution should be employed in the interpretation of the results of the current study given that the different sexes differed in the average number of progeny included in the analysis (Table 1), this difference in family size between sexes could be a source of bias in the estimated variances.

Even though the results of the GWAS analysis highlighted regions of the genome potentially responsible for variation in recombination rate, we failed to find any major gene unequivocally responsible for genome-wide recombination rate across all populations. We found evidence that the four populations differed in the genomic regions that explained the highest amount of variance for this trait. Nonetheless, we discovered genes in common between the four populations, and between sex and breed classes. Even though breed was a more significant factor than sex for the number of genes shared, we will restrict the discussion to genes found exclusively between members of a given sex as they might relate to heterochiasmy. The E2F transcription factor 3 (E2F3) gene was found to be shared between the sire population at both threshold levels and was found to be present in the top genomic windows in the LW sire population. The E2F gene is a member of the E2F gene family, which has been found to have a role in DNA replication, cell proliferation and cell cycle transition, being linked to transcriptional activation as well as transcriptional repression (Leone et al., 1998; Rotgers et al., 2019). Genes of interest identified solely in dams include Jumonji and AT-rich interaction domain containing 2 (JARID2) and Paired box 3 (PAX3). These genes were found to be shared between dams at the low threshold level and have functions related to cell cycle regulation, specifically with cell proliferation and transcription regulation with chromatin remodelling (Boudjadi et al., 2018; Sanulli et al., 2015). None of the genes identified in all four populations were found to have any explicit role in meiotic recombination. In LR dams, we found Glutamate-cysteine ligase modifier subunit (GCLM), a gene that has been previously associated with genome-wide recombination rate in Holstein cattle (Ma et al., 2015). The GCLM gene has been hypothesized to have a role in oocyte spindle function and pronucleus development via the enzymatic control of the intracellular antioxidant glutathione (GSH). A few genes, such as REC8, REC114, CPLX1 and RNF212B, have been found in multiple studies (Baudat et al., 2013; Johnston et al., 2018; Sandor et al., 2012; Shen et al., 2018) to be highly associated with genome-wide recombination rate and related traits such as hotspot activity. None of these genes were found in the present analysis for any population studied, which might be due to differences in the genetic architecture for recombination rate between species, differences

in trait definitions and/or the relatively small sample size of the current investigation. Overall, we intend the results of the GWAS to be taken as a starting point for further study into the genomic architecture of recombination rate in swine, as the current lack of information available precludes any comparison with the results found.

5 | CONCLUSION

In this study, the effects of breed, sex and age were found to contribute significantly to differences in meiotic recombination in swine. We anticipate the results for sex differences to contribute to the large body of evidence for this phenomenon, and the results for breed and age to be a starting point for further research that looks into the implementation of this information in swine. The phenotypic variance of GWRR and RO was found to have a sizable additive genetic component, especially for GWRR in dams, which can be used to justify the inclusion of these traits as targets of selection in swine. The genetic correlation estimates found indicate a shared genetic architecture for recombination between sexes. However, the results of the GWAS performed showed preliminary evidence of sex and breed differences in the identified genomic regions that explained the largest amount variance. Further research should be done to investigate the genetic architecture of recombination in swine with a larger number of individuals to validate the present results and identify the merit of inclusion of recombination traits in swine selection programs.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used in this study, including animal pedigree and genotypic information, are the sole property of SPG (Rose Hill, NC). Restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of SPG. A request to SPG for accessing data may be sent to Kent Gray, General Manager (kgray@smithfield.com).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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