Bhatia, V., Fortin, F., Harding, J., Dyck, M., Plastow, G., PigGen Canada, Dekkers, J. (2026) Association of natural variation in the CD163 and CD169 genes with disease resilience of grow-finish pigs, *Proceedings 13th World Congress on Genetics Applied to Livestock Production* 23625: https://doi.org/10.31274/wcgalp.23625 ©2026 Bhatia, et al. CC BY-NC-ND

Association of natural variation in the CD163 and CD169 genes with disease resilience of grow-finish pigs

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Introduction

Porcine reproductive and respiratory syndrome (PRRS) continues to be one of the costliest infectious diseases in pigs. Host genetics plays an important role in PRRS virus (PRRSV) susceptibility and disease outcomes, including key genes like *CD163* and *CD169.* Several strategies have been developed to mitigate the effects of PRRSV, including the knocking out of exons of *CD163*, creating complete resistance (Whitworth *et al.*, 2016). However, the use of gene-edited pigs is limited by the high cost and technical complexity of their integration in breeding programs, by regulatory issues, and by societal acceptance issues. Selection on genetic markers associated with disease resilience offers an alternative, as it can be implemented in nucleus breeding programs, where direct selection for disease resilience is not feasible because they must be kept disease-free. Genome-wide association studies of experimental PRRSV infection have identified SNP WUR10000125 (WUR) as strongly associated with host response to PRRSV (Boddicker *et al.,* 2012; Waide *et al.,* 2017), with subsequent fine-mapping localizing the effect to *GBP5* (Koltes *et al.,* 2015), conferring partial resistance. The SNP panels used did, however, not include *CD163* and *CD169* because they were not included in the genome build that these panels were based on. Subsequently, Dong *et al.* (2021) genotyped pigs from the studies of Waide *et al.* (2017) for SNPs in *CD163* and *CD169* and found several associations with response to PRRSV infection, as well as interaction effects with WUR. In parallel, Putz *et al.* (2019) and Cheng *et al.* (2020) used data from a large-scale natural polymicrobial disease challenge model (NDCM), which included PRRSV, to study the genetic basis of disease resilience. A GWAS of these data by Cheng *et al.* (2022) was again based on a panel that did not include *CD163* and *CD169,* but Jeon *et al.* (2021) did find WUR to be associated with disease resilience in the NDCM. Against this background, our objective was to investigate associations of the naturally occurring SNPs in *CD163* and *CD169* of Dong *et al.* (2021) with disease resilience in the NDCM and their interactions with WUR.

Materials & Methods

Data. Data used were from the first 50 batches of the NDCM, which consisted of three phases: a biosecure quarantine nursery (qNur) for ~19 days after weaning at ~21 days of age; a challenge nursery(cNur), where pigs (~40 days old) were exposed to the disease challenge for ~28 days; and a grow-finish stage (Fin) to slaughter at ~26 weeks of age (Putz *et al.,* 2019; Cheng *et al.*, 2020). Using continuous flow, a batch of 60 or 75 clinically healthy Landrace x Yorkshire weaned barrows entered the NDCM every 3 weeks from a clean multiplier from one of the seven PigGen Canada members (identified as A - G). All pigs were genotyped using a 650k SNP array and, for the purpose of this study, also for the 19 SNPs in *CD163* and the 4 SNPs in *CD169* of Dong *et al.* (2021). Traits analysed included average daily gain (ADG), which was assessed across all three phases (qNur, cNur and Fin), and mortality (MOR, 0/1 for survived/died) and individual therapeutic treatment rates (TRT), which were assessed within the cNur and Fin phases. In addition, combined measures across cNur and Fin were defined for mortality (AllMOR) and treatment rate (AllTRT), as described by Putz *et al.* (2019).

Statistical analyses. Linkage disequilibrium (LD) between SNPs in each gene was quantified across and by company using r^2 in Haploview 4.2 (Barrett *et al.,* 2005). SNPs that were in high LD (r^2>0.9) were merged. Associations of the 23 SNPs with resilience phenotypes were estimated using mixed linear models in ASReml 4.2, with fixed effects of batch and SNP*Company*WUR; the covariate of entry age; and random effects of pen within batch, litter, and additive genetics, using the genomic relationship matrix of Cheng *et al.* (2020). All estimates are presented in units of phenotypic standard deviations (SD).

Results & Discussion

Across companies, *CD163* SNPs 1, 4, 9, and 14 were in near complete LD (r^2=0.99) and had very low LD with other *CD163* SNPs. SNPs 11, 12, and 13 were also in high LD (r^2>0.93), while SNP 5 was in only moderate LD with 11_12_13 (r^2=0.38–0.41). By company, SNPs 1, 4, 9, and 14 were fixed for A, B, D, and G and were in high LD (r^2>0.8) for C, E, and F. LD among SNPs 11, 12, and 13 was high for all companies. SNP5 was in high LD with the merged SNP11_12_13 only for B. For *CD169* across companies, SNPs 1, 3, and 4 were in moderate LD (r^2=0.27–0.38), while SNP2 had very low LD with the other SNPs (r^2<0.18). For company B, all four SNPs were in very low LD with each other (r^2<0.28). High LD among SNPs in *CD163* and *CD169* were also reported by Dong *et al.* (2021).

The minor allele at SNP2 in *CD163* was significantly associated with higher cNurADG (0.1±0.06) and FinADG (0.21±0.07), and with lower FinTRT (-0.11±0.07) and AllTRT (-0.1±0.07). The minor alleles at *CD163* SNP3 and 11_12_13 were significantly associated with higher FinADG (0.12±0.05; 0.13±0.06), but also with lower cNurMOR (-0.07±0.04) for SNP3 and higher FinMOR (0.06±0.05) for 11_12_13. For *CD169*, the major alleles at SNP1 and 2 were associated with, respectively, higher and lower FinADG (0.06±0.04; -0.06±0.05).

Table 1. Estimates (SE) of minor allele substitution effects (in phenotypic SD) on traits by company (A-G) for *CD163* and *CD169* SNPs with significant interaction effects (p< 0.1).

SNP[1]	Trait	A	B	C	D	E	F	G	p
CD163									
1_4_9_14	FinADG	NA[2]	NA[2]	-1.4(0.60)	NA[2]	-0.20(0.30)	0.10(0.20)	NA[2]	0.03
3	FinADG	0.30(0.10)	-0.20(0.10)	0.30(0.10)	0.10(0.10)	0.20(0.10)	0.00(0.10)	0.10(0.10)	0.01
5	cNurTRT	0.00(0.21)	1.03(0.36)	0.41(0.37)	-0.02(0.16)	-0.21(0.24)	0.35(0.24)	-0.07(0.12)	0.06
7	AllTRT	-0.16(0.09)	0.08(0.10)	0.00(0.10)	-0.02(0.10)	0.25(0.10)	-0.03(0.09)	0.02(0.10)	0.09
	cNurMOR	0.03(0.08)	-0.01(0.09)	-0.09(0.09)	-0.21(0.08)	0.04(0.09)	0.14(0.08)	0.01(0.09)	0.08
8	FinADG	-0.20(0.10)	0.10(0.10)	0.10(0.10)	0.00(0.10)	-0.20(0.10)	0.10(0.10)	-0.10(0.10)	0.07
	cNurTRT	-0.11(0.09)	-0.06(0.10)	-0.03(0.11)	0.01(0.08)	0.26(0.09)	0.13(0.10)	0.07(0.10)	0.09
	AllTRT	-0.13(0.10)	-0.08(0.12)	0.00(0.13)	-0.03(0.10)	0.30(0.10)	0.08(0.12)	0.18(0.11)	0.04
10	FinADG	-0.20(0.10)	0.10(0.10)	0.10(0.10)	0.00(0.10)	-0.20(0.10)	0.10(0.10)	-0.10(0.10)	0.07
	AllTRT	-0.14(0.10)	-0.08(0.12)	0.01(0.13)	-0.03(0.10)	0.29(0.10)	-0.02(0.12)	0.17(0.11)	0.04
	cNurMOR	0.08(0.07)	0.03(0.07)	0.01(0.08)	-0.09(0.06)	0.04(0.06)	0.16(0.07)	-0.07(0.07)	0.09
15	FinADG	-0.20(0.10)	0.10(0.10)	0.30(0.10)	0.10(0.10)	-0.10(0.10)	0.10(0.10)	0.0(0.10)	0.04
	AllTRT	-0.13(0.09)	-0.05(0.12)	-0.12(0.10)	-0.04(0.10)	0.23(0.10)	0.01(0.10)	0.15(0.09)	0.06
16	cNurADG	-0.10(0.10)	-0.10(0.10)	0.20(0.10)	0.10(0.10)	0.10(0.10)	-0.10(0.10)	-0.10(0.10)	0.07
19	FinADG	-0.20(0.10)	0.10(0.10)	0.30(0.10)	0.10(0.10)	-0.10(0.10)	0.20(0.10)	0.00(0.10)	0.03
	AllTRT	-0.13(0.09)	-0.04(0.12)	-0.11(0.10)	-0.05(0.10)	0.22(0.09)	0.01(0.10)	0.15(0.09)	0.07
CD169									
3	cNurMOR	-0.11(0.07)	-0.01(0.08)	0.13(0.07)	0.02(0.08)	-0.12(0.07)	0.13(0.07)	0.07(0.06)	0.06
4	cNurADG	0.00(0.10)	-0.20(0.10)	0.00(0.10)	0.20(0.10)	-0.10(0.10)	0.10(0.10)	0.10(0.10)	0.06
	FinTRT	0.06(0.09)	0.00(0.09)	-0.06(0.09)	0.09(0.10)	0.09(0.08)	-0.28(0.10)	-0.02(0.09)	0.09

[1] Single Nucleotide Polymorphism [2] SNP was fixed for that company

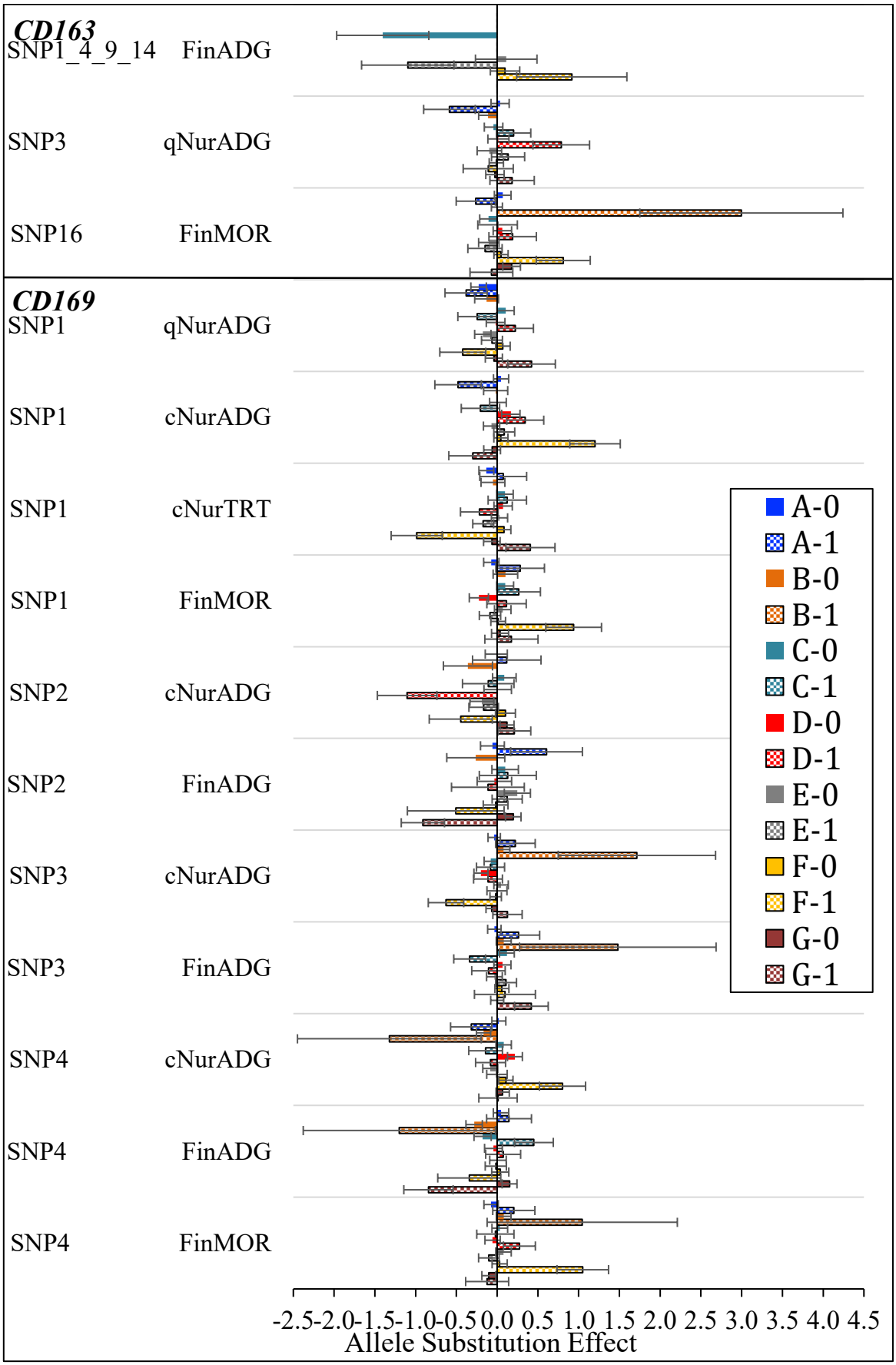

Figure 1. Minor allele substitution effects (in phenotypic SD) for *CD163* and *CD169* SNPs on disease resilience by company (A-G) and WUR genotype (0/1) for SNPs with significant interaction effects ($p<0.1$).

Table 1 shows results for *CD163* and *CD169* SNPs for traits for which the interaction of SNP with company was significant ($p<0.1$). The minor allele of *CD163* SNP1_4_9_14 was associated with lower FinADG for company C (18%, $p=0.03$) and also for companies E and F, but was not significant. The minor allele of *CD169* SNP3 was associated with lower cNurMOR for companies A and E ($p=0.06$) but with higher cNurMOR for companies C and F.

Figure 1 illustrates significant interaction effects with company and WUR of *CD163* and *CD169* SNPs on traits. Only three *CD163* SNPs showed significant SNP*Company*WUR interactions ($p<0.1$), while all *CD169* SNPs had significant associations with resilience phenotypes for specific company and WUR combinations. The minor allele at *CD163* SNP16 was associated with higher FinMOR for companies B and F, but with lower FinMOR for pigs from company A that were heterozygous for WUR. For *CD169*, the minor allele at SNP1 was associated with lower qNurADG for company A for both WUR genotypes (0 and 1) and also with lower cNurADG among pigs that were heterozygous for WUR.

In our study, the major allele at *CD163* SNP5 was associated with fewer treatments in cNur for companies B, C, and F, and Dong *et al.* (2021) reported this SNP to be significantly associated with PRRS viral load. The *CD169* SNP1 was associated with cNurTRT, cNurADG, and qNurADG for different companies and WUR genotypes and Dong *et al.* (2021) also found this SNP to be associated with host response to PRRS and PRRS/PCV2b co-infection. Dong *et al.* (2021) also reported significant interactions of *CD163* SNP5 and 11_12_13 and *CD169* SNP1 with WUR genotype for weight gain after infection but we were able to validate this interaction only for *CD169* SNP1.

Conclusions

This study evaluated associations of naturally occurring SNPs in the *CD163* and *CD169* genes with performance and disease resilience phenotypes under a natural polymicrobial disease challenge. Several SNPs showed significant associations with growth, health treatments, and mortality rates, as well as significant interactions with company and company-by-WUR genotype, indicating differences in genetic background among breeding populations. Overall, these results partially corroborate previous findings, indicating a role for natural variation in *CD163* and *CD169* in resilience to multifactorial disease that includes PRRS. These associations can be leveraged in commercial breeding programs to improve disease resilience, while underscoring population- and context-specific differences in SNP effects and their interactions with WUR genotype. Funding from Genome Alberta, Genome Canada, PigGen Canada, and USDA-NIFA grant # 2017-67007-26144.

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