Variants in the *CD163* and *CD169* Genes Associated with Host Response to PRRS and PCV2b in Nursery Pigs

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Summary and Implications

Recently, pigs with complete resistance to PRRS have been produced by editing the *CD163* gene. In this study, we genotyped pigs from previously conducted porcine reproductive and respiratory syndrome (PRRS) vaccination and PRRS-porcine circovirus type 2b (PCV2b) co-infection studies for several single nucleotide polymorphisms (SNPs) in *CD163* and other candidate genes. The main reason for genotyping these additional SNPs was because *CD163* was not included on the commercial porcine SNP panel originally used to genotype these animals. The objective of this study was to identify natural variation in these genes associated with host response to PRRS virus (PRRSV) and PCV2b co-infection following prior vaccination, or not, with a PRRS modified live virus (MLV) vaccine. Several SNPs were significantly associated with PRRS and PCV2b viral load (VL), as well as average daily gain (ADG) following vaccination and following co-infection. The effects of some SNPs depended on previous vaccination for PRRS or genotype at the WUR10000125 (WUR) SNP (previously associated with host response to PRRS and co-infection with PRRSV and PCV2b). Interestingly, one SNP in *CD163* and one SNP in *CD169* causing amino acid substitutions had significant effects on PRRSV/PCV2b VL and/or ADG, regardless of whether/not pigs had been vaccinated for PRRS. The identified SNPs are potential genetic markers that can be used to select for increased natural resistance to PRRSV and PCV2b co-infection.

Introduction

Porcine *CD163* is a receptor for PRRSV and *CD163* knockout pigs are fully resistant to PRRSV infection. Several SNPs in immune response candidate genes *CD163*, *CD169*, *TRAF1,* and *RGS16* were previously identified to be associated with response to PRRSV or PCV2 (*RGS16* only) infection.

The WUR SNP is a genetic marker for a major gene associated with natural resistance to PRRS, where the B allele is favorable and dominant. In a PRRS vaccination and PRRS-PCV2b coinfection trial, vaccinated pigs with the B WUR allele had significantly lower PRRS vaccine VL and greater ADG following PRRS vaccination, as well as lower PRRS VL (and PCV2b VL for vaccinated pigs) following co-infection. In addition, results from a previous study showed that porcine *CD163* polymorphisms interact with WUR genotype for anti-PRRSV responses in infected pigs.

The objective of this study was to evaluate associations of nineteen naturally occurring SNPs in *CD163*, four in *CD169*, two in *RGS16*, and two in *TRAF1*, on host immune response to PRRS vaccination and to PRRSV and PCV2b co-infection. Interactions with genotype at the WUR SNP were also investigated.

Materials and Methods

Large White/Landrace crossbred nursery barrows from one genetic supplier in two trials of the PRRS Host Genetics Consortium were pre-selected for genotype at the WUR SNP (n=184 AA and n=212 AB pigs). Pigs were randomly assigned to one of two rooms. Pigs in one room were vaccinated (Vx) using a PRRS MLV vaccine and four weeks later, all pigs were challenged with field isolates of PRRSV and PCV2b and followed for 42 days post infection (dpi). Blood samples were collected to quantify PRRS VL post vaccination (VxPRRS) and PRRS and PCV2b VL post co-infection (PostPRRS and PostPCV). Growth rate post vaccination (VxADG) and post co-infection (PostADG) were also evaluated.

SNP genotyping was performed using the Agena Mass Spec platform. Haploview 4.2 was used to quantify linkage disequilibrium (LD) between SNPs in the same gene. Phenotypes recorded on Vx vs. non-vaccinated (NonVx) pigs were treated as separate traits. The phenotype and genotype data were analyzed using ASReml 4.1 using bivariate animal genetic models, fitting the effect of each candidate SNP one at a time, along with WUR genotype and its interaction with the candidate SNP as fixed effects.

Results and Discussion

Two groups of four SNPs in *CD163* and two SNPs in *TRAF1* were in complete LD. Three other SNPs in *CD163* were fixed. Two SNPs in *TRAF1*, twelve SNPs in *CD163*, one SNP in *RGS16*, and two SNPs in *CD169* were found to be significantly ($p<0.1$) associated with PRRS or PCV2b VL, or with VxADG or PostADG, some of which the effects depended on previous vaccination for PRRS or WUR SNP genotype. Interestingly, one SNP in *CD163* and one SNP in *CD169* that cause amino acid substitutions had significant effects on PRRS/PCV2b VL and/or ADG for both Vx and NonVx pigs. These results are in the process of being validated in independent populations and, if confirmed, the identified SNPs can serve as genetic markers

to select for increased natural resistance to PRRSV and PCV2b co-infection.

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