Factors Associated with Neutralizing Antibody Response in Piglets Experimentally Infected with Porcine Reproductive and Respiratory Virus

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Summary and Implications

Host genetic differences and other factors associated with neutralizing antibody (NAb) response were examined in 464 Large White-Landrace piglets that were experimentally challenged with porcine reproductive and respiratory virus (PRRSv) isolate NVSL-97-7895. Serum samples and viremia data were collected on piglets periodically for 42 days post infection (dpi). NAb response was defined as the inverse of the highest 1:2 serial dilution of serum without cytopathic effects. Heritability and other factors associated with NAb response were estimated using an animal model in ASReml. These analyses identified two aspects of viremia that were associated with NAb response: viral load (area under the curve from 0-21 dpi) and virus rebound (a two Log increase in viremia after the virus had started to clear). These results also suggested that NAb response may be lowly heritable and provided the groundwork for further characterization of NAb response.

Introduction

PRRS is a global devastating disease that has plagued the United States pork industry for nearly three decades and costs over half a billion dollars annually. The aim of the PRRS Host Genetics Consortium is to identify genomic markers and pathways associated with host responses to PRRSv infection in order to aid in containment of this disease.

A marked characteristic of PRRS is a delayed and unusually weak NAb response to PRRSv infection. The level and breadth of NAb response likely contributes to the host's ability to fight infection. Understanding the factors that contribute to variability in NAb response may provide insight for enhancing NAb response to infection, which has potential for aiding containment of PRRSv. The objectives of this study were to identify the presence of a genetic heritable component and to elucidate other factors influencing NAb response.

Materials and Methods

The data used in this study was obtained from sera collected from 464 Large White-Landrace crossbred piglets from three separate experimental infection trials. All piglets were experimentally challenged with PRRSv isolate NVSL-97-7895 at 28-35 days of age. Serum samples were periodically collected for up to 42 days post infection (dpi) and viremia determined by qPCR assays.

Serum samples collected at 42 dpi were assayed for NAb response by incubating 200 50% tissue culture infectious dose ($TCID_{50}$) of the virus with 1:2 dilutions of serum and then transferring to tissue culture plates with confluent MARC-145 cells; PRRSv cytopathic effects were assayed 4 days later. The inverse of the highest serum dilution without cytopathic effects was recorded as the NAb titer and this ranged from <8 to >1024. For statistical analysis, NAb response was converted to an adjusted Log_2 scale (0-8).

Viremia, quantified using qRT-PCR, increased and peaked for all pigs at 7-14 dpi and thereafter declined. Viral load was defined as the area under the curve of Log viremia from 0-21 dpi. A piglet was classified as having rebounded if a two Log increase in viremia was observed after the virus had started to clear. A SNP on chromosome 4 (WUR10000125) that was previously found to be associated with viral load in this data set was also examined, and was defined as the number of B alleles.

All analyses were carried out using an animal model in ASReml 3, with NAb response assumed to be normally distributed: experiment nested with parity, WUR, viral load, and virus rebound were fitted as fixed effects; dam, animal, experiment nested with pen, and day nested with plate were fitted as random effects.

Results and Discussions

NAb response at 42 dpi was found to be approximately normally distributed. Therefore, statistical analyses in ASReml were carried out assuming normality.

Variance components were estimated using an animal model in ASReml. The results suggest that NAb response is lowly heritable (0.057 but with a standard error of 0.097). Plate explained a large portion (12.1%) of the variability in the data. Pen and litter components may also explain some of the variability of NAb response (1.1 and 2.1%). Large standard errors were present for all estimates except for plate, indicating that further data is needed for more accurate estimates of these variance components.

Other factors were fitted as fixed effects in an animal model in ASReml to examine their association with NAb

response. Viral load had a small but significant negative effect on NAb response. Conversely, virus rebound, which was observed in 24.4% of infected piglets, had a sizable and significant positive effect on NAb response. Viral load and virus rebound were not correlated with each other (p=0.30). Interestingly, the WUR SNP on chromosome 4 that was previously found to be associated with viral load in this data set, was not associated with NAb response (p=0.84).

These results demonstrate that NAb response to PRRSv independently either influences or is influenced by both level of viremia immediately following infection and virus rebound following initial clearance. These results also suggest that NAb response is not associated with the WUR SNP that has been identified for viral load and growth following infection.

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