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Dynamic and Genetic Signatures of Resistance and Tolerance of pigs to PRRS

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ABSTRACT: Using SNP data, we demonstrate that a previously identified QTL conferring resistance of pigs to PRRS does not confer tolerance. Similarly, variation in tolerance cannot be found at sire level. However, by analysing the dynamic relationship between both traits using individual resistance – tolerance trajectories we find significant SNP effects affecting the shape of these trajectories. Evidence of underlying genetic variation suggests it may be possible to target a specific trajectory type, or shift in trajectory, for genetic improvement. This would provide breeders with a means to simultaneously improve resistance and tolerance and their timely interactions.

Keywords: Tolerance; Resistance; PRRS; Trajectories

Introduction

Porcine reproductive and respiratory syndrome (PRRS) is a viral disease which causes reduction in growth and mortality in growing pigs. A growing body of evidence suggests considerable genetic variation in host response to the PRRS virus (PRRSV) making selective breeding a promising control method to lower the devastating effects of PRRSV (Lunney & Chen (2010)). For livestock production, two alternative types of host response strategies to PRRSV are important: *resistance*, the ability of a host to limit or inhibit pathogen replication, thus reducing infection severity and *tolerance*, the ability of the host to limit the impact of infection on performance, without necessarily impacting on pathogen burden per se (Raberg & Sim (2007)). In a recent large-scale genomic study a quantitative trait locus associated with resistance/ resilience to PRRSV was identified on Sus scrofa chromosome (SSC) 4 (Boddicker et al. (2012; 2014)). The favorable genotypes (AB and BB) were associated with lower cumulative virus load and higher weight gain in experimentally challenged young pigs. However, it is not known whether the higher weight gain in "resistant" individuals is a direct consequence of resistance, or reflects genetic variation in tolerance. Quantitative genetic studies usually treat resistance and tolerance as static traits. This stands in contrast to immunological studies that suggest the outcome of infection is controlled by a carefully timed, dynamic interaction between resistance and tolerance mechanisms (Schneider (2011)). The dynamic interplay of these mechanisms can be captured by 2D resistance-tolerance trajectories, generated by plotting pair-wise (longitudinal) individual measurements of infection severity (e.g., viral load) and performance (e.g., weight gain) over time (Schneider (2011); Doeschl-Wilson et al. (2012a). Using theoretical arguments, Doeschl-Wilson et al. (2012a) proposed that the trajectory characteristics may be genetically determined, providing the opportunity to target desirable trajectory types or characteristics (i.e., the dynamic co-expression of resistance and tolerance over the time course of infection), rather than resistance or tolerance, in genetic improvement programmes.

The aims of this study were to determine (1) whether there is genetic variation in host tolerance to PRRSV; (2) whether the previously identified resistance QTL confers differences in tolerance to PRRSV; and (3) whether different host resistance and tolerance genotypes also map into different PRRS trajectory types.

Materials and Methods

Data. Data were provided from the PRRS Host Genetics Consortium trials, where crossbred nursery pigs (n=1355) were infected with PRRSV (Lunney et al (2011). Pigs were taken from high health farms and placed randomly in pens of 10-15 pigs in 8 separate trials. Measures of body weight (BW) and blood samples (for virus load) were collected weekly up to 42 days post infection (dpi) for every individual. Data from the first 5 trials had been used by Boddicker et al. (2012, 2014) to identify host response QTL.

The weekly BW measures provided estimates for average daily gain (ADG) between consecutive weeks and over several weeks. Log-transformed viremia profiles for each individual were smoothed as outlined in Islam et al (2013). All pigs were genotyped and assigned to one of three genotypes based on the WU10000125 SNP locus (AA (n=961), AB (n=338) and BB (n=42), where the B-allele confers resistance to PRRSV).

Statistical analysis of tolerance. In line with Boddicker et al. (2012, 2014), only the time period between 0-21 dpi was considered in the statistical models for tolerance.

Tolerance model. To estimate genetic variance in tolerance or to determine whether the PRRSV resistance genotypes also confer difference in tolerance, the following statistical model was used:

$$y_{ij} = \mu + a_{0j} + b_j VL_{ij} + \varepsilon_{ij} \quad (1)$$

where the subscript *j* refers either to sire *j* (fitted as random effect, for estimating genetic variance of tolerance), or to genotype *j* (fitted as fixed effect, for assessing genotype differences in tolerance), respectively, and y_{ij} refers to the adjusted ADG of individual *i* with sire/genotype *j*, μ is the population mean; a_j is sire / genotype specific intercept (vigour); b_j refers to the tolerance of genotype / sire *j*; VL_{ij} is the cumulative virus load of individual *i* with genotype / sire *j* and ε_{ij} is the residual. The adjusted ADG were obtained by adjusting the individual ADG for individual vigour (ADG in the absence of infection) and for the fixed and random effects as outlined in Boddicker et al. (2012). The fixed effects used were trial-by-parity interaction, and random effects were pen nested within trial and litter. Genetic variance was estimated as four times the sire variance.

Analysis of host resistance and tolerance trajectories. Resistance-tolerance trajectories were generated by plotting for each individual the 6 weekly measurements of ADG against the corresponding weekly VL estimates. Connecting scatter points corresponding to successive weeks k and k+1, resulted in 2D vectors $\mathbf{v}_k=[VL_{k+1}-VL_k,\ ADG_{k+1} - ADG_k]^T$, which, when joined together, form a 2D trajectory in the VL-ADG plane (Figure 1). Assuming that reduction in VL corresponds to expression of host resistance, and increase in ADG despite positive VL corresponds to expression of host tolerance, the direction of these vectors then represents whether or not resistance and tolerance mechanisms are co-expressed during the corresponding time period. For the statistical analysis, the calculated vector directions were classified into one of four categories ($1 = R^-T^-$, $2 = R^+T^-$, $3 = R^-T^+$, $4 = R^+T^+$) according to whether or not (+/-) resistance (R) and tolerance (T) were expressed (Figure 2). This resulted in a sequence of 6 integers for every individual. Pairwise Hamming distances were calculated to compare trajectory sequences between individuals, and a permutation test was used to determine whether the different PRRSV resistance genotypes differ significantly in their trajectory sequences.

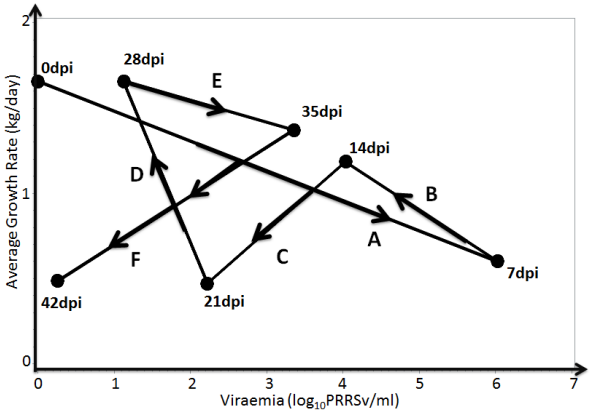

Figure 1. A representative of a trajectory showing measures (0-42dpi) and vectors (A-F): Max viremia is reached at 7 dpi, from where, the host reduces pathogen load while fluctuating in ADG.

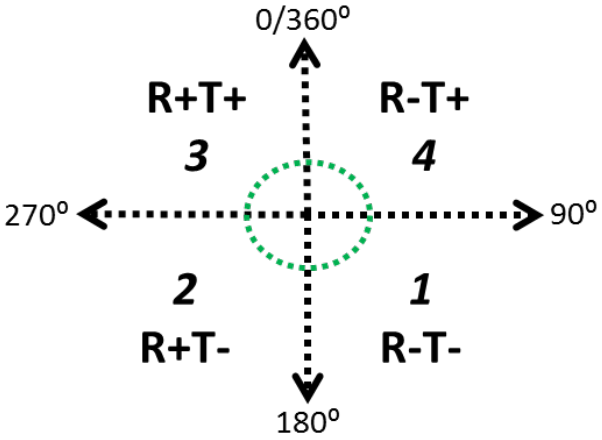

Figure 2. Quadrants with associated sequence number (1-4) defining the direction of a trajectory vector, where R/T stands for Resistance/Tolerance and +/- denotes exhibiting/not exhibiting R or T. For example, the trajectory (vectors ABCDEF) of the individual in Figure 1, corresponds to the sequence{132312}.

Results and discussion

Genetic Variation in Tolerance. Although the genotypes confer genetic variation in resistance, we did not find evidence of underlying genetic variation in tolerance (sire model ($p=0.88$) or genotype model ($p=0.15$)). This would imply that genetic variation in the reduction of ADG due to infection is determined by genetic variance in resistance alone.

Trajectory analysis. According to the sequence permutation test, a significant difference between trajectories of genotypes AA and AB was found ($p<0.05$), implying variation in timing and expression of tolerance-resistance responses between the two genotypes. Additionally, a significant difference between trajectory sequence totals of AA and BB ($p<0.01$) and AB and BB ($p<0.05$) was found. This may indicate that the dynamic co-expression of resistance and tolerance mechanisms, as well as the dominant immune strategy may be partially controlled by genotype. Further tests to disentangle the genotype effects on the trajectory sequences from other potentially confounding factors are currently under way.

Conclusion

Resistance-tolerance trajectories provide deeper insight into how resistance and tolerance together regulate the impact of infection on health and performance. Our study revealed that the previously established PRRS resistance QTL has no influence on tolerance to PRRSV, but aids in regulation of their dynamic patterns of co-expression. These dynamic signatures provide a potential profile for which a breeder can select, to reduce both infection severity and its impact on performance.

Acknowledgments

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