163 Equine exertional rhabdomyolysis: A phenotypically and genetically heterogeneous syndrome

Equine exertional rhabdomyolysis: a phenotypically and genetically heterogeneous syndrome

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Application: The equine muscle disorder exertional rhabdomyolysis (ER) is an animal welfare concern that has substantial financial implications for equine industries. Breeders may inadvertently be selecting for the disease (1), and identifying genetic disease markers could inform future breeding programmes. Recognition of specific clinical presentations across different breeds might reveal separate causes enabling more refined treatments and prophylaxis.

Introduction: Equine exertional rhabdomyolysis (ER) is a clinically heterogenous myopathy. The clinical signs, which can include intermittent episodes of muscle fasciculations and myofibre necrosis, stiffness, sweating, myoglobinuria, recumbency and even death, vary in character and in severity between episodes and between affected animals suggesting that ER might be a syndrome consisting of multiple distinct diseases (2); identifying distinct phenotypic patterns might facilitate future studies into the genetic architecture, aetiopathogenesis, and treatment of these diseases.

Materials & methods: Signalment, clinical history and histological features from 196 horses with ER selected from the muscle biopsy service database of the RVC Comparative Neuromuscular Diseases Laboratory were used in this study. Firstly, k-means clustering was performed on the clinical and histological features. Chi-square testing was used to identify features that varied significantly between clusters. Moreover, hierarchical clustering (Ward method) was implemented on cases and variables. Then a support vector machine (SVM) algorithm was trained to assign cases to cluster, and 66 horses with genotypes (Connemara ponies: 16 cases; Warmblood horses: 50 cases; 670k HD SNP array) were then assigned. Case-control genome-wide association studies (GWAS) (n=127, including 61 controls) were performed using GEMMA, with case populations split into 2 groups.

Results: Cluster selection using both approaches reflected the heterogenous nature of the dataset. The k-means clustering of clinical and histological features identified 4 clusters, with one cluster not associated with any particular feature (termed the ‘classic’ cluster) and the others associated with gait abnormalities, myalgia, paresis, ataxia and reluctance to move. A similar pattern was seen using k-means clustering in clinical signs alone, with 5 clusters associated with repeated episodes, Thoroughbred breed, stiffness, myalgia, poor performance, gait abnormalities, ataxia and lethargy, and one ‘classic’ cluster. Hierarchical clustering notably clustered the clinical signs of poor performance, exercise intolerance, stiffness, reluctance to move, myalgia and gait abnormalities together. The SVM algorithm could perfectly predict between classic and non-classic clusters. GWAS analysis revealed a

distinct genetic architecture for ER susceptibility between classic and non-classic ER clusters (see Fig 1).

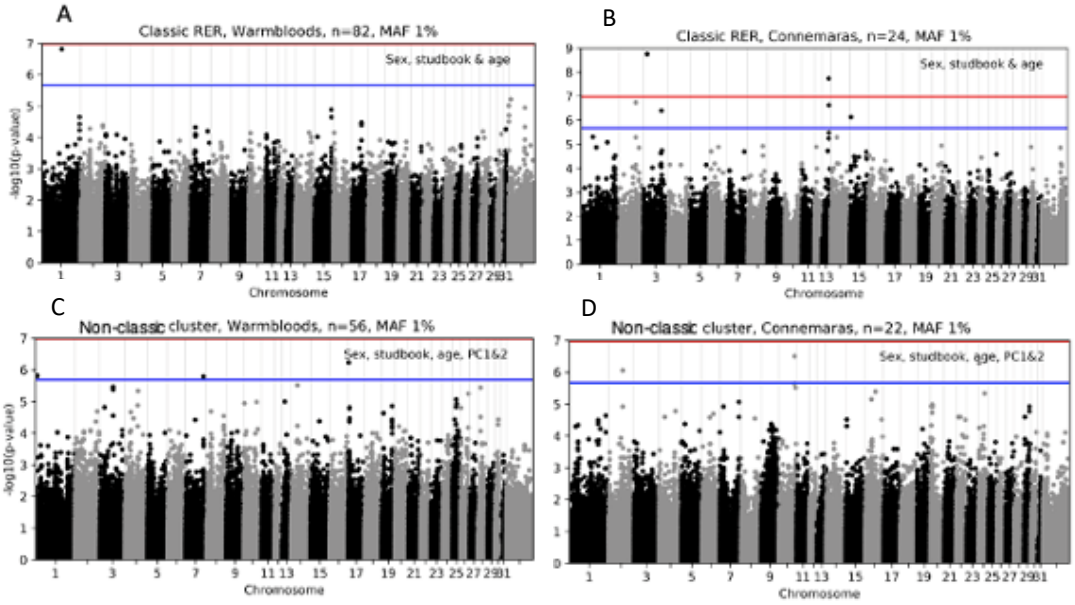

Figure 1: Manhattan plots of marker location by -log$_{10}$(P-value) of GWAS of A) classic cluster versus controls in WB B) classic cluster versus controls in CP C) non-classic cluster versus controls in WB D) non-classic cluster versus controls in CP. The red line indicates the significance threshold (Bonferroni-corrected), and the blue line the suggestive threshold (as per (3))

Conclusions: According to our results the presence of distinct patterns in ER disease phenotype are detectable, and specific clinical signs are consistently used to distinguish clusters. GWAS results supported that distinct phenotypic clustering is reflecting genetic differences between ER cases.

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Presenter biography: Victoria Lindsay is a PhD student in equine genomics at the Royal Veterinary College. Her research interests include the genetic component of complex disease susceptibility in various animal species.