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## Phenotypic and genetic characterisation of disease subtypes of equine recurrent exertional rhabdomyolysis

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### Application

Identification of clinical subtypes of RER improves our ability to study the genetic basis and aetiopathogenesis of the disease, as well as seek potential treatments. This improves the welfare of the animals as well as having an impact on the huge financial losses suffered by the racing industry due to RER.

### Introduction

Equine recurrent exertional rhabdomyolysis (RER) is a myopathy characterised by exercise-induced episodes of myofibre necrosis. RER is clinically heterogenous, with variation between clinical signs and severity of those signs between individuals and between episodes, with severe cases resulting in recumbency, kidney failure and even death. RER is a moderately heritable disease ( $h^2 = 0.34-0.49$ ) (Norton et al., 2016), but causal genetic variants have not yet been identified. Previous studies in another exertional myopathy, polysaccharide storage myopathy, identified disease subtypes with differing genetic basis (McCue et al., 2008, 2009). We aimed to identify possible disease sub-types within the RER syndrome.

### Materials and methods

We applied principal components analysis, k-means clustering and hierarchical clustering methods to 209 RER horses retrospectively from the Royal Veterinary College's Comparative Neuromuscular Diseases Laboratory diagnostic biopsy service, to identify clusters of cases based on clinical history and histological records. We then tested variables for association with clusters using Chi-square testing.

A support vector machine algorithm was trained successfully to differentiate between classic and non-classic RER cases, and this algorithm was applied to a dataset of 127 Warmblood horses (WB) and Connemara ponies (CP) (CP: 16 cases, 17 controls; WB: 50 cases, 44 controls).

Genome-wide association studies (GWAS) were carried out within and across breed and disease subtype.

Using 69 samples of equine semimembranosus muscle from Arabian, Thoroughbred and WB horses (24 classic RER, 12 non-classic RER, 26 negative controls, and 7 with myofibrillar abnormalities), we carried out a blinded histological study comparing features identified by a specialist between disease groups from a standard panel of myopathy staining and immunohistochemistry, including for

desmin. We selected features with  $p < 0.1$  on a univariate contingency table or two-way ANOVA for inclusion in a binary (between the subtypes) or multinomial logistic regression model.

## Results

Consistently, horses grouped into 'classic' and 'non-classic' RER subtypes: cases with no particular defining features, versus cases associated with gait abnormalities ( $p < 0.001$ ), muscle pain ( $p < 0.001$ ), weakness ( $p = 0.001$ ), ataxia ( $p = 0.001$ ), and reluctance to move ( $p = 0.001$ ).

GWAS identified different patterns of genetic associations between breeds and between the disease subtypes. No convincing histological differences were identified between the disease subtypes, supporting our clustering analysis, and indicating that any histological differences between disease subtypes are not captured by current staining panels.

## Conclusions

Overall, RER is a complex disease, likely consisting of multiple disease subtypes with possible distinct genetic associations.

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samples.

## References

McCue, M.E., Valberg, S.J., Miller, M.B., Wade, C., DiMauro, S., Akman, H.O., Mickelson, J.R., 2008. *Genomics* 91 (5), 458–466.

McCue, M.E., Armién, A.G., Lucio, M., Mickelson, J.R., Valberg, S.J., 2009. *Vet. Pathol.* 46 (6), 1281–1291.

Norton, E.M., Mickelson, J.R., Binns, M.M., Blott, S.C., Caputo, P., Isgren, C.M., McCoy, A.M., Moore, A., Piercy, R.J., Swinburne, J.E., Audin, M., McCue, M.E., 2016. *J. Heredity* 107 (6), 537–543.

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Microbiological etiology of infectious infertility in Arabic mares

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