Unravelling the genetic mechanisms underlying fracture risk in horses

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Bone fractures caused by overloading (rather than a direct trauma) often occur in Thoroughbred racehorses. Fracture is the most common reason for a horse to be euthanised on the racecourse and non-fatal fractures are the most common type of musculoskeletal injury to occur in horses in both racing and training.

The risk of fracture is affected by various environmental factors, but despite improvements in race conditions, the number of fatal fractures has remained relatively static over the past decade. Previous work has shown that, in addition to environmental risk factors, there is also a genetic risk to fracture in Thoroughbreds that results in some horses being more inherently predisposed to fracture than others.

A previous study demonstrated that there were a number of DNA markers across the genome that were associated with an increased risk of fracture and one particular region of DNA on chromosome 18 was most strongly associated with risk.

Using a small number of fracture case and control horses, we have studied the entire DNA sequence of each horse using a technique called 'whole genome sequencing' and computer analysis to look for differences in the sequence between the cases (with fractures) and controls (without fractures). We found more than 100 differences in the DNA sequences (variants) that were predicted to change the way proteins function and many others that might affect how much protein is produced. We now need understand which of these variants and proteins are most important in fracture risk.

In this project we will perform whole genome sequencing on a much larger number of fracture cases and controls to create a more accurate list of DNA variants that might be associated with fracture risk. We will then measure up to 500 of the variants in a large group of up to 250 fracture cases and 250 fracture control horses to identify those that are significantly associated with fracture.

For those variants that are associated with fracture, we will determine how frequently they occur in Thoroughbreds and other breeds that do not commonly suffer from fractures. Variants that are common across many breeds are less likely to be involved in fracture. Variants that are more restricted to the Thoroughbred will then be used in further computational approaches to predict if they are likely to affect the way the protein works or how much of it is produced. Up to five of the variants that are predicted to have the biggest effects will then be studied in the laboratory to measure their actual functional effects.

Identifying DNA variants that contribute to increased fracture risk will help us to develop a genetic test to identify and manage horses that are at high genetic risk and enable vets and breeders to make informed decisions to reduce the risk of future racehorses having catastrophic fractures. Understanding how the DNA variants exert their effects to contribute to fracture risk will also allow us to develop new therapies and interventions for high risk horses in the future.