////Title: Polymorphisms in the Myostatin Gene Influence Muscle Fibre Composition and Race Distance Aptitude in Thoroughbred horses

////Stand-first:

The Thoroughbred is a horse breed best known for its use in racing. Intense selection for speed and stamina has led the Thoroughbred to develop energy-efficient muscles, with a high aerobic capacity relative to skeletal muscle mass. Dr Mary F. Rooney and her colleagues from University College Dublin and Trinity College Dublin, Ireland, investigated how different myostatin genotypes [gene-o-types] in equine muscle are correlated with muscle fibre composition and, ultimately, influence the race distance aptitude of the Thoroughbred horse.

////Body text:

Centuries of genetic selection have equipped the Thoroughbred horse breed with a remarkably high aerobic capacity relative to skeletal muscle mass and an optimal combination of speed and stamina during racing. The lean muscle mass in the Thoroughbred is regulated by a protein known as myostatin, which acts as a pronounced inhibitor of skeletal muscle growth. Dr Mary F. Rooney investigated the effect of variation in the myostatin gene on the muscle fibre composition and cellular aerobic activity in Thoroughbred horses. Dr Rooney's research explains why different forms of the myostatin gene are significantly correlated with best race distance in the Thoroughbred.

Horse skeletal muscle is made up of different types of fibres, each type containing different densities of mitochondria [mai-tow-kon-dree-uh], the sites where cellular respiration occurs.

Some skeletal muscle fibres are known as the slow-twitch type and are characterised by having high mitochondrial and capillary density. Fast-twitch fibres, on the other hand, have low mitochondrial and capillary density.

There are other fibres similar to the fast-twitch fibres but with a higher mitochondrial density. Different forms of the myostatin gene result in different muscle fibre proportions and different suitability for distance racing. The horses of the genotype known as homozygous [how-muh-zai-guhs] C are best suited to short distance sprint racing requiring short bursts of speed that may be facilitated by fast-twitch muscle fibres. Homozygous T genotype horses are best suited to longer distance races, requiring more stamina, and thus the higher oxidative capacity provided by slow-twitch fibres.

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In a study published in 2017, Dr Rooney and her colleagues from Trinity College Dublin and University College Dublin, Ireland, measured the mitochondrial abundance and skeletal muscle fibre composition in whole muscle biopsies from 82 untrained Thoroughbred horses. The aim of the study was to characterise the mitochondrial abundance and the activity of the mitochondrial electron transport chain in Thoroughbred horses with different myostatin genotypes.

The study confirmed that homozygous T genotype horses had greater mitochondrial content than homozygous C genotype horses. The study also confirmed that the homozygous T genotype horses had a higher proportion of slow-twitch fibres. The mitochondrial electron transport chain activity

studies showed that there is lower Co-Enzyme Q10 activity in the mitochondria of skeletal muscle tissue of homozygous T horses compared to homozygous C. Co-Enzyme Q10 is critically important for the production of energy from cellular respiration. Although produced endogenously in enough quantities to sustain the energy requirements of the body, the levels of Co-enzyme Q10, also known as ubiquinone, can be boosted by dietary supplementation.

The data from Dr Rooney's publication suggest that homozygous T horses may benefit from dietary supplementation of ubiquinone, which has been shown to have a range of health benefits relating to exercise. This data and a subsequent whole animal study by the same group led to the development of a CoQ10 supplement for Thoroughbred horses, called EnergeneQ10, sold by Irish Equine Science company, Plusvital [plus-vy-tel].

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In another study published in 2018, Dr Rooney investigated how these genetic variations, known as polymorphisms [po-lee-maw-fuh-zmz], in the myostatin gene, result in such differences in mitochondrial abundance, fibre proportion and the consequent association with best race distance in the Thoroughbred.

The first polymorphism studied was a single nucleotide [nyoo-klee-uh-taid] change in the gene, which is denoted as SNP [snip] for simplicity. The second polymorphism was an insertion of 227 nucleotides, denoted as SINE [sign] for simplicity.

The aim of the study was to evaluate the effects that the relative contribution of the SNP and the SINE insertion have on the myostatin gene expression using a combination of molecular biology cell-based assays and skeletal muscle biopsies from Thoroughbred horses.

After determining the levels of gene expression in skeletal muscle, the authors showed that significantly higher levels of myostatin mRNA transcripts were associated with the wildtype genotype with no SINE insertion compared to either SNP heterozygous or SNP homozygous C genotypes with SINE insertion. The study also showed that the SINE insertion was responsible for a 4.5 fold decrease in myostatin protein levels. In contrast, the SNP had no measurable effect on its own nor did it aid or attenuate the effect of the SINE insertion. These results provide evidence that the SINE insertion is uniquely responsible for inhibiting the expression of myostatin.

The authors showed that the SINE polymorphism adversely affected the transcription initiation at the myostatin transcription start site in horse skeletal muscle. Since inhibition of the expression of myostatin results in more skeletal muscle fibres of the fast-twitch type, it can be concluded that the presence of the SINE insertion provides myostatin with a 'speed gene effect'. It is likely that this significant mutation of the myostatin gene became more prominent due to heightened popularity for shorter-distance races at the turn of the 20th century.

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Dr Rooney's studies of the myostatin gene in Thoroughbred horses have led to important findings that significantly advance our understanding of how the relative proportions of different skeletal muscle fibres are controlled at gene expression level for maximal speed or stamina.

Another key finding of this research was that nutritional supplementation with ubiquinone may aid to restore or enhance coenzyme Q10 activity in certain myostatin genotype Thoroughbred horses.

Dr Rooney and her colleagues also provided evidence for the first time of a mechanism that explains the decreased myostatin production in the presence of a 227 nucleotide sequence known as the SINE insertion, near the promoter region of the myostatin gene. The insertion uniquely accounts for the myostatin "speed gene" effect, promoting speed over stamina in the Thoroughbred horse.

This SciPod is a summary of the papers:

'The "speed gene" effect of myostatin arises in Thoroughbred horses due to a promoter proximal SINE insertion' published in the open access journal PLOS One. https://doi.org/10.1371/journal.pone.0205664

and

'Skeletal muscle mitochondrial bioenergetics and associations with myostatin genotypes in the Thoroughbred horse', also published in PLOS One. https://doi.org/10.1371/journal. pone.0186247

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