Researchers find genetic variant for speed of hair graying, susceptibility to skin melanoma in horses

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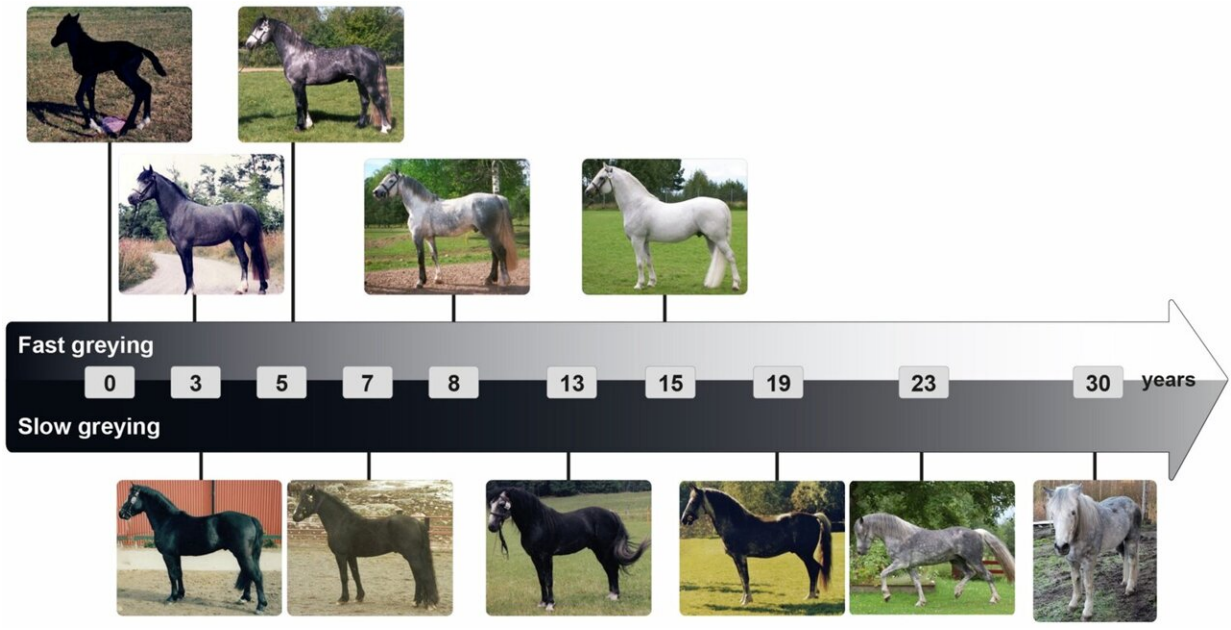

Illustration of fast and slow greying Connemara Ponies. Two individual horses, one fast greying (upper timeline) and one slow greying (lower timeline), were used for the illustration. Photo, from left to right: Fast Grey 1,2 Madeleine Beckman, 3 Maria Johansson, 4,5 Beckman Archive. Slow Grey 1–4 Maria Johansson, 5-6 Marlen Näslin. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-51898-2

Graying with age is a common coat color variant in horses, characterized

by progressive hair graying and susceptibility to skin melanoma. In a new study published in *Nature Communications*, an international consortium led by scientists from Uppsala University (Sweden) now reports that the speed of graying and susceptibility to melanoma are determined by the copy number of a small duplicated DNA sequence in the gene Syntaxin 17.

Gray horses are born normally colored but already during their first year of life a hair graying process is initiated that usually results in them becoming completely white later in life, one of the most iconic coat color variants in animals.

At an older age, white horses carrying the Grey mutation often develop skin melanomas that are usually benign but some develop into a malignant form. These horses have white hair but completely black skin and do not get melanoma because they are sensitive to UV damage, a major risk factor for human melanoma, but due to an intrinsic effect of the Grey mutation.

"In a previous study, we reported that graying with age is associated with a duplication of a small piece (4,600 base pairs) in an intron of the gene that codes for the protein Syntaxin 17," explains professor Leif Andersson (Uppsala University).

"We also showed that the duplicated sequence constitutes an enhancer that upregulates expression of Syntaxin 17 as well as the neighboring gene NR4A3." (An enhancer is a piece of DNA that does not code for any protein but takes part in the regulation of gene expression).

"In this new study we show that there are three different gene variants at the Grey locus in horse, G1 with no duplication (wild type), G2 with two copies of the duplicated sequence causing slow graying and no detected higher risk of melanoma and G3 with three copies of the duplicated

sequence and a significantly elevated risk of skin melanoma," explains Dr. Carl-Johan Rubin (Uppsala University), first author on the study.

Since a horse has two copies of each chromosome, a horse can have two, three, four, five and six copies of the duplicated sequence depending on its genotype at the Grey locus.

"We find a remarkable dosage effect where the speed of graying and melanoma susceptibility increase as a function of the copy number of the duplicated sequence," continues Andersson. "There appears to be a threshold effect, so that the G3 variant with three copies is needed in order to see an increased risk of melanoma."

The discovery reported in this study is based on the association between slow graying and the G2 gene variant in two different breeds, Swedish Connemara ponies and Japanese Thoroughbred horses.

"The discovery that G2 arose by mutation from a G3 variant in our Japanese pedigree provides the ultimate evidence that the duplication is causing hair graying," explains one of the co-authors Teruaki Tozaki (Laboratory of Racing Chemistry, Tochigi, Japan). "The G3 variant simply lost one of the copies when the gamete was formed, illustrating genetic instability when a sequence occurs in multiple copies on a chromosome."

In this study, the authors genotyped 1,400 horses representing 78 breeds. They found the G3 variant associated with fast graying and white color in 62 breeds, while the G2 allele associated with slow graying and gray color was only found in eight breeds.

"It is likely that there has been a strong selection for the G3 variant because of the preference for the beauty of white horses, says Prof. Rebecca Bellone at Veterinary Genetics Laboratory (UC Davis), who

was responsible for the genotyping of the 1,400 horses. "Now we have a genetic test to offer that can tell at an early age whether a horse will be gray or white later in life, and whether it has an elevated risk of skin melanoma."

"The remaining mystery we hope to solve in future research is why an elevated expression of the Syntaxin 17 and/or NR4A3 genes results in progressive hair graying and susceptibility to melanoma," says Andersson. "If we can solve this enigma, it has implications for understanding tumor development in general, and may have important implications for prevention and/or treatment of melanomas in these horses."

More information: Carl-Johan Rubin et al, An intronic copy number variation in Syntaxin 17 determines speed of greying and melanoma incidence in Grey horses, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51898-2

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