Second gene modifies effect of mutation in a dog model of ALS

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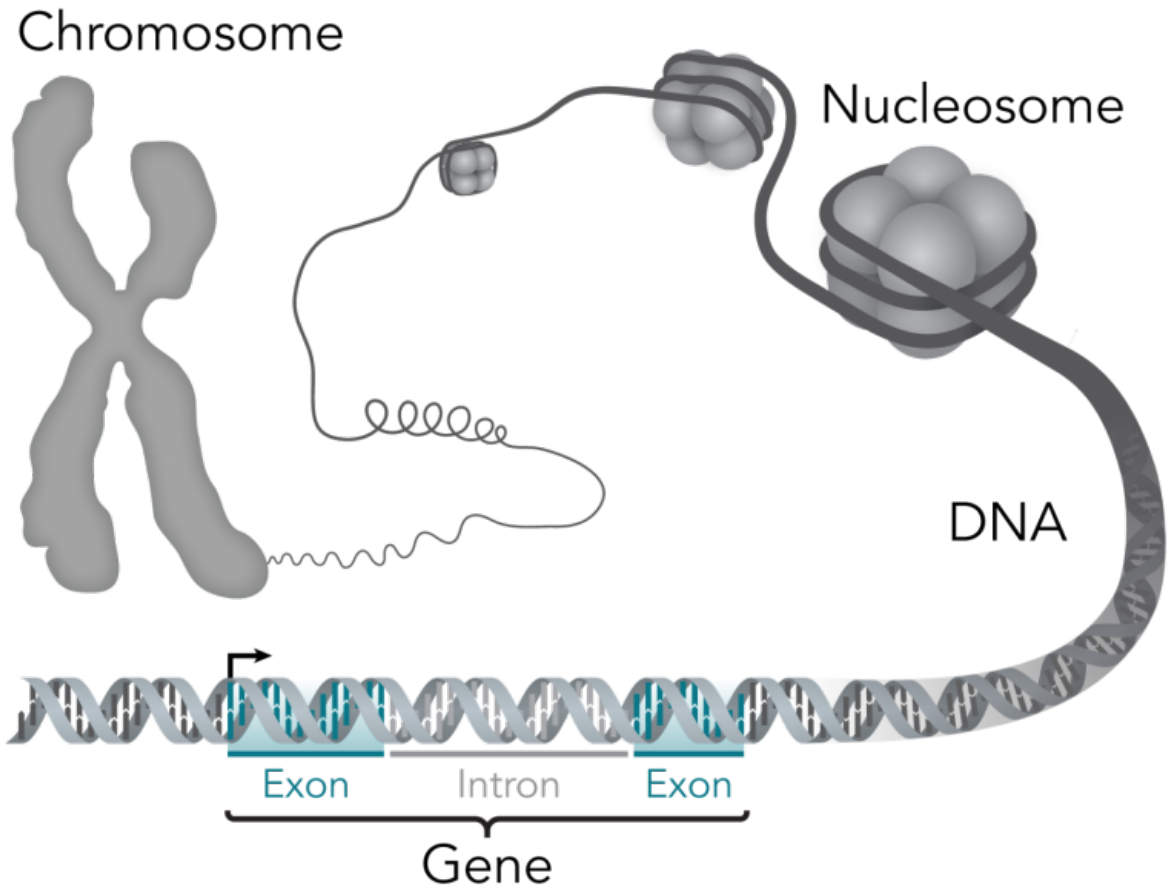

This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

Canine Degenerative Myelopathy (DM) is a neurodegenerative disease in dogs with similarities to ALS in humans. Scientists at Uppsala University, SciLifeLab and the Broad Institute of MIT and Harvard, in collaboration with researchers at the University of Missouri, have discovered a modifier gene that affects the risk of developing DM in Pembroke Welsh Corgis (PWC). The study is published in *PNAS* this week.

Degenerative Myelopathy is a naturally occurring, progressive adult onset disorder of the spinal cord that leads to paralysis and death. In 2009, a SOD1 mutation was associated with risk of developing the disease (link to previous press release). However, not all dogs with the mutation became affected, prompting the hypothesis that additional genes could modify disease risk.

Genome-wide association analysis comparing affected and unaffected PWC with the SOD1 mutation identified a haplotype within the gene 'SP110 nuclear body protein' that was associated with increased risk of developing DM and early age of onset.

We discovered several variants in SP110 that were more common in the PWCs that developed DM says Emma Ivansson, former PostDoc at Uppsala University leading the study.

Our functional studies revealed that the variants alter expression of SP110 in blood cells continues Sergey Kozyrev, senior scientist at Uppsala University.

Whether SP110 affects the risk of DM also in other dog breeds requires

further investigation, says Kate Megquier, veterinarian and PhD student at Uppsala University and Broad Institute.

SP110 is a regulator of gene expression, mainly in immune cells. It is known that the immune response is important in neurodegeneration, but inflammation can be either protective or damaging and the exact mechanisms are still unclear.

Many studies have investigated the role of immunity in ALS, and our finding that a gene regulating the immune response is important in this canine model of ALS could provide a new angle says Emma Ivansson.

More information: Variants within the SP110 nuclear body protein modify risk of canine degenerative myelopathy, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1600084113

T. Awano et al. Genome-wide association analysis reveals a SOD1 mutation in canine degenerative myelopathy that resembles amyotrophic lateral sclerosis, *Proceedings of the National Academy of Sciences* (2009). DOI: 10.1073/pnas.0812297106

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