# A gene finding links severe canine juvenile epilepsy to mitochondrial dysfunction

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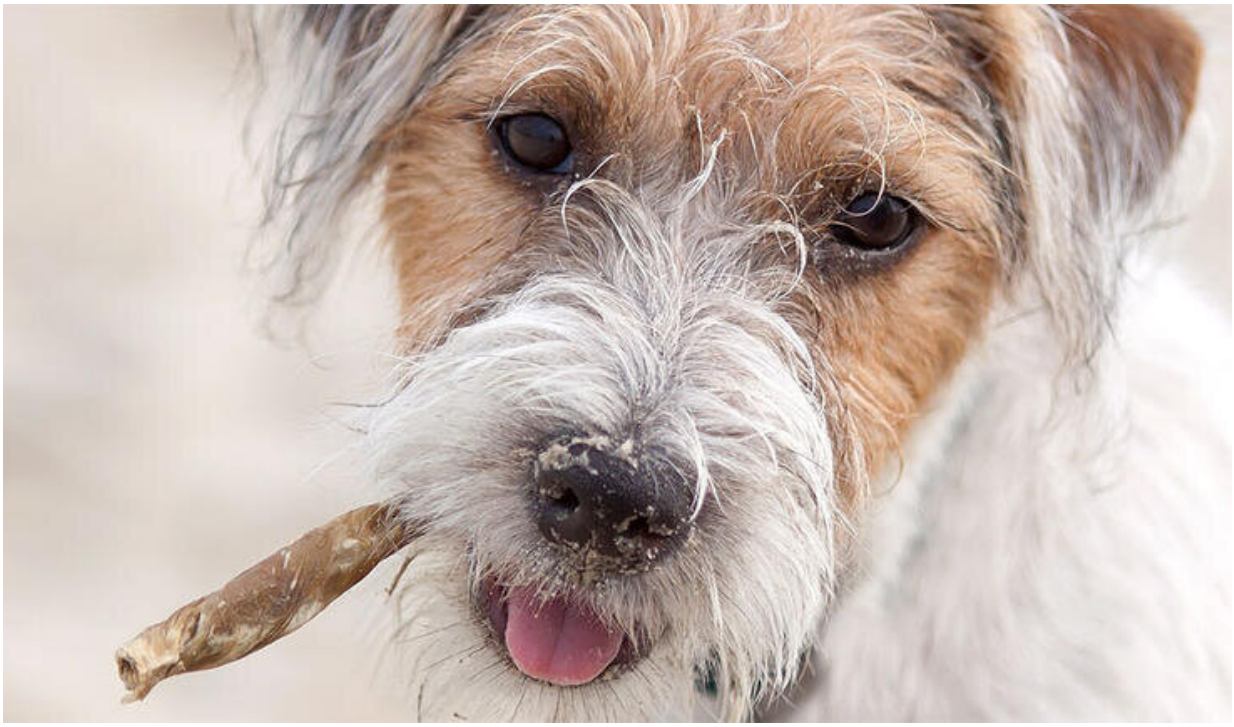

Credit: University of Helsinki

In a study conducted at the University of Helsinki, researchers found a cause for severe epilepsy resulting in death in Parson Russell Terrier puppies at a few months of age. A change in the PITRM1 gene can lead to a dysfunction of mitochondria, the cellular energy pumps. Concurrently, amyloid-β accumulation and widespread

neurodegeneration associated with Alzheimer's disease were identified in the puppies' brains. Changes to the PITRM1 gene in humans also cause a severe but slowly progressing brain disease.

Some Parson Russell Terrier puppies were seen to suddenly develop epileptic seizures at 6 to 12 weeks of age. The disease progressed very rapidly, in a matter of hours in the worst cases, to a situation where the seizures were continuous and unresponsive to medication.

"All of the sick dogs either died spontaneously or had to be euthanised. On the tissue level, neuronal necroses, or dead neurons, were identified throughout the brains of the deceased dogs. In the neurons, we observed crowding of mitochondria, the cellular energy pumps, and accumulation of amyloid-β typical of Alzheimer's disease. Such an accumulation is expected to be found in old dogs only," says Docent Marjo Hytönen from the University of Helsinki and the Folkhälsan Research Center.

With the help of several research groups at the University of Helsinki and international partners, samples were collected from around Europe, making it possible to pinpoint the gene defect underlying the disease to the PITRM1 gene. This gene encodes an enzyme that is important to mitochondrial function. Due to their responsibility for cellular energy metabolism, mitochondria are key to the functioning of cells.

"In the study, we determined the presence of the variant in nearly 30,000 dogs from 374 breeds, identifying the gene defect only in Parson Russell Terriers. Fortunately, the carrier frequency was low, only 5%. The findings will benefit dogs immediately, as a gene test made available based on the results helps identify carriers and avoid breeding them to produce sick puppies. We have already previously reported the gene test results for the roughly 700 dogs tested in the study," says Professor Hannes Lohi from the University of Helsinki.

The disease associated with Parson Russell Terriers is a recessive trait, which means that, for the disease to develop, the defective gene must be copied from both parents to the offspring. The defect is found in this specific breed only.

"The PITRM1 protein serves as a kind of mitochondrial cleaner that breaks up unnecessary pieces of protein and also the harmful amyloid-β. The accumulation of these substances in mitochondria disturbs their function, while neurons in particular tolerate deficient cellular respiration poorly, which explains the early-onset neurodegeneration in dogs. The gene defect results in the disappearance of two amino acids in the PITRM1 enzyme and inhibits it from functioning normally," Hytönen says.

In humans, changes in the same PITRM1 gene also cause neurodegeneration that results in cerebellar ataxia with psychiatric and cognitive abnormalities.

"The human disease progresses slower, but the clinical picture and mechanisms are similar. Our canine study confirms the significance of PITRM1 to mitochondrial and neuronal function, also strengthening the link between mitochondrial dysfunction and neurodegeneration. For now, there are few human patients diagnosed with this disease, which makes the canine model groundbreaking in terms of understanding it," says Professor Lohi.

**More information:** Marjo K. Hytönen et al, In-frame deletion in canine PITRM1 is associated with a severe early-onset epilepsy, mitochondrial dysfunction and neurodegeneration, *Human Genetics* (2021). DOI: 10.1007/s00439-021-02279-y