Canine Hereditary Ataxia

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KEYWORDS

- Cerebellar abiotrophy • Spinocerebellar • Purkinje neuron
- Granuloprival degeneration

KEY POINTS

- Hereditary ataxias are a heterogeneous group of neurodegenerative diseases characterized clinically by cerebellar ataxia.
- Classification of the disorders in veterinary medicine has been based on neuropathologic changes into cerebellar cortical degeneration, spinocerebellar degeneration, canine multiple system degeneration, cerebellar ataxias without significant neurodegeneration, and episodic ataxia.
- Genetic tests for these diseases are emerging and will help to reduce prevalence of disease, make a definitive diagnosis, and identify potential therapies.

INTRODUCTION

The hereditary ataxias are a large group of diseases that have inherited cerebellar or spinocerebellar dysfunction at their core. Although each individual disease is rare, as a group they are an important cause of movement disorders in purebred dogs.[1] The recent rapid increase in our understanding of their genetic basis has culminated in the availability of genetic tests for certain diseases, with the potential to reduce prevalence or eliminate them in the near future. This article outlines the current classification system in veterinary medicine and compares it with the system used in human medicine. Key clinical and diagnostic features of well-described diseases are highlighted and, where known, the genetic basis is described. There are several other neurodegenerative disease processes that target the cerebellum. Most notably, these include many lysosomal storage diseases as well as neuroaxonal dystrophies and spongy degeneration of the cerebellum but these diseases are classified separately and are not discussed here.

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CLASSIFICATION

In human medicine, hereditary ataxia is currently classified according to the mode of inheritance and genetic cause or locus (**Box 1**).[2–4] However, the current human classification system evolved from a neuropathologic classification divided into olivopontocerebellar atrophy, cerebellar cortical atrophy, and spinocerebellar degeneration in the early twentieth century, through a combination of clinical presentation and genetic mapping in the 1980s[5] to the current twenty-first century system. This evolution was vital because a purely neuropathologic classification led to incorrect diagnoses and incomplete understanding of the disease mechanisms. Genetic mapping of these disorders in humans has revolutionized the understanding of this group of diseases and highlighted the ability of diverse underlying defects to produce the same neuropathologic endpoint. For example, autosomal dominant spinocerebellar ataxia (SCA) can be caused by a mutation in a growth factor gene (FGF14), a gene for a cytoskeletal component (β-III spectrin) or an ion channel (*CACNA1A*, a calcium channel).[3] Conversely, one mutation can produce extremely diverse clinical phenotypes in

Box 1
Classification of hereditary ataxias in humans

Autosomal dominant ataxias

Spinocerebellar ataxias:

- Thirty-seven different genetic subtypes recognized to date; this number increases steadily

Episodic ataxias:

- Six different episodic ataxias are currently recognized

Autosomal recessive ataxias

- Friedreich ataxia
- Ataxia telangiectasia
- Autosomal recessive ataxia with oculomotor apraxia type1
- Autosomal recessive ataxia with oculomotor apraxia type2
- Autosomal recessive spastic ataxia of Charlevoix-Saguenay
- Ataxia with isolated vitamin E deficiency
- Marinesco-Sjögren syndrome
- Autosomal recessive ataxias due to POLG mutations (MIRAS, SANDO)
- Cerebrotendinous xanthomatosis
- Refsum disease
- Abetalipoproteinemia
- Other autosomal recessive ataxias

X-linked ataxias

- Fragile X–associated tremor/ataxia syndrome
- Other X-linked ataxias

Ataxias due to mitochondrial mutations

The primary categorization is based on the mode of inheritance and then subdivided by pathology, clinical syndrome, or mutation.

Data from Jayadev S, Bird TD. Hereditary ataxias: overview. Genet Med 2013;15:673–83.