Ataxia Neuropathy Spectrum

Subjects: Genetics & Heredity
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Ataxia neuropathy spectrum is part of a group of conditions called the *POLG*-related disorders. The conditions in this group feature a range of similar signs and symptoms involving muscle-, nerve-, and brain-related functions. Ataxia neuropathy spectrum now includes the conditions previously called mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).

Keywords: genetic conditions

1. Introduction

As the name implies, people with ataxia neuropathy spectrum typically have problems with coordination and balance (ataxia) and disturbances in nerve function (neuropathy). The neuropathy can be classified as sensory, motor, or a combination of the two (mixed). Sensory neuropathy causes numbness, tingling, or pain in the arms and legs, and motor neuropathy refers to disturbance in the nerves used for muscle movement.

Most people with ataxia neuropathy spectrum also have severe brain dysfunction (encephalopathy) and seizures. Some affected individuals have weakness of the external muscles of the eye (ophthalmoplegia), which leads to drooping eyelids (ptosis). Other signs and symptoms can include involuntary muscle twitches (myoclonus), liver disease, depression, migraine headaches, or blindness.

2. Frequency

The prevalence of ataxia neuropathy spectrum is unknown.

3. Causes

Ataxia neuropathy spectrum is caused by mutations in the *POLG* gene or, rarely, the *TWNK* gene.

The *POLG* gene provides instructions for making one part, the alpha subunit, of a protein called polymerase gamma (pol γ). The *TWNK* gene provides instructions for making a protein called Twinkle. Pol γ and Twinkle function in mitochondria, which are structures within cells that use oxygen to convert the energy from food into a form cells can use. Mitochondria each contain a small amount of DNA, known as mitochondrial DNA (mtDNA), which is essential for the normal function of these structures. Pol γ and Twinkle are both integral to the process of DNA replication by which new copies of mtDNA are produced.

Mutated pol γ or mutated Twinkle reduce mtDNA replication. Although the mechanisms are unknown, mutations in the *POLG* gene often result in fewer copies of mtDNA (mtDNA depletion), and mutations in the *TWNK* gene often result in deletions of large regions of mtDNA (mtDNA deletion). MtDNA depletion or deletion occurs most commonly in muscle, brain, or liver cells. MtDNA depletion causes a decrease in cellular energy, which could account for the signs and symptoms of ataxia neuropathy spectrum. It is unclear what role mtDNA deletions play in the signs and symptoms of the condition.

3.1. The genes associated with Ataxia neuropathy spectrum

- POLG
- TWNK

4. Inheritance

Ataxia neuropathy spectrum can have different inheritance patterns depending on the associated gene.

Mutations in the *POLG* gene cause a form of the condition that is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Mutations in the *TWNK* gene cause a form of the condition that is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

5. Other Names for This Condition

- ANS
- MIRAS
- mitochondrial recessive ataxia syndrome
- SANDO
- sensory ataxia neuropathy dysarthria and ophthalmoplegia

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