National Ataxia Foundation

X-Linked Cerebellar Ataxias

What is XLCA?

X-Linked Cerebellar Ataxias (XLCA) are a group of rare neurodegenerative disorders. There are many types of XLCA, with new forms of XLCA still being discovered. Each type of XLCA is caused by mutations in different genes. Some genes that cause XLCA have been identified, and others have not.

The frequency of XLCA disorders varies. Most are quite rare. However, some forms of XLCA are more common, such as FXTAS (1 in 8,000 people) and Rett syndrome (1 in 10,000 women).

XLCA Symptoms

Like many other forms of Ataxia, XLCA is marked by poor balance and coordination. In fact, the word Ataxia means incoordination. There can also be problems coordinating muscles that control speech and swallowing.

The other symptoms that someone with XLCA experiences depend on their specific ataxia type.

- **X-linked spinocerebellar ataxia (SCA-X1)** is caused by mutations in the *ATP2B3* gene. Symptoms are usually present from birth. This includes ataxia, decreased muscle tone, delayed early developmental milestones, difficulty speaking, and slow eye movements. Symptoms are known to vary between patients, even within the same family.
- **X-linked ataxia with spasticity (SCA-X2)** is caused by mutations in an unknown gene. Symptoms are present from birth. This includes ataxia, spasticity, head tremor, intellectual disability, and premature death.
- **X-linked ataxia with deafness (SCA-X3)** is caused by mutations in an unknown gene. Symptoms develop during infancy. This includes ataxia, deafness, decreased muscle tone, delayed early developmental milestones, cross-eyed gaze, and premature death.
- **X-linked ataxia with dementia (SCA-X4)** is caused by mutations in an unknown gene. Symptoms first appear in childhood, and progress over time. Initial symptoms include delayed walking and tremor. In their teenage years, people with SCA-X4 develop mild but progressive ataxia. In their mid-thirties, patients develop progressive dementia, leading to premature death in their sixties.
- **X-linked congenital ataxia (SCA-X5)** is caused by mutations in an unknown gene. Ataxia symptoms are present from birth, along with eye and speech symptoms. Symptoms tend to improve with age.
- **X-linked sideroblastic anemia with spinocerebellar ataxia (SCA-X6)** is caused by mutations in the *ABCB7* gene. Symptoms begin during infancy. They include slowly progressive ataxia and anemia. Some patients also develop speech symptoms, eye symptoms, or spasticity.
- **Oligophrenin-1 syndrome** is caused by mutations in the *OPHN1* gene. Symptoms first appear in childhood. They include ataxia, decreased muscle tone, intellectual disability, and delayed early developmental milestones. Some patients also experience seizures. Symptoms are known to vary between patients, even within the same family.
- **CASK syndrome** is caused by mutations in the *CASK* gene. Symptoms first appear in childhood. People with CASK syndrome tend to have smaller heads, intellectual impairment, and ataxia. Some people may develop hearing loss or eye symptoms. Some people with CASK syndrome have seizures, but this is more common for girls than boys.
- **Christianson syndrome** is caused by mutations in the *SLC9A6* gene. Symptoms first appear in early childhood. They include ataxia, intellectual disability, impaired eye movements, decreased muscle tone, having small head, seizures, delayed developmental milestones, and developmental regression.
- **Fragile X-associated tremor/ataxia syndrome (FXTAS)** is caused by mutations in the *FMR1* gene. Symptoms begin in late adulthood. Please visit our FXTAS information page for more information.

XLCA Symptoms (continued)

- **X-linked cerebellar hypoplasia and spondyloepyphiseal dysplasia** is caused by mutations in the *RPL10* gene. Symptoms first appear in childhood. They include ataxia, intellectual disability, having a small head, slowed growth, seizures, and minor facial anomalies.
- **Allan–Herndon–Dudley syndrome (AHDS)** is caused by mutations in the *MCT8* gene. Symptoms first appear in early childhood. They include ataxia, intellectual disability, difficulty speaking, spasticity, weakness, reduced muscle mass, and delay of developmental milestones.
- **Rett syndrome (RTT)** is caused by mutations in the *MECP2* gen. Symptoms begin in early childhood. After typical development, patients with Rett syndrome regress around age 6-18 months. They develop ataxia, repetitive hand movements, breathing challenges, seizures, epilepsy, loss of speech, and increased reflexes. Rett syndrome is more common in girls than boys. Please visit the International Rett Syndrome Foundation to learn more.

Prognosis

The prognosis for people with XLCA depends on their specific ataxia type. Many forms begin during childhood and progress over time. Treatments such as physiotherapy, occupational therapy, and speech-language therapy can also significantly improve the lives of people with XLCA. Depending on a person's type of XLCA, there may also be symptomatic or disease-specific treatments available.

Genetics

XLCA is a group of genetic disorders, which means that they are inherited diseases. Each type of XLCA is caused by mutations in different genes.

Genes are microscopic structures within the cells of our bodies that contain instructions for every feature a person inherits from his or her parents. The abnormal gene responsible for different forms of XLCA is passed along from generation to generation by unaffected family members who carry it. Sometimes, these mutations will also randomly develop in someone when they are conceived.

XLCA are X-linked disorders, meaning that the genes that cause these disorders are found on the X chromosome. Usually, women have two X chromosomes (XX) and men have one X and one Y chromosome. Due to this difference, X-linked disorders impact men and women differently.

X-Linked Recessive Ataxia

Most forms of X-linked ataxia are recessive.

Men who carry the mutation for an X-linked recessive ataxia will develop that condition. This is because they only have one X chromosome, which is affected by the ataxia mutation. Men are more commonly impacted by X-linked recessive ataxia.

Women who have one copy of the mutation for an X-linked recessive ataxia will not usually develop the condition. This is because they have two X chromosomes, and the unaffected X chromosome can protect them from developing symptoms. People who have a mutation for an X-linked recessive ataxia without developing symptoms are called carriers. Depending on the type of XLCA, some carriers may also experience mild features of the disorder. If a woman has two copies of the mutation for an X-linked recessive ataxia, one on each X chromosome, then she will develop that condition.

Genetics (continued)

The likelihood of passing on an X-linked recessive ataxia is complicated. It depends on the sex of the parent passing on the gene, and the sex of the child receiving the gene. You can learn more about X-linked recessive condition inheritance patterns through the NHS National Genomics Education Programme.

X-Linked Dominant Ataxia

Only one copy of a mutation for an X-linked dominant ataxia is needed to develop the condition. Thus, both men and women can be affected by X-linked dominant ataxia, if they have one copy of the mutated gene. Since they only have one X chromosome, men tend to have more severe symptoms than women. Sometimes the symptoms are so severe, boys with X-linked dominant ataxia either die in utero or shortly after birth. Rett syndrome is one example of an X-linked dominant ataxia.

Genetic Counseling and Testing

Gene tests can be performed for diagnostic purposes to determine what kind of Ataxia is within a person or family. Genetic testing can also be done, in some circumstances, even before there are symptoms to determine whether a person carries the abnormal gene or genes that cause Ataxia. This is called predictive or presymptomatic testing. A gene test can also be used to determine whether a fetus has an abnormal Ataxia gene. This is called prenatal testing. Anyone who is considering a predictive or prenatal test should consult with a genetic counselor to discuss the reasons for the test, the possible outcomes, and how those outcomes might affect the person emotionally, medically, or socially.

Diagnosis

A neurologic examination can determine whether a person has symptoms typical of XLCA. A neurologist is often the most helpful specialist in recognizing symptoms and diagnosing the disease that causes Ataxia.

Providing a detailed family history is critical for accurately diagnosing X-linked conditions. There are several potential follow-up tests. MRI brain imaging may be used to confirm cerebellar atrophy. Metabolic testing may be used to rule out other forms of ataxia that have similar symptoms to XLCA. A definitive diagnosis of XLCA is established following genetic testing. This confirms that someone has a mutation that causes XLCA.

What kind of support is available after the diagnosis?

The National Ataxia Foundation (NAF) is committed to providing information and education about Ataxia, support groups for those affected by Ataxia, and promoting and funding research to find the cause for the various forms of Ataxia, better treatments, and, hopefully someday, a cure. As Ataxia research moves into the clinical phase, pharmaceutical companies will begin recruiting participants for clinical trials. Individuals with Ataxia or who are at-risk for Ataxia are encouraged to enroll in the CoRDS Ataxia Patient Registry. To access the Registry, go to NAF's website www.ataxia.org and click on the "Enroll in the Patient Registry" tab and follow the directions on the CoRDS website.

NAF provides accurate information for you, your family, and your physician about Ataxia. Please visit the NAF website at www.ataxia.org for additional information, including a listing of ataxia support groups, physicians who treat Ataxia, social networks, and more. For questions contact the NAF directly at (763) 553-0020 or naf@ataxia.org.