



ALS and genetics

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While researchers are still working to understand the exact causes of amyotrophic lateral sclerosis (ALS), it is widely understood that ALS develops as a result of a number of different risk factors, some of which are genetic and some of which are environmental.

While approximately 90-95% of cases are seemingly “sporadic”, with an unknown cause of disease, 5-10% of cases are associated with a family history of ALS. It is important to note that familial ALS and sporadic ALS both present with the same general signs and symptoms.

SPORADIC ALS

In most cases of sporadic ALS, the cause is unknown; however, it is still possible that an individual’s genetics are playing a role. There is a growing appreciation for the number of cases of sporadic ALS that can be traced to genetic mutations, even if a person does not have a family history of ALS. Sometimes information on previous generations is unclear or unavailable, amongst other reasons why a family history of ALS could have been missed. It is also possible that a mutation may be occurring for the first time in an affected person and could be passed onto future offspring.

FAMILIAL ALS

In familial ALS, an inherited genetic mutation causes ALS. Many different genetic mutations have been linked to ALS, and not all families have the same mutation as the cause of their ALS.

The most common pattern of inheritance for familial ALS genetic mutations is called autosomal dominant. This means that a person only needs one copy of the mutated gene to be affected. Each child has a 50% chance of inheriting the mutation, regardless of whether it is their mother or father who is affected. Inheriting the mutation does not guarantee ALS, but it does significantly increase the risk of developing it.

Other patterns of inheritance, such as autosomal recessive (two copies of the defective gene are required to cause disease), or X-linked inheritance (defective genes are passed on in a sex-specific manner), do exist, but are much less common.

Families affected by familial ALS often have questions about ALS and genetics. Unaffected family members may feel conflicted about whether to take a genetic test to assess their own risk of developing ALS. Both affected and unaffected family members may struggle with fear, guilt, and isolation at different points in their experience.

WHAT IS THE DIFFERENCE BETWEEN FAMILIAL AND SPORADIC ALS?

FAMILIAL ALS

- 5 - 10% of cases
- Caused by genetic mutations
- Mutations can be inherited or new
- Often associated with an earlier age of onset
- Some specific mutations are associated with either very rapid or very slow rates of disease progression
- Most of the time there is a family history of ALS that can be traced. Some mutations are associated with family histories of different symptoms, such as dementia
- In most cases, each child of an individual with familial ALS has a 50% chance of inheriting the mutation

SPORADIC ALS

- Clinically indistinguishable
- Both environmental and genetic factors are relevant
- 90 - 95% of cases
- ~10% of cases are explained by known genetic mutations
- There is usually no family history of ALS; however, there are multiple reasons why a family history could have been missed
- If a genetic mutation is the cause of the seemingly sporadic cases, mutations may be occurring for the first time, or be inherited
- First-degree relatives of people with sporadic ALS have a 1% chance of developing ALS

WHAT DO WE KNOW ABOUT GENETICS AND ALS?

Research has uncovered multiple genetic mutations linked to ALS, many of which have only been discovered in the last 10 years due to advances in scientific technology. The mutations most commonly associated with ALS are SOD1, C9ORF72, TARDBP, and FUS. These explain a high percentage of ALS cases, with many others causing a smaller number of cases. More than two-thirds of cases of familial ALS can currently be explained by known genetic mutations, meaning there is still much research to be done to uncover the other causes.

SOD1

- Stands for Superoxide Dismutase 1.
- 1st genetic mutation discovered as causing ALS, in 1993.
- Mutations in this gene account for 20% of familial cases of ALS and ~2% of all cases of ALS (sporadic and familial).
- Research mice are often artificially given this mutation so that they develop ALS.

C9ORF72

- Called a repeat expansion mutation – consists of multiple repeating copies (sometimes upwards of thousands) of a small, specific sequence of DNA, or genetic code.
- Discovered in 2011.
- Accounts for approximately 40% of familial ALS cases, and approximately 7-10% of sporadic cases in people of European ancestry.
- This mutation is associated with development of ALS symptoms, a specific type of dementia called frontotemporal dementia (FTD), or a mix of both ALS and FTD. Affected individuals may have a family history of ALS, FTD, both, or lack a family history entirely.

TDP-43

- Stands for TAR DNA Binding Protein 43. Also called TARDBP.
- Linked to both ALS and FTD.
- Accounts for ~4% of familial ALS cases and a smaller number of sporadic cases.
- While the number of sporadic cases caused by a mutation in this gene is low, scientific evidence shows that the protein encoded by this gene is somehow implicated in 97% of sporadic cases.

FUS

- Stands for Fused in Sarcoma.
- Accounts for ~4% of familial ALS cases.
- Commonly associated with a very young age of onset, and rapidly progressing disease.

SHOULD I TAKE A GENETIC TEST?

As a relative of someone living with ALS, you may feel conflicted about whether to take a genetic test.

A genetic counselor can help you decide if genetic testing is right for you. A genetic counselor will take a detailed medical and family history and discuss the impact of genetic testing. The decision of whether to test is always yours.

Genetic testing is not recommended for people under 18, because they cannot give their full consent.

REASONS PEOPLE MAY WANT TO TEST

- Assist in family planning decisions
- Be proactive about their health (e.g. getting a diagnosis earlier)
- Give themselves time to adjust to the idea that they may develop ALS
- Reduce anxiety if they find they do not have the mutation
- Proactive identification of genetic status for future therapeutic trials, and contribution to research, to further our understanding of ALS

REASONS PEOPLE MAY NOT WANT TO TEST

- It can be difficult to live with the knowledge of a possible impending illness
- It can cause tension with other family members, who may not wish to know your genetic status
- Your genetic status may inadvertently reveal the status of another family member (you want to get tested, but your parent does not)
- Avoiding guilt about passing on the illness to children, or testing negative when others test positive

FUTURE DIRECTIONS

Genetic research is an important component of ALS research. Researchers frequently use genetically modified animals as models for ALS. They can use these to understand the disease, and to test new potential treatments for ALS.

While the number of mutations associated with causing ALS is ever expanding, there is also growth in our understanding of how genetics play a role in increased risk, types of symptoms a patient gets, or how their disease progresses, without directly being the cause of their ALS.

There are currently numerous therapies in development for the genetic forms of ALS. While some are only just entering clinical trials, some are much further along with preliminary data available. With a very specific target identified, these kinds of therapies are offering hope for a future without ALS.

SUMMARY

- The causes of ALS can be familial or sporadic. Familial ALS is related to genetic factors, while in sporadic ALS, the cause of the illness may be genetic or environmental.
- 5-10% of ALS is familial, while 90-95% is sporadic.
- Researchers have identified several genes linked to ALS, and are working to better understand the genetic underpinnings of familial ALS.
- People with ALS and their families face a difficult choice about whether to be tested for ALS-linked genes. The decision to be tested is personal, and must be made with the rest of the family in mind.
- There is support available. Genetic counsellors can help families understand the pros and cons of testing, and you can consult with one without committing to a test.

ADDITIONAL RESOURCES

[Common mutations of interest in the diagnosis of amyotrophic lateral sclerosis: how common are common mutations in ALS genes?](#)

[State of play in amyotrophic lateral sclerosis genetics](#)

[Clinical genetics of amyotrophic lateral sclerosis: what do we really know?](#)

[Potential Environmental Factors in Amyotrophic Lateral Sclerosis](#)

KNOW THAT WE ARE HERE TO HELP! For people and families living with ALS in Ontario, ALS Canada can assist in connecting you to support services, equipment, and ALS clinics. Whether you are a person living with ALS, a family member or a caregiver, we will strive to support you along this journey. If you live outside of Ontario, please contact your provincial ALS Society for information on support available in your region. Learn more at www.als.ca.

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