

# ALS AND GENETICS

While researchers are still working to understand the exact causes of ALS, it is widely understood that ALS develops as a result of multiple different risk factors, some of which are genetic and some of which are environmental. This complex relationship between genetic susceptibility and risk factors related to lifestyle is not yet understood, but significant progress is made every year.

Approximately 10% of individuals with ALS will have a family history of the disease. In these cases, ALS is caused by a change in the genetic code, called a mutation or variant, and is passed from parent to child. This is traditionally termed “familial” ALS and in some cases, there may also be a shared history of frontotemporal dementia (FTD). For the 90% of individuals with ALS without a family history, traditionally termed “sporadic”, it is estimated that more than 10% of cases are caused by known ALS genes. Familial ALS and sporadic ALS both have the same general signs and symptoms and are clinically indistinguishable.

## 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 disease. In approximately one-third of cases of inherited ALS, a mutation has not yet been discovered.

Some genetic mutations are associated with a high likelihood that someone will develop ALS symptoms, while other mutations may not cause ALS in everyone. This is a phenomenon called penetrance. Some mutations are also linked to specific disease symptoms or rates of progression. Further, it is likely that lifestyle and environmental risk factors play some role in how or when ALS develops in people with an inherited mutation. It’s important to note that many known genetic mutations in ALS are still not well understood, and only the most common ones have a solid base of knowledge.

## SPORADIC ALS

In most cases of sporadic ALS, the cause is unknown; however, it is still probable that an individual’s genetics are playing a role in a significant number of cases. Rather than a single gene mutation, there is likely a complex genetic susceptibility that researchers have yet to understand.

There is also a growing appreciation for the number of cases of sporadic ALS that can be traced to single, known genetic mutations, even if a person does not have an obvious family history of ALS. This may be the result of a mutation occurring spontaneously for the first time, or due to an inherited ALS-associated mutation in an individual where family history information is lacking or unknown. In both cases, the mutation could be passed on to future offspring.



## SHOULD I TAKE A GENETIC TEST?

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



Speak to your neurologist, or other ALS expert clinician, to help you decide if genetic testing is right for you. Your neurologist may be able to connect you with a genetic counsellor, who will take a detailed medical and family history and discuss the impact of genetic testing. The decision of whether to be tested is always yours.

It is important to note that there are many mutations in known ALS genes that don't yet have sufficient research and information to fully understand their impact on someone. Some physicians may hesitate to order genetic testing out of discomfort with not being able to provide comprehensive support in understanding a complicated result. However, given that ALS-associated mutations have been identified in seemingly sporadic cases of ALS, and that therapies targeting these mutations are entering, or are ongoing in, clinical trials, many experts are pushing for everyone to be offered genetic testing, accompanied by genetic counselling. The availability of genetic testing and counselling varies from region to region, so it is important to note that genetic testing practices in ALS are rapidly evolving, but not sufficient yet to meet the needs of everyone.

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

If you are a blood relative of someone affected by ALS, in whom a causative mutation has been identified, you may also be eligible for genetic testing. Genetic testing in an individual at risk of developing a disease, but who is not currently exhibiting any symptoms, is called predictive testing. Predictive testing requires extensive genetic counselling. Further research is needed in this area.

Reasons people may want to be tested	Reasons people may not want to be tested
<ul style="list-style-type: none"> <li>● Assist in family planning decisions</li> <li>● Be proactive about their health (e.g. getting a diagnosis earlier)</li> <li>● Give themselves time to adjust to the idea that they may develop ALS</li> <li>● Reduce anxiety if they find they do not have the mutation</li> <li>● Proactive identification of genetic status for future therapeutic trials, and contribution to research, to further understanding of ALS</li> </ul>	<ul style="list-style-type: none"> <li>● It can be difficult to live with the knowledge of a possible impending illness</li> <li>● It can cause tension with other family members, who may not wish to know the test results</li> <li>● Genetic status may inadvertently reveal the status of another family member (e.g. if someone wants to get tested, but the parent does not)</li> <li>● Avoiding guilt about passing on the illness to children, or testing negative when others test positive</li> </ul>

## 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 gene 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. A better understanding of the role genetics plays in ALS provides critical information to understanding the ALS disease spectrum as a whole.

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 significant hope for the near future.

### LEARN MORE

Visit ALS Canada's YouTube channel to view a webinar about genetics and ALS.

[https://www.youtube.com/watch?v=LegL2d\\_d4z4](https://www.youtube.com/watch?v=LegL2d_d4z4)

### KNOW THAT WE ARE HERE TO HELP

The ALS Society of Canada can assist in connecting people and families living with ALS in Ontario to support services, equipment, and ALS clinics. We also invest in the most promising Canadian ALS research, advocate federally and provincially for the needs of people affected by ALS, and provide information to empower Canadians affected by the disease. Learn more at [www.als.ca](http://www.als.ca) where you can also find more resources in the "What is ALS?" section.

If you live outside of Ontario, please contact your provincial ALS Society for information on support available in your region.

## References

Collectively, all of this information and much more can be gathered from the following open access, peer reviewed manuscripts:

<https://pubmed.ncbi.nlm.nih.gov/25300936/>

<https://pubmed.ncbi.nlm.nih.gov/34974309/>

<https://pubmed.ncbi.nlm.nih.gov/30045958/>

<https://pubmed.ncbi.nlm.nih.gov/34343141/>

<https://pubmed.ncbi.nlm.nih.gov/35020823/>

<https://pubmed.ncbi.nlm.nih.gov/28159885/>

<https://pubmed.ncbi.nlm.nih.gov/35027459/>

<https://pubmed.ncbi.nlm.nih.gov/28159885/>

<https://pubmed.ncbi.nlm.nih.gov/32497448/>

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