ALS SLA CANADA

GLOBAL NEURO YCARE

Talking to youth about

ALS/MND GENETICS

A resource for families affected

MELINDA S. KAVANAUGH, PHD, MSW, & CAROLINA JUNG, BSC (HONS)

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This resource is meant to provide basic information on the genetics of amyotrophic lateral sclerosis (ALS/MND), as well as support for families affected on how to approach genetic conversations within the family, with children in particular. We recommend using this resource as an addition to genetic counseling, wherever you are in the world.

This resource was created in collaboration with Global Neuro YCare and the ALS Society of Canada.

Melinda S. Kavanaugh, PhD, LCSW
Global Neuro YCare

Dr. Kavanaugh is a licensed clinical social worker (LCSW), Professor of social work at the University of Wisconsin – Milwaukee, and founder and CEO of Global Neuro YCare. She has over 25 years' experience in practice and research with families and youth living with neurological disorders. She is a global leader in children and youth as caregivers and is one of the few U.S. based experts in her field. Dr. Kavanaugh holds an MSW from Washington University in St. Louis, and a PhD in social welfare from the University of Wisconsin-Madison.

Carolina Jung, BSc (Hons)
ALS Society of Canada

With experience in research and knowledge translation, Carolina has been working at ALS Society of Canada since 2021. Carolina remains dedicated to her passion for accessible and timely scientific and medical communication by driving multiple ALS Canada initiatives and resources, empowering people affected by ALS to make informed decisions, and working towards recognition of ALS research in Canada. Carolina holds a Bachelor of Science with Honours from Western University, and further advanced her education by obtaining a certificate in Biomedical Communication and Visualization from the University of British Columbia.

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Our support for families affected by a genetic form of ALS/MND

The emotional toll of ALS/MND and disease progression can be overwhelming for anyone living with it. Adding potential genetic implications for your family makes it even more difficult to manage.

This resource was created to provide support on these discussions, and clarification on genetic terms and concepts. We wrote this resource in a way that will help guide your own understanding of ALS/MND genetics, as well as to help guide you while talking to children and youth about genetics.

From our research and clinical experience, we know children ask lots of questions, some of which you will be able to answer after reading these materials. Other questions may be more difficult to answer because you need more information, or you need time to process the emotions attached to it. Take it one question at a time, using this guide to help with each one.

If you need more guidance, please reach out to your local ALS/MND organization to get more support. Anyone living with ALS/MND, or with a known genetic risk of ALS/MND, deserves genetic support and to understand how genetics may impact them and their families.

Note: This resource is written from the perspective of a parent talking to their children. However, we recognize this will not always be the case, and other family members might also be involved or leading the conversation. Additionally, the parent may not necessarily be the one with an ALS/MND genetic variant or be aware of their genetic status. Each family is unique, so please change the language or the scenarios as needed to best fit your family situation.

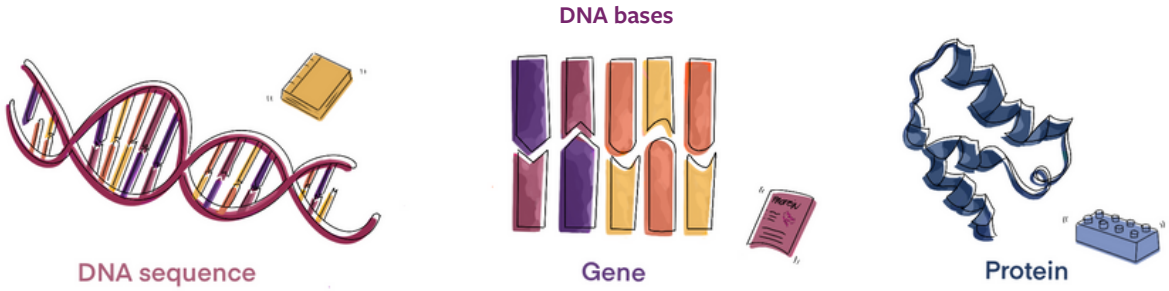
We would like to thank all the genetic counselors and families affected by ALS/MND, as well as End the Legacy and Dr. Elizabeth Finger, for all the support and guidance in building this resource.

EXPLAINING THE GENETICS OF ALS/MND

Genetics might be a topic addressed at school, so it is helpful to explore and ask questions to your children to assess how much they understand it, before explaining the specifics of ALS/MND genetics to them. If they haven't learned about it, below is a brief FAQ on ALS/MND genetics that can help your own understanding of it, to help you prepare for discussions within the family and with children. At the end of this resource, you can also find an ALS/MND genetics glossary and additional resources.

1. WHAT ARE GENES?

Humans are made up of cells, which are the building blocks of our organs and body. Inside each cell, we have a DNA sequence. This sequence is the blueprint needed to build and maintain a human being, and it is made up of individual DNA pieces, called bases. A specific section of DNA bases is known as a gene, and the collective combination of thousands of genes defines a person's unique traits and characteristics.



Genes are passed on from parent to child, resulting in family members having similar features. They carry instructions for how to produce things our body needs, such as proteins. Proteins, in turn, are building blocks for cells and pieces that our body needs for normal functioning.

2. WHAT ARE VARIANTS (MUTATIONS)?

Sometimes, our DNA may be exposed to something that leads to an error in the sequence. Our cells also have to copy our DNA sequence over and over as part of normal cell functioning, and this can also lead to errors in our DNA sequence. These errors happen all the time, in every person. While our bodies have mechanisms to fix these errors, sometimes corrections are not possible, leading to permanent variations in our genes.

A genetic variant is an alteration in the normal sequence of a gene, where a DNA base is altered, missing, or added.

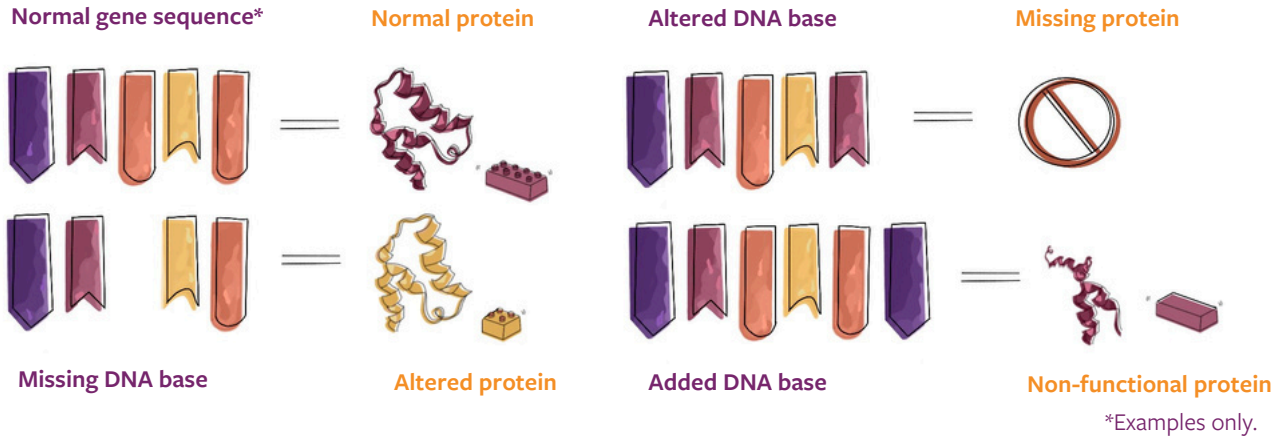
Usually these variants are harmless (benign), but sometimes they can be harmful (pathogenic).

RECIPE BOOK ANALOGY

Let's look at genes with a recipe book analogy: If the cell is our kitchen, the DNA sequence inside our cells is a cookbook. Each gene is a specific recipe inside of it, and the resulting protein is the resulting dish created.

If we change any of the instructions on the recipe page (erase an ingredient, or change its quantities), the dish will be different. Some of these changes can be harmless, for example, swapping chocolate for vanilla when making a cake. However, if we don't include the flour, the cake will fall apart.

Similarly, proteins created from some genetic variants can result in a defective protein or the protein not being created at all.



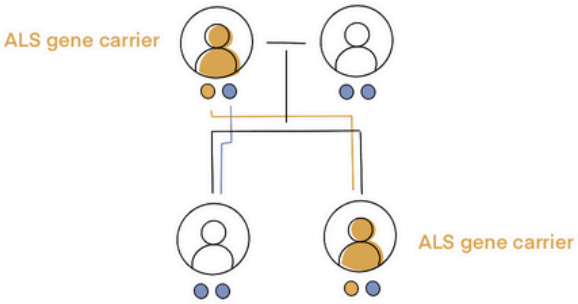
*Examples only.

Pathogenic variants can change the instructions for protein production. Proteins produced from these altered genes might not function the way they are supposed to, or the body might not be able to produce them at all. This can alter normal bodily functions, and potentially lead to disease.

Genetic code errors are frequently referred to as "mutations." This resource will use the term "variant" where possible, which means the same thing.

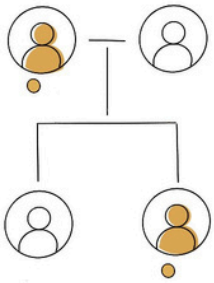
3. WHAT ARE HEREDITARY MUTATIONS?

We have two copies of every gene, one that comes from our mother and one from our father. If your mother, for example, has one copy of a gene variant, you might receive the copy with the variant or the one without. Therefore, not every variant the parent has will be passed on to their children. Gene variants that are inherited from your parents are called hereditary. You can also develop new variants throughout your life, called acquired variants, and there is little to no risk of passing these genes on to your children.



4. WHAT IS A FAMILY HISTORY AND FAMILIAL ALS/MND (FALS/MND)?

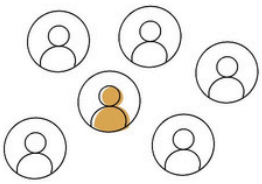
FAMILIAL



5-10%

GENETIC AND HEREDITARY

SPORADIC



90-95%

11-16% OF CASES HAVE A GENETIC COMPONENT

MAY OR MAY NOT BE HEREDITARY

While researchers are still working to understand the exact causes of ALS/MND, it is known that some cases are caused by a genetic variant.

Several genes have been identified that, when altered, can contribute to disease. Approximately five to ten per cent of people living with ALS/MND will have a family history of the disease. A family history means multiple family members have been affected by the disease, due to a hereditary variant in a gene related to ALS/MND.

This is traditionally termed "familial" ALS/MND (FALS), and in some cases, there might be a shared history of frontotemporal dementia (FTD). Family members may be affected by both diseases, or some may develop ALS/MND while others FTD. The exact causes that lead to the onset of one or both diseases are unknown, but for some genes, like C9orf72, the relation to FTD is stronger than for other ALS genes.

Even with a family history of FTD, it is unadvised to associate symptoms with a diagnosis of cognitive impairment without the support of a qualified clinician. There are specialized tests to help detect cognitive changes associated with ALS/FTD.

The genetic link between ALS/MND and FTD is especially important in the context of having these conversations with children. Individuals affected might experience cognitive changes (thinking, memory, language), as well as changes in behavior and personality, which can have an emotional impact on youth. Although this resource focuses on ALS/MND, it is important to understand both diagnoses by seeking clarification with your clinician and genetic counselor, and learning how to best reassure your children about behavioral changes and FTD in the family.

5. WHAT IS "SPORADIC ALS/MND?" CAN IT BE GENETIC?

For the 90-95% of individuals living with ALS/MND without an obvious family history, traditionally referred to as "sporadic," it is estimated that between 11-16% of cases are caused by known ALS/MND variants. This means individuals living with seemingly "sporadic" ALS/MND might have developed a spontaneous (acquired) variant throughout their lives, their family history information was lacking, or the disease didn't manifest in other family members. There is current debate about how the terms "sporadic" and familial ALS/MND are outdated and need to be reevaluated in terms of genetic ALS/MND.

THE FOUR MOST COMMON GENETIC CAUSES OF ALS/MND ARE DUE TO VARIANTS IN FOUR GENES: C9ORF72, SOD1, FUS, AND TARDBP.

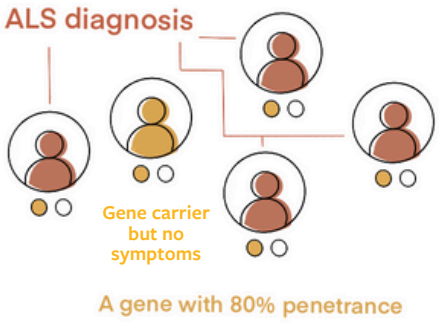
For more detailed information on these and other ALS/MND genes access the ALS Canada Gene Hub at als.ca/genehub

6. IF I HAVE A KNOWN ALS/MND VARIANT, WILL THE VARIANT BE PASSED TO MY CHILDREN?

A genetic counselor is the best person to advise on the risk of an altered ALS/MND gene being passed on to your children. In the majority of cases, the variant has a **50%** chance of being passed on to each family member of a new generation.

The parent has no control over whether the altered gene will be passed on to their children. Whether it is passed on or not is determined by genetic chance, and nothing can be done to change this. Consultation with a genetic counselor can help with understanding aspects of family planning.

If a child does not inherit the gene variant for ALS/MND, they cannot pass it on to their own children.



7. WHAT IS PENETRANCE?

Not every person with a gene variant for ALS/MND will develop symptoms. The proportion of individuals with a genetic variant who will eventually develop the disease is known as penetrance. If a variant has 80% penetrance, 80% of gene carriers will eventually show symptoms of the disease. Different variants have different penetrance, hence the importance of genetic counseling to assess your family risk.

COMMUNICATING WITH CHILDREN: YOUR FEELINGS

HAVE I PASSED ALS/MND TO MY CHILD?

Before we dig into this, it is important to make it clear - this is out of the parent's control, and nothing could have been done to change which genes were inherited. As a parent, you want to do everything you can to protect your child, and the fear of passing along an illness can be very overwhelming. It is normal for some parents to carry feelings of shame and guilt.

If you feel overwhelmed with these feelings, it is important to address them first before starting any conversations with your child. Children will often model and learn from their parent's coping mechanisms and behaviors. Both you and your child deserve to have as much support as possible in preparing for these often emotional conversations.

Familial ALS/MND is much like other illnesses where multiple family members are affected, leaving families feeling isolated and fearful. Often, it will be known as "their family's disease", because they only know other family members who have it. This fear and isolation can cause families to be closed off to outsiders, including people who may want to help and support the family. Additionally, it can make families not be open to having these conversations with their loved ones, including to their children and youth, often because they don't know what to say.

Given the previous lack of accessible genetic information over the years, many families didn't have much information to share, thus the genetic conversation wasn't included in many family guides. Yet, as more research is conducted, knowledge about the genetic variants of ALS/MND is growing every day, providing more information and support for families. It is our hope that families affected by a genetic form of ALS/MND can use this resource to open discussions, including to start conversations with their children.

Even though the great majority of ALS/MND (and all FTD) cases will manifest in adulthood, it is important to discuss your family's genetic status earlier. This resource provides information on why it is important to initiate those conversations, how to go about the conversations, and suggestions for when a good time may be to discuss with children and youth — encouraging an open communication style in families.

COMMUNICATING WITH CHILDREN:
THE WHY

If children have seen multiple family members affected by ALS/MND or FTD, they might already begin to understand that there is something going on in the family. However, due to variable age onset and progression rates, each family will be unique. Whatever your family situation is, the topic should be addressed directly, as they might feel anxious and unsure about their understanding. Some of the questions they might begin to ask themselves are, "When will I get it? Does everyone get it? How can I stop from getting it?" Children often carry these concerns and fears with them, often conflating their own role in your ALS/MND diagnosis, wondering if they might have caused it or could have done something to stop it.

— Some parents might also feel like they are protecting their children by not talking about it or making them worry. Much like the initial conversation about you being diagnosed with ALS/MND, hearing the genetic component from their own family is always better than having to figure out by themselves or seeking information elsewhere. Access to genetic information is increasing rapidly, particularly with the internet. Often, information found online can be misleading and overwhelming. Avoiding the internet and initiating accurate and simplified personal conversations is best.

— Children want to be included in what is happening with you and family discussions. They might feel anxious and excluded if they are being left out of important conversations, such as if you have decided to move or participate in a clinical trial, particularly if you have not shared details about the diagnosis and they looked it up online. It is OK to share this type of information with your child. Again, they know something is going on, and might have overheard conversations. Openly sharing this with them can help lessen their fears and concerns.

If they find out ALS/MND has a genetic component on their own, it might bring them a lot of different feelings, doubts, and uncertainty they might not know how to manage. It may also impact their future trust in you and your relationship.

COMMUNICATING WITH CHILDREN:
THE WHY

— Creating a space for open and honest conversations in the family can help your child open up to you about what they are feeling, and how they are taking in the news. When you model honest conversations, including that you also have concerns and fears, they see this and know they can share honestly and openly with you as well. However, don't be thrown off if your child or youth doesn't want to talk about it. They may need to process or take it in their own time. Alternatively, they may need to write out their feelings, go for a walk, listen to music — whatever it may be so they can process in their own way. But if you keep the door open, and share your own feelings, it makes it clear to your children that they can come to you with questions/concerns.

— Avoiding relaying genetic testing results can substantially increase anxiety and hurdles later on, when another family member or themselves are affected by ALS/MND. As with all conversations about ALS/MND, talking about it earlier might give children/youth the space and time needed to sit with the news. You can shape how they view ALS/MND and empower them to be more prepared for it, particularly if they or another family member are also affected in the future. Denial won't change the chances of the family developing ALS/MND. Indeed, it often breeds more fear, and mistrust — two things that create divisions in families and can be long lasting.

— If they do inherit an ALS/MND genetic variant, and eventually develop symptoms in adulthood, learning what to expect and having family history information may greatly reduce time to diagnosis, and get them to a specialized physician faster.

Earlier diagnosis in adulthood is essential in accessing standard of care, therapies, receiving medical coverage, and participating in clinical trials.

An earlier diagnosis of ALS/MND can drastically change their quality of life and care.

— Researchers are also investigating new links between environmental factors and ALS/MND, which might influence your children's lifestyle and career choices. Currently, the only environmental risk factor that is generally accepted to be associated with ALS/MND is smoking. Given that smoking is a major risk factor for many common health problems, the risk of ALS/MND is only one of the many reasons for recommending against it.

More research is needed and is currently being conducted to assess the influence of other environmental factors on ALS/MND disease onset and progression. Thus, sharing information earlier and keeping on top of new research may inform how both you and your child/youth can manage lifestyle, activity, and potential factors relating to ALS/MND.

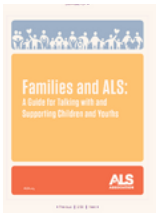
THE HOW
TELLING THEM ABOUT ALS/MND

This resource only approaches genetics, so please explore the resources below on how to talk about ALS/MND and FTD with children before initiating conversations about the genetic component.

First, be careful not to assume your children already knows or understands ALS/MND - even if they grew up seeing ALS/MND in other family members. Just like adults, children and youth can create images or knowledge about something based on limited information — often gleaned from the internet or overheard conversations. This may provide not only false information, but also false security or confidence in what they know. That can make the conversation more difficult to manage, so it is helpful to share information with them before they can access it elsewhere. Therefore, it is important to assess what your children already know, or think they know, about ALS/MND in general, basic genetics, and then moving into ALS/MND genetics.

Using resources to talk about ALS/MND. We have several tools designed to help children and youth understand the basics of ALS/MND. Global Neuro YCare has a Family Guide on how to talk about ALS/MND, and several books written for children and youth across ages to help them understand ALS/MND, its progression, and how they can talk to other kids and get support. The Families and ALS guide has more information on age groups, with details on how children feel and how to approach this conversation at different ages.

These resources are freely available at Global Neuro YCare (globalneuroycare.org), in several different languages.



Families and ALS guide
How do I talk to my children about ALS/MND? This book uses clinical expertise and interviews with families to guide the conversation, providing examples of discussions, according to age and development and when and how to discuss death and dying. In English, Spanish and Dutch.

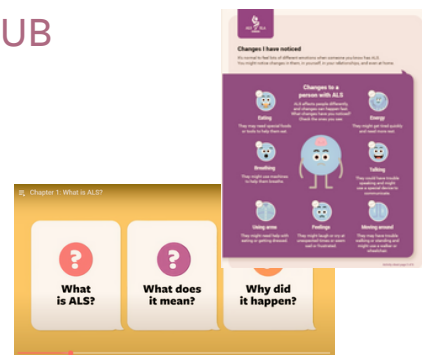
Real Kids Talk about ALS
Graphic novel – Using the words of children and youth, sharing their stories of ALS/MND and how they feel. In English, Zulu, Dutch, German, French, Turkish, Spanish, Sesotho, Vietnamese, and Italian.

Additional resources for teens, young adults, and schools are also available.

CHILDREN AND YOUTH RESOURCE HUB

ALS Canada also has a hub providing essential resources and support for children and youth impacted by ALS. Explore resources including videos, activity sheets, and guides designed to help families navigate ALS with age-appropriate support and guidance.

Available at als.ca/get-support/childrens-hub



THE HOW
TELLING THEM ABOUT ALS/MND

In addition to the books and guides, children and youth often learn by watching films. The animated short film, LUKi & the Lights, was created to provide an animated story to help kids understand ALS/MND. The film focuses on a robot, LUKi, who is full of lights. Initially diagnosed with ALS/MND, as it progresses, the lights go out.

The progression, integration of assistive devices, and caregiving from their friends are all part of the film, showing the breadth of life with ALS/MND in an easily accessible format, using no language, only visuals. In addition to the movie, several materials were created to support the many conversations that will come from watching the film, including a coloring book and FAQ guide for families and children.

NOTE to parents: The film was created specifically not using humans, to lessen the potential fear around seeing ALS/MND on a person. Moreover, it was created with no language to allow for accessibility across culture and countries. That said, it is a true depiction of ALS/MND, which may be jarring for children who have not had any exposure.

We recommend parents watch the film first and download the education packet, which includes:

- FAQ's about the film
- FAQ's about ALS/MND written for both younger and older youth
- Questions to ask as families watch the film to help guide the conversation.

Visit globalneuroycare.org/luki-the-lights/ for all LUKi™ materials.

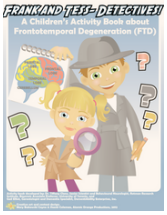
EXPLAINING GENETICS

We hope to create specific resources explaining the genetics of ALS/MND directly to children, but in the meantime, you can use the information from this resource to initiate genetic discussions. Additionally, there are several existing resources explaining general genetics to children on the internet. We encourage you to find educational material specific to their age group, reaching out to their school if needed or educational websites and channels, as well as connecting with your genetic counselor.

As described in the resources above, the amount of details you provide can vary by age group. You don't have to explain everything at once, but instead keep the conversation open as they grow up and are able to understand more concepts and how this relates to them.

To explain FTD and non-motor aspects of ALS/MND to children, explore resources from the FTD Association (theaftd.org/living-with-ftd/kids-and-teens).

With changes in behavior and communication, it is important to explain that the family member cannot control these changes. Emphasize that this is not the child's or youth's fault. These resources also provide more information on conversations by age groups.



THE HOW
TELLING THEM ABOUT ALS/MND

TIMING OF DISCUSSIONS

You don't have to discuss everything at once. In fact, we encourage you to start when you are doing something "normal" — playing games, hanging out, at mealtime, watching a show, etc. We recommend a calm, familiar setting and not making it a major conversation. This models the normality of your life now, and the ease with which they can come to you and ask future questions. Ask what they know and what they would like to know. This conversation can happen over several time points, especially as they grow up — not everything in one go. It keeps the door open for future conversations when they are ready, knowing they can talk at any time.

Too much at once can be overwhelming for your child, but also for you. Make sure with any of these conversations, you are managing your own feelings and capacity, and don't be afraid to say you don't know the answer to a question. Let them know you will get the right answer, then follow-up with your local ALS/MND organization. You also deserve to be supported during these conversations, so don't hesitate to reach out to your mental health professional, ALS/MND organizations, and peer support groups.

THE WHAT
GENETICS DISCUSSION

Depending on your family situation, as well age of the child/youth, topics discussed can vary, as well as how many details you provide. Even if you think your children might already know some of this information, they might not fully understand what it means to them or your family. Try to cover all the basics of ALS/MND and genetics, respecting their pace if they feel confused, overwhelmed, or closed off to the conversation at the moment.

To keep in mind the value of having conversations with your child/youth, research in Huntington's Disease found youth desired to know more about their genetic status, and specifically, to be able to discuss it with their parents. Open conversions with their parents helped them deal with their own potential diagnosis.

TOPICS THAT ARE IMPORTANT TO BE COVERED:

- **Basics of ALS/MND genetics: How are genes passed on? What are genetic variants?**
  - If you can, gather resources, drawings, and media from your genetic counselor – to explain genetics in an easy and clear way. Use the genetics FAQ earlier in this resource, as well as external resources appropriate for their age.
  - Emphasize this is not something that anyone in the family can control, and it is not influenced by anything that you or they might have done.
  - This can be a fraught discussion, so take your time and make sure you read through this document for detailed support.

THE WHAT

GENETICS DISCUSSION

TOPICS THAT ARE IMPORTANT TO BE COVERED:

- **The likelihood of other family members/themselves being affected.**
  - Were other family members also affected by ALS/MND? How might themselves be affected? Who else might be? Do other family members want to know, or do they prefer not to?
  - How might other family members want to be involved in the discussion? They don't need to be, but given the family nature, let your child know you will ask how other family members feel about it. Your child might want to talk to them or bring it up.
- **Research is constantly evolving to target genetic ALS/MND.**
  - This can be extremely supportive and positive in the context of ALS/MND. There is hope in a genetic diagnosis, so share that researchers across the globe are working towards genetic treatments. You can share the growing research with them, with careful optimism. We emphasize that it is extremely important to find accurate and credible research resources. If in doubt, reach out to your local ALS/MND organization or ALS/MND physician for support and clarification on upcoming research and therapies.

FOR OLDER CHILDREN, IT IS ALSO IMPORTANT TO CONSIDER DISCUSSING:

- **Your genetic testing results and your genetic variant.**
  - Is there information on your family's penetrance and ALS/MND or FTD presentation?
- **Current research and therapies available.**
- **The choice to get genetic testing when they are older.**
  - How does testing work? What should they consider? (Page 19)

For more information on genetic research access the ALS Canada Gene Hub at als.ca/genehub

A word of support – make sure you are ready to share the details of your own diagnosis. As we discussed in earlier sections, often parents still feel overwhelmed with their own diagnosis and genetic results. Before sharing with your child, if you are feeling unsure and overwhelmed, connect with your local ALS/MND organization or a mental health professional for support to process your own diagnosis, before sharing it with them. If you start the conversation with feelings of anxiety and distress, children will often pick up on it, which can make them feel more emotional.

THE WHAT

Making a list about any potential questions your children may have and doing the research to figure out the answers can decrease anxiety on your end.

We recommend reaching out to a genetic counselor if needed to help you navigate any questions. Below are some common questions we have seen in our clinical practice and research over the years. Use these to help you prepare for the conversation, recognizing that your child may have different questions, or not want to know any of the below:

1. **Did you know about ALS/MND before you had me?**
2. **Who did you ask about having ALS/MND (or about carrying a genetic variant)?**
   - **Can be helpful in connecting your child with healthcare professionals, and talking about your journey and how you felt.**
3. **How can I get tested for it? Do I need to be a specific age to get tested?**
4. **Can they do something to take the gene out?**
5. **If I have it, does that mean my kids will have it?**
6. **Is it only in men/women? (Depending on which family member is affected.)**
7. **Do I need to tell my friends about it? (or HOW do I tell friends about it?)**
8. **If I have the gene, will I get it the same way you did? Or what will it look like in me?**
9. **How will I know what progression looks like - who can I talk to about it?**

Some of these questions are tough, but we include them to help you consider how other children and youth have thought about genetics and ways in which they try to apply it to them. You don't need to answer all of them, but being prepared for what may come up is helpful for many families across genetic disorders.

ASKING THEM QUESTIONS

In addition to prepping the questions above, check in to ask what they want to know. This opportunity gives you a chance to clarify any misunderstandings, or preconceived notions they have about genetics, and helps them talk about it. This also shows them that what they are thinking and want to know is important to you. It shows their ideas/questions deserve to be addressed and are valued.

They might not know at first what they are confused about, or how they feel, so let them lead with what they think they know or want to know. But don't be surprised if they don't have questions or say they are fine. Let them process the information in their own time, and tell them they can check in with you any day. The most important thing is to keep the conversation going and keep it open, whenever they want to engage on whatever topic they want to discuss.

THE WHEN

Knowing when to have a tough conversation varies by family and by each person in that family. Families are unique in their relationships, development, and connections, including when and how they share a diagnosis and genetic discussion. There is no wrong time to do it. Each family will have a timing that works best for them. Below, we discuss suggestions for potential timing for the discussion of ALS/MND and genetics.

Families often state they want to wait for the "right time" to discuss both ALS/MND and its genetic implications. While you know your children better than anyone, we suggest you have all conversations sooner than later. As discussed, the internet has changed how easily information is accessed. Therefore, before your child/youth comes across incorrect or overwhelming information, consider having the conversation early.

SUGGESTIONS FOR STARTING THE CONVERSATION WITH YOUR CHILDREN:

- **After you have talked to a genetic counselor and healthcare provider about your (or another family member's) genetic test results and what do they mean.**
- **You might also find it useful to have practiced the conversation with another family member or friend.**
  - Say all the things – good and bad. Sometimes hearing it out loud helps shape the specifics of the conversation. Verbalizing also helps pare down what to say and what words to use by age.
  - Additionally, given the genetic discussion, you may have lost other family members to ALS/MND, or have other recently diagnosed members as well. This can be extremely overwhelming for you as a parent and may inform how you share your own information. As with any of these discussions, seek the guidance of a counselor first to process your own grief and loss, so that you can support your child in their grief, loss, and genetic risk.

THE WHEN

Acknowledging that you might not be able to discuss certain topics when they are older:

As ALS/MND or FTD progresses, you might not be able to have longer conversations, or you might not be here anymore. You can talk to your partner or other family members to prepare them with the information needed to continue to have these conversations with your children.

Write down information about:

- Your genetic variant and test results
- Your family history
- Your genetic counseling notes
- Information on your ALS/MND physicians
- Genetic and ALS/MND resources

In addition to writing details about the disease, genetics, and resources – consider writing how you feel about it, and how you feel about your child/youth. Even if you cannot verbally express it, sharing how you feel about them is powerful and extremely important for them as they process their own genetic risk. Leave it with someone trusted that can navigate this conversation later on.

ADDRESSING CHILD/YOUTH FEELINGS

None of these conversations are easy — for anyone. They have the potential to bring up fear, anger, anxiety, depression, and overall feelings of helplessness. Therefore, it is vital to be extremely aware of how your child typically responds to major issues. Pay attention to any change in behaviors after initial discussions.

WHEN HAVING THE DISCUSSION AROUND GENETICS:

You know your children best. Pay attention to their body language, and how open or closed they seem to continue the conversation. Don't push, especially when discussing potential genetic implications. Give them the basics, make sure they know they can and should come to you for questions, but let them process in whatever way they need. Have resources for immediate outside support if your child asks:

- Local ALS/MND organizations
- School counselor & Clergy/religious support
- Family friends

Ask them about anyone they trust, who may be known to your child and be a support – particularly after the initial genetic discussion. Then follow-up with that person to share the discussion and ask if they would be willing to support your child, if needed. Make sure they have these resources, and others ALS/MND resources if needed, so they are using the same information as you are using.

ADDRESSING CHILD/YOUTH FEELINGS

SHARING WITH OTHERS

What to tell others on behalf of your child? Often, families want to share with school staff, social workers, counselors, to make sure the child gets support while at school. This is very helpful — but only after you have shared this with your child and let them know your plans. It can be extremely painful for a child to be called aside by a well-meaning school staff member, when what the child really wants is the anonymity school can provide them — respite from the stress and emotion of home.

Talk to your child first, get their feedback and opinion on whether they want people to know. Ask them what they are comfortable sharing and even if they want to be a part of the conversations with school staff. The same applies for other family members and friends, should they want to support your children as well. This will continue to build trust between you and your child, as they process and continue asking questions.

TAKING ACTION

After sitting with their feelings, they might want to learn more about research and how to get involved (advocating for ALS/MND, fundraising, etc.) Taking action by learning and being involved in the community can support them as they cope and help with any feelings of helplessness. Reach out and get information from ALS Canada or your local ALS/MND organization on ways to volunteer and advocate.

OLDER CHILDREN MIGHT ALSO WANT TO BE INVOLVED IN CONVERSATIONS WITH YOUR GENETIC COUNSELOR

This is particularly critical as they achieve their independence, pursue career choices, and consider relationships. This time is often the most difficult for them, and often feels the most confusing as to what to do next. They need as much support as possible, including discussions around dating, pregnancy, and family planning. Connecting with a genetic counselor and a mental health professional is highly encouraged at this point. Additionally, finding peer support groups or talking to people in a similar situation can be helpful to them.

GENETIC TESTING

Genetic testing has become more accessible for many reasons, including more ALS/MND genes being identified, and further research into gene-targeting therapies. For a person living with ALS/MND, genetic testing can now be very important for treatment choices and opportunities to participate in research and clinical trials. It can be a big life decision, and interpretation of results is often challenging. This is why appropriate genetic counseling should always accompany testing.

Genetic testing in an individual at risk of developing a disease (with a known family history), but who is not currently exhibiting any symptoms, is called predictive testing.

Predictive testing requires extensive genetic counseling, and at the moment, only a subset of clinics offer predictive testing to at-risk, asymptomatic family members of an ALS/MND patient with a confirmed genetic variant.

As you communicate your genetic diagnosis with your children, they might start asking about genetic testing.

As youth under 18 years old cannot give their full consent, genetic testing for ALS/MND is not offered or performed in children as a consensus. It is extremely rare for ALS/MND cases to manifest in childhood*, and FTD will only manifest in adulthood.

For that reason, you can communicate to young children they don't have to think about testing. However, this can be a very sensitive topic for older youth, particularly if they are in a relationship and thinking about their future. As we have seen with other genetic disorders, giving young adults as much information as possible is critical, so that they can make the best decision for themselves.

**Although the great majority of ALS/MND cases only manifest in adulthood, it is important to note that variants in the FUS gene are shown to have an earlier onset of disease. Rarely, other variants also show early onset. Talking to your genetic counselor about your family risk is highly recommended for any exceptions in testing.*

GENETIC TESTING

TEST RESULTS

It is important to note that a positive genetic test or inheriting a gene variant with a higher risk of ALS/MND does not guarantee a person will develop symptoms of the disease. Looking at family history and talking to your genetic counselor may help determine individual level of risk. Additionally, researchers are also studying environmental risk factors for ALS/MND, which may influences a person's risk of developing the disease. Research is always on-going to identify genes related to ALS/MND, and for some variants, the likelihood of developing ALS/MND is stronger and penetrance is higher, while for others, it is still unclear.

It is also important to note that in some cases, some families with a family history of ALS/MND may undergo genetic testing, but the test will be negative. This can mean the family might have an unknown variant in an unknown ALS/MND gene, since not all genes for ALS/MND have been identified yet, but this cannot be confirmed.

VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

For some variants, test results might show a variant of uncertain significance (VUS), meaning variants in genes related to ALS/MND have been identified, but the relationship between these specific variants and developing ALS/MND is uncertain. When tests are inconclusive with a VUS, genetic counseling and staying on top of the latest genetic research on ALS/MND can be very important. Often a VUS does not change clinical management, nor would predictive testing of family members be recommended. Sometimes there may be some follow up that the clinician can recommend to try to clarify the significance of the VUS, such as testing another family member with ALS/MND (if applicable).

You and your family should always speak with your genetic counselor and neurologist for further details and interpretation of test results.

GENETIC TESTING

CONSIDERATIONS OF GENETIC TESTING

Children don't have to make a decision about genetic testing. You can make it clear to them they should not feel pressured to think about it. But as they reach adulthood, it is important to start considering it and initiating discussions. Decisions about genetic testing can always change, especially as they think about their future and as ALS/MND research progresses. A lot of time might be needed to consider the right choice for them, and some individuals will choose to get tested before a major life decision (e.g., marriage or having children of their own). Discussions with a genetic counselor are encouraged.

You should emphasize to older youth/adults that the decision to get tested should be their own, but answering their questions and discussing the reasons why some people choose to get tested can be helpful.

REASONS WHY ADULTS AT-RISK MIGHT WANT GENETIC TESTING:

- Reducing anxiety and uncertainty around the likelihood of developing ALS/MND.
- Having time to accept and process the results if they are positive.
- Facilitating earlier diagnosis if symptoms manifest.
    - Earlier diagnosis of ALS/MND can be extremely significant in symptom management, eligibility for therapies and participation in clinical trials.
- Being able to self-advocate for themselves and the community.
- Finding a community, support, and services at an earlier stage.
- Opportunity to participate in research and future therapeutic trials.
    - Participating in research can be an empowering way to face ALS/MND. There are observational studies for individuals with a known variant of ALS/MND who have not developed symptoms, and these are extremely important in further understanding and unraveling ALS/MND progression.
    - Additionally, interventional research with potential therapeutics for pre-symptomatic individuals is emerging.
- Considering life decisions.
    - This can be important as they consider career, health insurance, financial planning, and lifestyle choices.
- Considering the decision to have children and family planning.
- Assisting in family decisions.

GENETIC TESTING

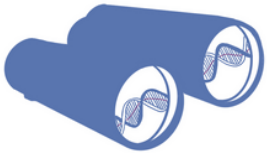
REASONS WHY ADULTS AT-RISK MIGHT NOT WANT GENETIC TESTING:

- Learning about the results of genetic testing for ALS/MND can be an incredibly challenging moment.
  - Some individuals might not be at the right time of their lives to face the results, especially if they don't have access to counselors or professional help.
- It can cause tension with other family members, who may not wish to know the test results.
- Genetic status may inadvertently reveal the status of another family member.
  - (e.g., if someone wants to get tested, but the parent does not, or siblings who are twins)
- Individuals who have biological children might need to deal with feelings of anxiety related to ALS/MND potentially being passed on.
- Potentially experiencing guilt about testing negative if other family members test positive.
- Positive results might cause anxiety and uncertainty about whether, when, and how disease might develop.
- Positive results might impact insurance, lifestyle, and career choices.

We encourage all families and individuals affected by a known genetic form of ALS/MND to stay on top of research breakthroughs and news relating to upcoming therapies in clinical trials, as this is a rapidly advancing field. This might change the decision to get genetic tested.

OBSERVATIONAL STUDIES

Learning from individuals who carry specific genetic variants that increase their risk of ALS/MND is critical for researchers' ability to understand and develop treatments targeting those genes, but also for all people living with ALS/MND. Contributing to research by enrolling in observational studies, as a genetic carrier who is not experiencing ALS/MND symptoms, can help researchers understand the biological processes that might occur at the earliest stages of the disease.



Find observational studies and research opportunities at the ALS Canada Gene Hub at als.ca/genehub

SUPPORT AND RESOURCES

ALS SOCIETY OF CANADA AT ALS.CA

Our mission is our everyday journey as an organization. We work with the ALS community to improve the lives of Canadians affected by ALS through advancing research, care, advocacy, and information.

Together, as a global community, we are working toward a world free of ALS.

Learn more about us

RESOURCES

- ALS Canada Gene Hub for more information on ALS/MND genetics, testing, research, and resources.
- ALS Canada's Genetics Glossary for a list of helpful genetic terms and explanations.
- Additional External Genetics Resources

For printed versions, find these resources at als.ca/genehub

- ALS Canada Children and Youth Resource Hub for essential resources and support for children and youth impacted by ALS.

For printed versions, find these resources at als.ca/get-support/childrens-hub

FIND SUPPORT IN CANADA als.ca/get-support/community-support

SUPPORT AND RESOURCES

GLOBAL NEURO YCARE AT GLOBALNEUROYCARE.ORG

Working directly with other non-profit organizations, the Global Neuro YCare foundation provides the accessible educational tools, support programs and resources across language and culture, for children, youth and families around the world.

Learn more about us

RESOURCES

- The YCare program – education, skills and professional guidance for children and youth providing care for a family member with ALS/MND.
- Families and ALS: A Guide for Talking with and Supporting Children and Youths
- Real Kids Talk About ALS - Graphic novel about ALS/MND. Available in 13 languages.
- The ALS experience: It's different and hard (A book for teens in families living with ALS/MND)
- At School: A Guide to Supporting Students who have been affected by ALS

For printed versions, find these resources at globalneuroycare.org/als-mnd-books

- LUKI & the Lights Full Movie & Educational Materials

For printed versions, find these resources at globalneuroycare.org/full-movie

SUPPORT AND RESOURCES

END THE LEGACY AT ENDTHELEGACY.ORG

End The Legacy is a nonprofit organization dedicated to supporting and advocating for their community. Operating under the ALS Hope Foundation umbrella, these organizations together will develop educational programs about familial ALS and FTD, establish support groups for members of the familial ALS and FTD community, engage the medical community to establish guidelines for care of asymptomatic gene carriers, and advocate for the hundreds of thousands of people at higher risk for developing ALS or FTD through the inheritance of a genetic variant that runs in their family.

Additional Resources

- I am Mindy Uhrlaub – How I Talked to My Teens About My Genetic Status

ALS CANADA
RESEARCH PROGRAM

ALS Canada Genetics Glossary

Last updated March 2025.

This genetics glossary contains a list of terminology and medical term definitions that are relevant to amyotrophic lateral sclerosis (ALS). The glossary was developed to help support knowledge-sharing by helping to provide clarity around terminology that may be unfamiliar to people affected by a genetic form of ALS.

Genetic-related acronyms

- **ASO** – antisense oligonucleotide
- **atDNA** – autosomal DNA
- **bp** – base pair
- **CNV** – copy number variation
- **DNA** – deoxyribonucleic acid
- **GTR** – genetic testing registry
- **GWAS** – genome wide association study
- **INDEL** – insertion or deletion
- **FALS** – familial ALS
- **FTD** – frontotemporal dementia
- **FUS** – fused in sarcoma
- **mRNA** – messenger RNA
- **nDNA** – nuclear DNA
- **NGS** – next-generation sequencing
- **PCR** – polymerase chain reaction
- **RNA** – ribonucleic acid
- **sALS** – sporadic ALS
- **SOD1** – superoxide dismutase 1
- **TDP-43** – TAR DNA-binding protein 43
- **SNP** – single nucleotide polymorphism
- **WES** – whole exome sequencing
- **WGS** – whole genome sequencing

Glossary of Genetic Terms

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

A

Adenine (A) - One of the four nucleotide bases in DNA and RNA. In DNA, it pairs specifically with the base thymine (T), and in RNA, it pairs with uracil (U).

Allele - The alternative versions of a gene. An individual will inherit **two alleles for each gene**, one from each parent. For example, different alleles explain why individuals have different blood types: they might have the A, B, or O blood type allele.

Amino acid - The 20 building blocks from which proteins are assembled. Just like letters of the alphabet can be combined to form a nearly endless variety of words, amino acids can be linked together to form a nearly endless variety of proteins.

Antisense Oligonucleotide (ASO) - Small pieces of DNA or RNA that can bind to specific molecules of RNA, blocking their ability to make proteins or perform other functions. Antisense oligonucleotides are being studied for the treatment of certain forms of ALS. Tofersen (QALSODY), a therapy approved to treat SOD1-ALS, is an ASO.

Autosomal DNA (atDNA) - DNA inherited from the autosomal chromosomes, rather than from the sex chromosomes.

Autosome - Non-sex chromosomes. Humans have 22 pairs of autosomes.

***ATXN2* -** The *ATXN2* gene provides instructions for making a protein called ataxin-2. This protein is involved in RNA regulation inside cells. Some variants in this gene are associated with an increased risk for ALS.

B

Base pair (bp) - Two nucleotide bases paired together in a DNA or RNA sequence. In DNA, adenine (A) pairs with thymine (T), and cytosine (C) pairs with guanine (G). In RNA, adenine (A) pairs with uracil (U), and cytosine (C) pairs with guanine (G).

C

Candidate Gene - A gene that is believed to be associated with a particular trait or disease, often based on its known biological function or its location in the genome.

Carrier - An individual carrying one copy of a genetic variant that is inherited in an autosomal recessive or sex-linked manner and does not manifest the disease. In some cases, carriers can have mild symptoms. Carriers can pass the variant to their children, even if they never manifest the disease.

Codon - A sequence of three nucleotide bases in DNA or RNA that encode for different amino acids. In humans, there are 64 different codons, each corresponding to an amino acid or a stop signal in protein synthesis.

Copy Number Variation (CNV) - A phenomenon where the number of copies of a specific gene or DNA sequence varies between individuals. CNVs are common features of the human genome and contribute to genetic diversity between individuals and groups.

Chromosome - Within the nucleus of every cell, our DNA is packaged up tightly into coiled-structures called chromosomes. Humans typically have 23 pairs of chromosomes, for a total of 46, inheriting half from each parent. These structures unravel when the DNA needs to be read by the cell.

CRISPR-Cas9 - CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. CRISPR/Cas9 is a gene-editing technology used in a laboratory to modify DNA sequences in living organisms, allowing researchers to remove, add, or alter parts of the sequence.

Cytoplasm - The jelly-like material that fills the inside of a cell. The cytoplasm houses all the different parts of cells (called organelles). It is typically considered one of the two major compartments of cells, with the other being the nucleus.

Cytosine - One of the four nucleotide bases in DNA and RNA. It pairs specifically with the base guanine (G).

***C9ORF72* -** The *C9ORF72* gene provides instructions for making a protein called C9ORF72 (chromosome 9 open reading frame 72), found in many regions of the brain. Unique variants in *C9ORF72* have been identified as the most common cause of ALS and frontotemporal dementia (FTD). The variant is referred to as a repeat expansion variant, as the sequence of nucleotides GGGGCC is repeated multiple times. Variants in the *C9ORF72* gene are linked to approximately 25-40% of ALS cases with a family history, and 5-10% of ALS cases with no obvious family history.

D

Deletion - A type of genetic variant when one or more DNA or RNA bases are removed from the sequence. This can affect how the sequence is read and impact protein production.

DNA - A double-stranded molecule composed of nucleic acids, formed by base pairs. Our DNA sequence constitutes our genome, containing all the information about our traits and normal body functioning.

DNA Sequencing - Techniques used in a laboratory to determine the exact sequence of nucleotide bases in a DNA sequence.

Dominant pattern of inheritance - With dominant traits, only one copy of the gene containing the variant needs to be present for the trait or disease to be expressed in an individual. Most ALS-linked genes have a dominant pattern of inheritance, meaning if the parent has one copy of the variant, the child has a 50% chance of inheriting the gene variant. If the child inherits the gene variant, they are at chance of developing symptoms of the disease.

E

Environmental Risk Factors - Factors in an individual's environment that can increase their susceptibility or predisposition to disease. Examples include smoking or exposure to radiation.

Epigenetics - The study of how an individual's behavior and environment can cause changes in the way their DNA sequence is read. Epigenetic changes are reversible modifications, as they do not alter the DNA sequence itself but rather how the cell machinery accesses and reads each gene.

Exon - Regions of the genome that code for messenger RNAs (mRNAs). Most exons will code for proteins. Collectively, they make up a person's exome.

Exome - The complete set of exons in the genome.

F

Familial ALS (FALS) - The inherited form of ALS. Approximately 5-10% of all ALS cases show a family history indicating the disease is triggered by variants in an ALS-associated gene passed from parent to child.

Family History - Past documented cases of the disease in an individual's family, usually meaning multiple family members were affected by the disease, due to a hereditary variant in a gene related to the condition.

First-Degree Relative - An individual's parent, sibling, or child.

Frontotemporal dementia (FTD) - A group of disorders caused by progressive loss of neurons in the brain's frontal lobes (the areas behind your forehead) or its temporal lobes (the regions behind your ears). Symptoms include difficulties in critical thinking and problem solving, language/speech deficits and behavioral problems. FTD symptoms can exist on a spectrum with ALS, especially related to some cases of genetic ALS, where people can range from very mild, almost undetectable cognitive symptoms to a full FTD diagnosis.

***FUS* -** The *FUS* gene provides instructions for making a protein called FUS (Fused in Sarcoma, which is believed to contribute to normal cell function by playing a role in the biology between RNA and proteins. Variants in the *FUS* gene are linked to approximately 3-6% of ALS cases with a family history, and 1% of ALS cases with no obvious family history.

G

Gene - A segment of DNA that carries the genetic instructions for making a specific protein or RNA molecule. For example, the *SOD1* gene will hold the instructions to make the SOD1 protein, which has an important function in cells and can cause ALS if there is an error (variant) in that code. Genes

are passed from parent to child and control the characteristics that the individual will have. Genes are bundled into chromosomes in the nucleus of cells.

Gene Therapy - The delivery of nucleic acids into a patient's cells as a treatment for a disease. Gene therapy is currently being explored to treat many diseases, including certain types of cancers as well as neurodegenerative diseases, such as ALS.

Genetic Counselling: Guidance and support relating to genetic disorders and genetic testing for an individual or a family. Pre- and post-counselling are always recommended for an individual considering genetic testing for ALS.

Genetic Predisposition - An inherited increase in the risk of developing a disease. Also known as genetic susceptibility.

Genetic Testing – A type of medical test that identifies variants in an individual's chromosomes, genome (DNA sequence), or gene expression. The results of a genetic test can confirm or rule out a suspected genetic condition or help to determine a person's chance of developing or passing on a genetic disorder.

Genome - The complete set of genetic material (DNA sequence) present in a person. It comprises all 23 pairs of chromosomes.

Genotype – An individual's unique DNA sequence (genome).

Genome-wide association study (GWAS) – This method of study looks at the entire DNA sequence (the genome) of a group of people. These types of studies help researchers identify genes associated with a disease or trait.

Guanine - One of the four nucleotide bases in DNA and RNA (abbreviated as G). It pairs specifically with the base cytosine (C).

H

Hereditary - In medicine, describes the passing of genetic information from parent to child through the genes in sperm and egg cells. Also known as inherited.

Heterogeneity - The phenomenon by which the same disease can be caused, or contributed to, by a variety of different genes. The disease characteristics of ALS are also said to be heterogeneous as many people living with ALS will have varying ages of onset, rates of progression, and areas of onset (e.g. bulbar vs. limb), etc.

Heterozygous - An individual that inherited different versions (alleles) of a gene, one from each parent**. "**Hetero" means different.

Homozygous – An individual that inherited the same versions (alleles) of a gene, one from each parent**. "**Homo" means same.

I

Insertion or deletion (INDEL) – An insertion or deletion of a part of the DNA or RNA sequence. They can range from a single base to multiple bases. Indels ≥ 50 bases in length are classified as structural variants.

Intron – A segment of DNA that is not transcribed into the mRNA sequence containing the information to make proteins. They can be referred to as "non-coding regions."

K

Knockout – Gene knockouts (KO) are used in genetic engineering to remove or silence a specific gene. This is commonly used in research to assess the function of a gene by observing the effects of their absence or reduced activity.

M

Messenger RNA (mRNA) – To make proteins, the DNA sequence is read and transcribed into mRNA. This process is called transcription. The resulting mRNA carries the instructions to make a protein.

Mutagen: A chemical or physical agent that can induce variants in a DNA sequence. Examples include tobacco products or radiation.

Mutation - A mutation is now commonly referred to as a **"variant."** A variant is a change in the DNA sequence. This variation can be benign (does not impact an individual's health), pathogenic (increases an individual's susceptibility to the disease), or of uncertain significance (not enough information to assess if it is benign or pathogenic). Everyone's DNA sequence has many variants, and most are harmless.

N

Nucleus: A spherical structure inside of the cell that contains a person's DNA sequence.

Nuclear DNA (nDNA) – DNA found only inside the nucleus (the central part of the cell), and not in the cytoplasm. Nuclear DNA is our genome.

Nucleic Acid – Polynucleotides (a chain of nucleotides). DNA and RNA are classes of nucleic acids.

Nucleotide – A base or "building block" that in a sequence, assembles DNA or RNA. DNA bases are adenine (A), cytosine (C), guanine (G), and thymine (T). RNA bases are A, C, G, and uracil (U).

Next-generation sequencing (NGS) – A technology that reads and sequences the genome. It can be used to detect genetic variants.

P

Pattern of inheritance – Describes how a trait or variant is inherited. The most common types are dominant, recessive, autosomal, or X-linked. The majority of ALS variants show an autosomal dominant inheritance, but documented cases have also shown autosomal recessive, or X-linked inheritances.

Polymerase chain reaction (PCR) – A technique used in a laboratory that allows for the amplification of a DNA fragment. PCR is essential for generating large quantities of DNA for various applications, including genetic analysis and research.

Penetrance - The proportion of individuals in a population who carry a specific genetic variant and develop clinical symptoms of the associated disease. For example, if a genetic variant is said to have 80% penetrance, then 80% of people with the variant will develop the disease and 20% will not.

Phenotype - The observable physical characteristics or traits of an individual, influenced by both genetic and environmental factors. ALS is often described as a disease with variable phenotypes, as symptoms can differ amongst people living with the disease.

Project MinE - A large-scale global research initiative aimed to determine the genetic basis of ALS. Find out more here and here.

Protein - The molecules responsible for almost all cellular functions (often referred to as the workhorses of the cell). Proteins consist of long chains of smaller units called amino acids. DNA contains the code for protein formation in cells.

R

Recessive pattern of inheritance – With recessive traits, two copies of the gene containing the variant need to be inherited for the trait or disease to be expressed (one from each parent). This means that in a recessive pattern of inheritance, both parents need to have at least one copy of the variant, and both of those need to be passed on, for the child to be affected. If only **one copy** of the variant is inherited, the trait (or disease) will not manifest. In this case, the child will be considered a **carrier.**

Recombinant - In genetics, describes DNA, proteins, cells, or organisms that are made by combining genetic material from two different sources. Recombinant substances are made in the laboratory and have applications in research, medicine, and biotechnology.

Repeat expansion variants – Genetic variations characterized by the abnormal repetition of a specific sequence of DNA. These expansions can disrupt normal gene function, alter protein production, and potentially lead to disease. In ALS, the *C9*ORF*72* gene is affected by a repeat expansion (the nucleotide sequence GGGGCC is repeated multiple times).

Ribonucleic Acid (RNA) - A single-stranded nucleic acid molecule. RNA acts as a messenger molecule, carrying genetic information from the nucleus to the cytoplasm where protein assembly occurs.

S

Sex Chromosome – Non-autosome chromosomes. Humans will have one pair of sex chromosomes: XX (individuals assigned female at birth) or XY (individuals assigned male at birth).

***SOD1* –** The *SOD1* gene provides instructions for making a protein called SOD1 (superoxide dismutase 1), which plays an important role in reducing oxidative stress within cells. SOD1 destroys DNA-damaging superoxide, a highly reactive form of oxygen (referred to as a free radical). Variants in *SOD1* are linked to approximately 10-30% of ALS cases with a family history and 1-4% of ALS cases with no obvious family history.

Single Nucleotide Polymorphism (SNP) – A common change or substitution of one single DNA base (nucleotide) in the genome, that is present in at least 1% of the population. For example, the base guanine (G) may be changed to a cytosine (C). SNPs can be used as biological markers, helping researchers locate genes associated with a certain disease.

Susceptibility – Refers to an increased chance of developing a disease due to one or more genetic variants and/or a family history suggestive of an increased risk of the disease. Susceptibility factors increase the chances of disease occurrence but do not guarantee it.

T

TARDP **-** The *TARDP* gene provides instructions for making a protein called TDP-43, which is an RNA-binding protein involved in ALS. Variants in the *TARDBP* gene are linked to approximately 4-5% of ALS cases with a family history, and 1% of ALS cases with no obvious family history. However, TDP-43 dysfunction is observed in about 98% of people living with ALS, even without a known *TARDBP* variant.

Thymine - One of the four nucleotide bases in DNA (abbreviated as T). It pairs specifically with the base adenine (A) in DNA. It is not an RNA base.

Tofersen – Sold under the brand name QALSODY, tofersen is an approved therapy in the US, Canada, and Europe for the treatment of SOD1-ALS. It is an ASO (antisense oligonucleotide), developed by Biogen.

Transgenic - Describes a living organism that has been genetically engineered to contain DNA from another organism. Transgenic mice, for example, are often used in preclinical ALS research as a model to study the disease.

U

Uracil - One of the four nucleotide bases in RNA (abbreviated as U). It pairs specifically with the base adenine (A) in RNA. It is not a DNA base.

V

Variant - A change or variation in the DNA sequence (genetic code). Variants can be benign (having no impact on an individual's health), pathogenic (increases an individual's susceptibility to disease), or of uncertain significance (not enough information to assess if it is benign or pathogenic). The term "mutation" was traditionally used to refer to pathogenic variants. Everyone's DNA sequence has many variants, and most are harmless.

Variant of Uncertain Significance (VUS) - A variation or change in the DNA sequence that has an unknown effect on an individual's health.

W

Whole Exome Sequencing (WES) - The process of reading a person's complete sequence of exons (exome) at a single time.

Whole Genome Sequencing (WGS) - The process of reading a person's complete DNA sequence (genome) at a single time.