



FAMILIAL ALS

RESOURCE BOOKLET

ALS
ASSOCIATION

TABLE OF CONTENTS

Acknowledgements	1
Facts About Familial ALS	2
What Causes Familial ALS?	3
How are ALS Genes Inherited?	4
Dominant and Recessive	5
Penetrance	6
What Are the Genes that Cause ALS?	7
Genetic Testing	9
Genetic Counseling	10
Gene-Based Treatments	12
Support and Resources	12

ACKNOWLEDGMENTS

During the creation of this book, The ALS Association was fortunate to work with several people living with ALS and their family members who were willing to share their stories and experiences surrounding familial ALS (fALS) and the impact of this disease on their family. The contributions of Stevie Hudson, Sandra Stanbery, and Diana Wunning can be seen throughout the book in the form of quotes. We would also like to thank the following ALS Association chapters for supporting this project and connecting us with the people they serve: Golden West Chapter, Mid-America Chapter, and St. Louis Regional Chapter.

We would also like to thank Dr. Michael Benatar, MD, PhD, Professor of Neurology at the University of Miami and principal investigator of the Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium, for his premier subject matter expertise. Dr. Benatar and the CReATe Consortium were instrumental in providing initial consultation and continued guidance throughout the development of this book.



Richard Robinson, a writer and editor with the National Association of Science Writers, compiled interviews, data, and hard science into a valuable resource for the familial ALS community. The genetics of ALS is nothing short of complicated and we are grateful for his ability to translate this into a book that is accessible and understandable.

There are many considerations and implications surrounding the decision to undergo genetic testing for ALS. We were fortunate to have the expertise and insight of Deborah Hartzfeld, MS, GCG, a genetic counselor with the US Department of Government Affairs, who served as the subject matter expert on the ins and outs of genetic testing and counseling.

A note to the reader: The ALS Association has developed the Familial ALS Resource Booklet for informational and educational purposes only. The information contained in these guides is not intended to replace personalized medical assessment and management of ALS. Your doctor and other qualified health care providers must be consulted before beginning any treatment.

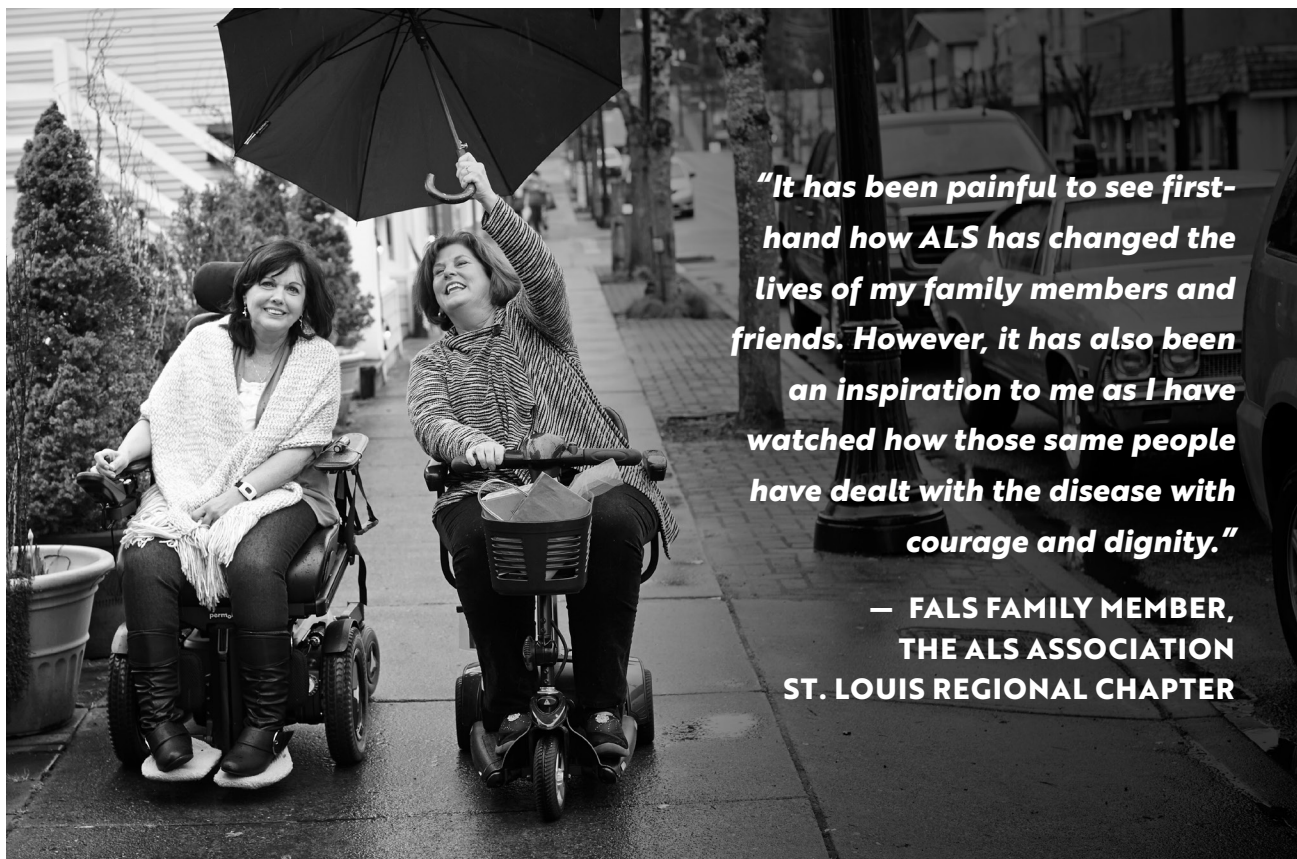
Familial ALS Resource Booklet

Copyright © 2018 by The ALS Association.

All rights reserved.

FACTS ABOUT FAMILIAL ALS

It can be overwhelming to learn that you or a family member has ALS. Learning that you have familial ALS can be even more so, raising extra questions and concerns about the future. In this booklet, you will find answers to many of those questions, and resources for further information and support for you and your family.



“It has been painful to see first-hand how ALS has changed the lives of my family members and friends. However, it has also been an inspiration to me as I have watched how those same people have dealt with the disease with courage and dignity.”

**— FALS FAMILY MEMBER,
THE ALS ASSOCIATION
ST. LOUIS REGIONAL CHAPTER**

FAMILIAL ALS: WHAT IS IT?

“Familial” ALS refers to ALS in which more than one family member is affected by the disease. About 10 percent of all people with ALS have familial ALS (fALS). The other 90 percent of ALS is called “sporadic,” meaning it has not occurred in other members of the family.

Familial and sporadic ALS are similar in their effect on the person who has the disease. Both forms lead to the loss of motor neurons (nerve cells that control muscle movement), and both forms cause muscle weakness and loss of the ability to walk, speak, eat, move, and eventually breathe. Both familial and sporadic ALS are quite variable, and even within families, family members who are affected may have different disease courses. Researchers are trying to understand these differences in order to learn more about how to slow the disease progression and treat the disease effectively.

WHAT CAUSES FAMILIAL ALS?

Scientists believe that most, if not all, cases of fALS are due to mutations in genes. As of 2017, about 60 percent of all cases of fALS have been linked to specific genes. Altogether, over two dozen genes have already been linked to ALS, and more are likely to be discovered.



Each gene serves as a “blueprint” for making a protein, and each protein performs a specific function within a cell. Chemically, a gene is a long string of the DNA “letters,” abbreviated A, T, C, and G. The exact order of these letters dictates the protein to be made. A gene mutation is a change in the sequence of the DNA letters. A mutation can be a change from one letter to another, the loss of one or more letters, or the gain of one or more letters. The mutation can cause the protein to not be made or to lose its normal function, or to gain a new, toxic function, or both. This contributes to dysfunction of motor neurons and their eventual death. The most common consequence of mutation in the genes that cause ALS is a toxic gain of function, but loss of function may also play a role in some cases.

A mutation can occur spontaneously (called a de novo mutation), but this is a very rare occurrence. Most people with gene mutations that cause fALS inherited the mutated gene from a parent, who also inherited it from a parent, for many generations. Once a gene is mutated, it can be inherited in the same way any other gene can.

Causative genes and risk factors: Some gene mutations cause such a significant change in cell function that anyone carrying the mutation is almost certain to develop ALS. The C9orf72 gene mutation, and many SOD1 mutations (see pg. 6), are causative gene mutations. Other, less powerful, mutations increase the risk of ALS but may not cause it without other contributing factors.

Researchers also believe that the risk of ALS can be increased from certain environmental factors, such as long-term exposure to certain toxins. It is at least theoretically possible that individual cases of familial ALS are due to family members sharing the same environment, instead of the same genes. Other cases of ALS may be due to a combination of risk genes and environment. Understanding all the risk factors that may contribute to ALS, including both genes and environmental factors, is a major area of research.

*“Receiving my diagnosis was devastating for my husband and me.
My family was also devastated after watching our paternal grandmother
and aunt pass away from ALS years before. We are closer now.
It can tear a family apart or pull them closer together.”*

— PERSON LIVING WITH FALS, THE ALS ASSOCIATION MID-AMERICA CHAPTER

HOW ARE ALS GENES INHERITED

Genes are carried on long strings of DNA called chromosomes. Each cell (except sperm and egg) contains 46 chromosomes, arranged in pairs. Chromosomes, and the genes they carry, are passed from parent to child. A child inherits one member of each pair from the father, and the other member of each pair from the mother.

Because chromosomes occur in pairs, every cell (except sperm and egg) has two copies of almost every gene. For instance, the C9orf72 gene is carried on chromosome 9, and since there are two copies of this chromosome, each cell carries two copies of the C9orf72 gene.

ODDS OF INHERITANCE

Egg and sperm each contain only one member of each chromosome pair, selected at random during sperm and egg formation. Thus, for a woman who is carrying one normal copy of the C9orf72 gene and one mutated copy, about half her eggs will contain the normal gene, and about half will carry the mutated gene. Thus, there is a 50% chance that she will pass on the mutant copy of the gene to any child. The chances of passing it on to successive children are not affected by whether previous children received it: the chances are still 50% for each child. The same is true for a man carrying the mutation and passing it on in his sperm.

The same calculation is true for almost all ALS genes: most people who have a mutated ALS gene carry one normal copy and one mutated copy, and the chances they will pass it along to a child is 50 percent for each child.



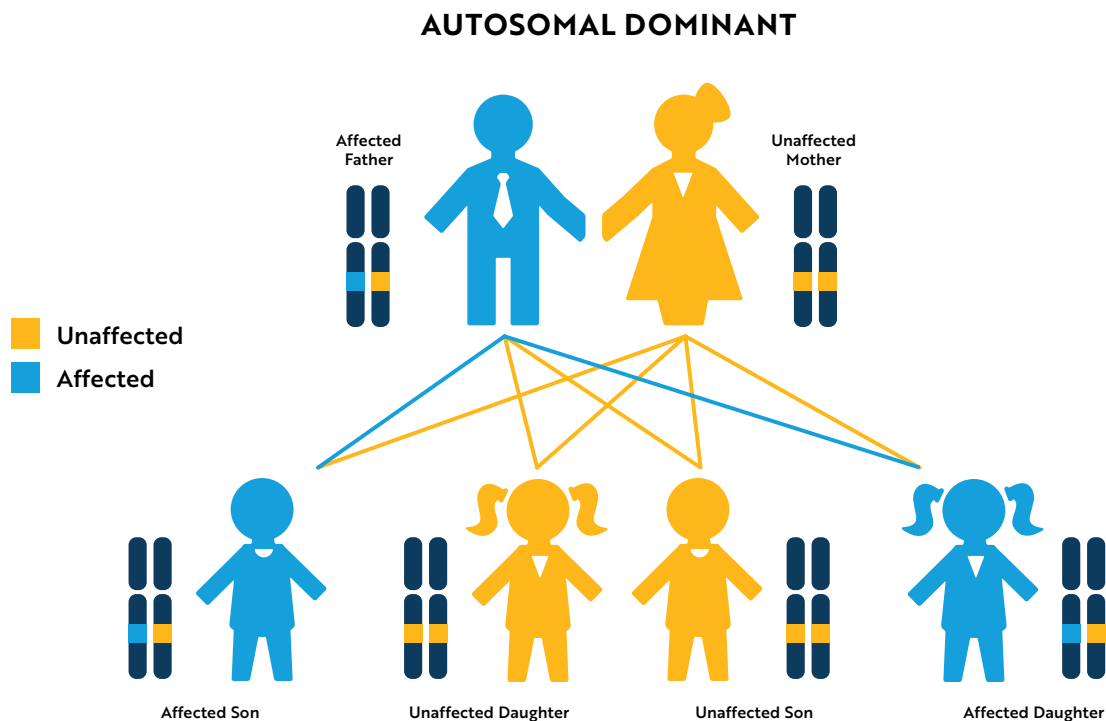
DOMINANT AND RECESSIVE

When both copies of a gene must be mutated in order to cause disease, the gene mutation is called recessive. When disease occurs with one mutated copy and one normal copy, the gene mutation is called dominant. Most ALS gene mutations are dominant.

Sex is determined by the two sex chromosomes, the X and Y chromosomes, which do not come in pairs. A person who inherits two X chromosomes will be female, while a person who inherits an X and a Y will be male. Few genes, and no ALS genes, are carried on the Y chromosome. Many more genes are carried on the X chromosome, including at least one ALS gene, UBQLN2.

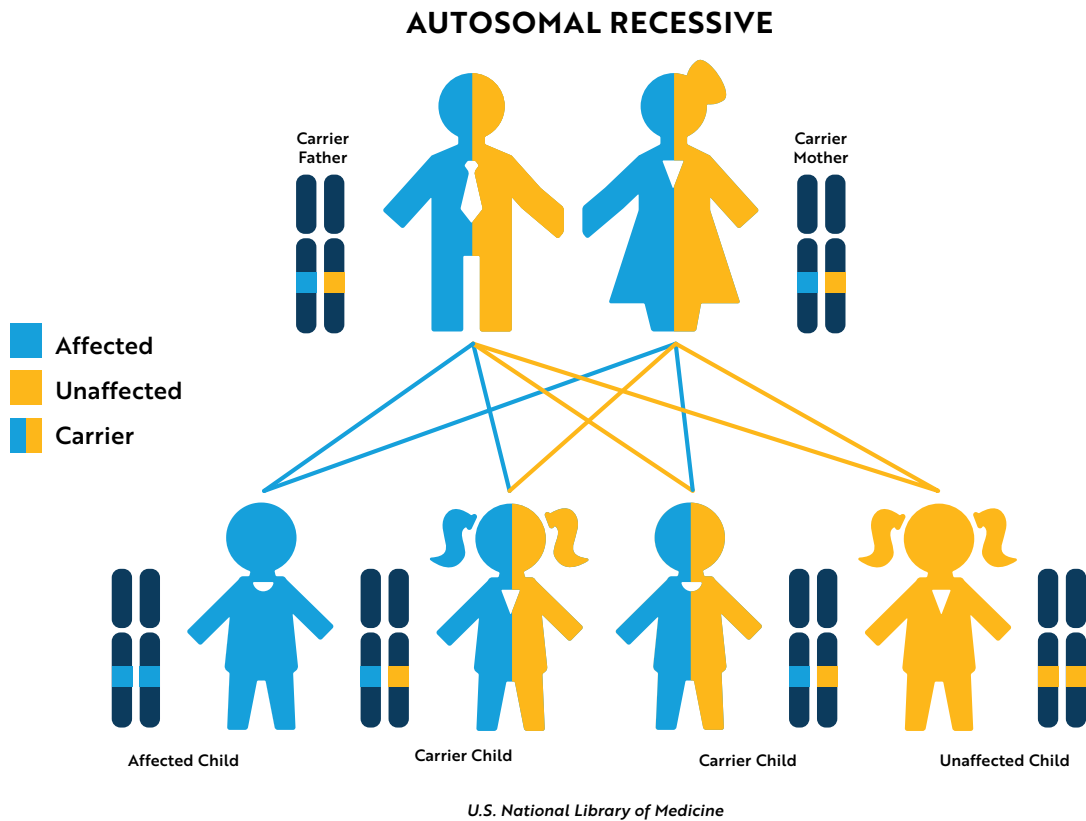
The other chromosomes are called autosomes, meaning non-sex chromosomes. Most ALS-related genes are carried on autosomes, and most mutations are dominant mutations. Therefore, they are inherited according to an autosomal dominant inheritance pattern: the disease-causing mutation can be inherited from either parent, the chances of inheriting it are 50 percent for each child of either sex, and a child who inherits the mutation will usually develop the disease.

In summary, for genes inherited according to the autosomal dominant pattern, including C9orf72 and SOD1, usually only one parent carries the mutation, and that person will usually develop ALS. That parent has a 50 percent chance of passing the mutation along to each child, and that child will also usually develop ALS.



U.S. National Library of Medicine

DOMINANT AND RECESSIVE



PENETRANCE

A person carrying an ALS-linked gene mutation will usually develop ALS, but not always. Penetrance refers to the likelihood that someone carrying a disease-causing mutation will actually develop the disease. Some ALS genes show incomplete penetrance, meaning not everyone with the mutation will go on to develop ALS. The penetrance of most ALS genes increases with age, so that the likelihood of developing ALS from a disease gene increases as a person gets older. The penetrance of the C9orf72 mutation is very high, meaning most people carrying the mutation will eventually develop ALS. The penetrance of the A4V mutation in SOD1, the most common form in North America, is estimated to be at least 90 percent by age 70.

WHAT ARE THE GENES THAT CAUSE ALS?

The table below lists the genes known to cause ALS, as of early 2018, and their inheritance pattern (see the next section for a discussion of inheritance patterns). The two most common genetic causes of ALS, mutations in the C9orf72 gene and in the SOD1 gene, are discussed below. Further information on these and other ALS genes may be obtained through discussion with your neurologist or genetic counselor.

GENE NAME	PROTEIN NAME	INHERITANCE PATTERN	CLINICAL NOTES
ANG	Angiogenin	AD	
C9orf72	C9orf72	AD	also causes FTD
CHCHD10	Coiled-coil-helix-coiled-coil-helix domain containing 10	AD	also causes FTD
CHMP2B	Chromatin modifying protein 2B	AD	also causes FTD
FUS	Fused in sarcoma	AD	also causes FTD
HNRNPA1	Heterogenous nuclear ribonucleoprotein A1	AD	also causes FTD
MATR3	Matrin 3	AD	
OPTN	Optineurin	AD/AR	
PFN1	Profilin 1	AD	
SOD1	Cu/Zn superoxide dismutase-1	AD/AR	specific mutation affects progression; the D90A mutation is recessive
SPG11	Spataccin	AR	juvenile onset
SQSTM1	Sequestosome 1	AD	
TARDP	TDP-43	AD	also causes FTD
TBK1	TANK-binding kinase 1		also causes FTD
TUBA4A	Tubulin Alpha 1	AD	also causes FTD
UBQLN2	Ubiquilin-2	XD	also causes FTD
VCP	Valosin-containing protein	AD	also causes FTD

*Additional genes have been proposed, but not yet confirmed, as fALS genes

AD= Autosomal dominant; AR=Autosomal recessive; XD= X-linked dominant; FTD= frontotemporal dementia

WHAT ARE THE GENES THAT CAUSE ALS?

C9ORF72

Mutations in the C9orf72 gene are the most common cause of familial ALS in the Caucasian population, accounting for approximately 35-40 percent of all familial cases. The same mutation is responsible for up to 10 percent of sporadic cases; in such cases, the gene mutation is inherited, but may not be expressed in every family member who inherits it, masking the familial nature of the disease (see “incomplete penetrance” above).

The same mutation also causes a second disease, called frontotemporal dementia (FTD). Some people with the mutation develop only ALS, some people develop only FTD, and some people develop both diseases. People within the same family, carrying the same mutation, may develop ALS or FTD or both. How the same gene mutation can cause the two diseases is not yet fully understood (although other genetic factors may have an impact), and it is not yet possible to predict which will develop, or whether both will develop, in a person carrying the mutation.

The normal function of the C9orf72 gene is not known. Researchers believe it may play a role in regulating the immune system.

The mutation in the C9orf72 gene that causes ALS is a hexanucleotide repeat expansion, meaning a six-letter repeated segment (GGGGCC) within the gene is expanded. The normal gene has half a dozen or so of these hexanucleotide repeat units, while the disease-causing mutation has hundreds to thousands of them.

There are several consequences of this expansion. There may a partial loss of normal function of the gene. More significantly, researchers have found, the extra DNA in the expanded segment leads to a toxic gain of one or more functions. Researchers are actively trying to understand all the effects of the C9orf72 expansion in hopes of designing treatments to mitigate them.

SOD1

Mutations in the SOD1 gene are the second-most common cause of familial ALS, found in about 20 percent of familial cases. There are over 150 different mutations known to occur in the SOD1 gene. Each specific mutation can influence several aspects of the disease, most notably the rate of disease progression. In North America, the most common mutation, accounting for about half of all SOD1-related cases, is called A4V (that shorthand indicates that the mutation changes the 4th amino acid in the protein from an alanine to a valine). The A4V mutation is generally associated with very rapid disease progression, although there are some exceptions.

The normal function of the SOD1 protein (called Cu/Zn superoxide dismutase-1) is to regulate certain reactions within cells. Loss of function does not contribute to the disease, according to research. Instead, the mutant protein gains a toxic function. That toxicity is believed to stem from the mutant protein misfolding and aggregating (clumping up) within the cell. The aggregates themselves may interfere with cell function, or the aggregates may cause other necessary proteins to misfold and lose their function. Researchers are looking for ways to prevent this aggregation.

GENETIC TESTING

Genetic tests are available to confirm the presence of mutations for a growing number of ALS disease genes. A genetic test is a laboratory test, usually done on a sample of blood or a cheek swab. DNA is isolated from the cells in the sample and tested for the presence of one or more ALS gene mutations. A genetic test is ordered by your doctor.

A genetic test can help confirm the cause of disease in a person who has already developed ALS. Such symptomatic testing is usually done only in people suspected of having a familial form of ALS. That suspicion is usually raised because other family members were diagnosed with the disease or are suspected to have had it. Many ALS clinicians have begun to recommend testing all their ALS patients for the C9orf72 mutation, because it is so common, because it can present with either ALS or FTD, and because it also occurs in sporadic ALS.

A genetic test can also be done in the healthy relatives of someone with a confirmed genetic cause of ALS. Such predictive testing is usually done to help the relative determine if they are at risk for developing ALS as well.

The results of a genetic test may be positive, negative, or uncertain:

- A positive result is one in which a known disease-causing mutation is found in a known ALS gene. For instance, finding the A4V mutation in the SOD1 gene is a positive result.
- A negative result is one in which no disease-causing mutations are found in the known ALS genes tested. For instance, finding that both copies of the C9orf72 have repeat sections of normal length is a negative result.
- An uncertain result is one in which a variant of unknown significance (VUS) is found in a known ALS gene. For instance, while there are many SOD1 mutations known to cause ALS, there are many more that have been identified whose significance for the disease is unknown. Often, this is because the variant is so rare that researchers have not been able to study it well enough to understand how it influences disease risk.

"I'm in good health but the possibility that it could change is never completely out of my mind. Things that others would never think were unusual, such as dropping something, stumbling, or having a muscle cramp, can sometimes be frightening."

**— PERSON AT RISK FOR FALS,
THE ALS ASSOCIATION ST. LOUIS REGIONAL CHAPTER**

GENETIC COUNSELING

Before you or a family member undergoes a genetic test, it is vital to think through and discuss all the implications of each possible test result, both for the person with ALS and for family members. Many people who get tested without these important discussions beforehand find that getting results, positive or negative, is more troubling than they expected, and may cause strife and confusion within the family.

Important issues that genetic testing raises include:

- How will the person with ALS use the results of the test, positive or negative?
How will the results affect family planning, career planning, and financial decision making?
- What will the results of a test mean for the children of the person with ALS?
Is the information they might learn information that can help them in their own life planning?
- How will the results affect insurance and employment?



The best way to prepare yourself and your family for genetic testing is by speaking with a genetic counselor. Genetic counselors are trained to guide individuals and families through these discussions before testing takes place. The genetic counselor is not there to convince you to get tested, or to not get tested. He or she is there to work with you to help you make the best decision for you and your family. A genetic counselor can help you understand the issues, think through your own concerns and questions, and offer guidance about how other families have used the information from the test results after deciding to get tested.

A genetic counselor will usually begin by collecting or reviewing the family history to learn more about the pattern or inheritance, and the nature of the disease within the family. The counselor may inquire about relatives you hadn't considered as being affected by ALS, recognizing that several ALS genes can also cause dementia and that this may be a manifestation of the same gene.

The counselor will assist you in understanding what a genetic test can and cannot tell you about the disease in your family. They will discuss the meaning of positive, negative, and uncertain results for each person tested, and for other family members. They will help you work through your and your family's concerns about the results and can answer your questions about the practical aspects of testing as well.

GENETIC COUNSELING

Questions you may want to ask yourself, and discuss with your family before or during the counseling process, include:

- Why do I want this test? Why do I want it now?
- What do the members of my family think about it?
- What will I do with the test result?
- How will a positive result affect me and my family? A negative result? An uncertain result?

Questions you may want to discuss with a genetic counselor may include:

- What are reasons to be tested? What are reasons not to be tested?
- Will my test results be definitive, or might there be some uncertainty in the result?
- If my test is positive, what does that imply about the gene in each of my family members?
- What are the implications of a positive test for my health insurance? My life insurance? My disability insurance? My long-term care insurance?
- Does insurance cover the test?
- What have other ALS families found about the consequences of testing, both interpersonally and practically?

If you decide to be tested, you may receive the results from the counselor, or from your neurologist. In any case, it is important to meet with the counselor afterward to discuss the results, and what they mean for the family going forward.

Your neurologist may have a genetic counselor as part of your care team. To find a genetic counselor, you can also contact the National Society of Genetic Counselors [<https://www.nsgc.org/>] to find a counselor near you.



GENE-BASED TREATMENTS

Researchers have made significant advances in developing antisense oligonucleotide (ASO) treatments for the two most common genetic causes of ALS, mutations in C9orf72 and SOD1. An ASO is a short sequence of a DNA-like material that binds to the “working copy” of the mutant gene and inactivates it. In recent years, ASO therapies have been shown to be effective in animal models, and initial testing in people with ALS indicates the treatment is safe. A trial of ASO therapy against the C9orf72 gene is scheduled to get underway in early 2018.



Many researchers believe that such gene-based therapy is the most promising treatment for genetic forms of ALS, because it stops the mutant gene from ever being “expressed,” or used to make protein or other products. If the gene can’t make the toxic products that cause disease, it should be rendered harmless. Development of other gene-based treatments is also underway. The ALS research community is committed to speeding these treatments along as fast as possible to make the most effective therapies available as soon as possible.

SUPPORT AND RESOURCES

ALS ASSOCIATION CHAPTERS

The Association’s chapter network provides much-needed care services and support to people living with ALS and their families. Chapters may offer support groups, insurance and benefit counseling, family and caregiver support, and other services. Some chapters may offer support groups for families living with familial ALS.

To connect with your local ALS Association chapter, visit www.alsa.org/community/chapters.

“Once I became involved with The ALS Association, I had the opportunity to meet other families dealing with familial ALS as well as families dealing with sporadic ALS. Frankly there is nothing unique about my family in that all families struggling with familial ALS are very different and yet they are all the same. We all have to face this hard disease, the knowing that the disease can be passed to our kids and the truth that you still have to live life the best you can.”

– FALS FAMILY MEMBER, THE ALS ASSOCIATION GOLDEN WEST CHAPTER

SUPPORT AND RESOURCES

ALS REGISTRIES AND RESEARCH STUDIES

You can enroll in an ALS registry, which supports research into the causes and cures for all forms of ALS.

Available registries include:

The National ALS Registry, a nationwide registry that is building a database to help researchers understand more about who gets ALS, and what its causes may be.

<https://www.cdc.gov/als/>

CReATe Connect, a way for people with ALS, related disorders, and their family members to learn about CReATe (Clinical Research in ALS and Related Disorders for Therapeutic Development) research studies they may be able to join. Participation is completely voluntary, and you may choose to withdraw at any time. There is no cost to join CReATe Connect. <https://www.rarediseasesnetwork.org/cms/create/patients/CRaTe-Connect>

Several ongoing research studies provide opportunities to people and families with ALS. Ongoing research studies that offer genetic testing for patients with ALS (and provide results) include:

CRaTe Phenotype-Genotype-Biomarker Study

<https://clinicaltrials.gov/ct2/show/NCT02327845>

Genomic Translation for ALS Care (GTAC) Study

<https://clinicaltrials.gov/ct2/show/NCT02795897>

Research studies that offer pre-symptomatic genetic testing include:

Pre-Symptomatic Familial ALS (Pre-fALS)

<https://clinicaltrials.gov/ct2/show/NCT00317616>

"I have participated in several ALS research studies including a longitudinal study that some family members and I have been in for 8 years. We will continue as long as we are needed. I am hopeful that in the near future that when a person is told they have ALS the next thing they are told will be '...and this is how we are going to treat it.'"

— PERSON AT RISK FOR FALS, THE ALS ASSOCIATION ST. LOUIS REGIONAL CHAPTER

The logo for the ALS Association, featuring the letters "ALS" in a large, bold, white sans-serif font, with the word "ASSOCIATION" in a smaller, white sans-serif font directly below it. The logo is centered on a red background that is decorated with a pattern of white, interconnected hexagonal shapes resembling a molecular or honeycomb structure. A solid yellow vertical bar is located on the far left side of the image.

ALS
ASSOCIATION