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Genetic Testing for ALS

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Q. Is ALS hereditary?

A. ALS is directly hereditary in only in a small percentage of families. The majority of patients with adult-onset ALS (90%) have no family history of ALS, and present as an isolated case. This is called sporadic ALS (SALS), and although there is likely a genetic predisposition involved, SALS is not directly inherited in a family. Rare exceptions are when familial ALS (FALS) is masked due to an incomplete family history, such as if the patient is adopted or the patient's parents died at ayoung age. The remaining10% of persons with ALS have a close second family member with ALS, which is referred to as familial ALS (FALS).

Currently the best tool to distinguish between SALS and FALS is the family history. A neurologist or genetic counselor will ask whether anyone else has ever been diagnosed with ALS, and if anyone else in the family had progressive walking or speech problems. If so, they will likely ask additional questions to see if the health problems were related to ALS or any number of other causes. They will also inquire about the ages that family members passed away to see if any close relatives passed away at a young age, meaning that a long health history is not available. It is very common to have limited information on one's family, but most families can still be reassured since the majority of instances of ALS are not hereditary. Older relatives are often good sources of family history information, and medical records can often be obtained with the help of a hospital's medical release form.

Q. How is FALS inherited?

A. To answer this question, it is helpful to review background information on genetics as it pertains to FALS. Every cell in the human body contains genes. Genes have many functions. Some genes contribute to traits like eye and hair color while other genes are responsible for making proteins that determine how our bodies circulate blood or send nerve signals to muscles. When a gene is disrupted by a change in its sequence (called a gene mutation), the gene cannot function correctly.

Genes are packaged in chromosomes. Chromosomes are present in pairs. The genes that reside within chromosomes are therefore also present in pairs. In each chromosome pair, one chromosome is inherited from the mother and one is inherited from the father. We have 23 pairs of chromosomes, giving us a total number of 46 chromosomes. The first 22 pairs are the numbered chromosomes in which both males and females share them in common. Only the 23rd pair differs between males and females since this pair is the sex chromosome where females typically have two Xs and males have an X and a Y.

There are at least 3 different inheritance patterns for FALS. The most common inheritance pattern for FALS is called autosomal dominant. Autosomal means that it is equally likely that a female or male would inherit the gene mutation for FALS because the gene is located on a numbered chromosome that both males and females share in common. Dominant refers to the fact that a person only needs one gene to have a mutation coding for FALS to have an increased risk for ALS. So someone who has FALS would have one gene with a mutation and one gene witout a mutation. Therefore, a child born to someone who has FALS has a 50% chance to inherit the FALS gene mutation and conversely, a 50% chance to not inherit the FALS gene mutation. The 1 in 2, or 50% chance, comes from the fact that parents randomly pass on only one member of their gene pair, so that either the gene with the mutation will be passed on or the gene without the mutation will be passed on. Even though parents often feel responsible for their children's health, they have no control over which gene they pass on, just as their parent had no control which gene they passed onto their child. It is also important to remember that inheriting the gene for FALS in no way guarantees that a person will develop

symptoms of ALS. If a child does not inherit the gene mutation for ALS, they cannot pass it onto their children.

Q. Is there a genetic test for FALS?

A. Yes, although genetic testing is still limited in FALS. Changes in one gene located on chromosome #21 and called superoxide dismutase (SOD1) have been found in about 20% of families with FALS. The SOD1 gene is composed of five regions called exons. If you think of your genetic material as a string of letters that together make up a book of instructions for the human body, the SOD1 gene is one chapter and composed of 5 different pages. SOD1's normal role is to detoxify substances called free radicals, which can be harmful to cells. Changes in the SOD1 gene are thought to create a new but still undefined function that is toxic to motor neurons. Most often, SOD1 changes are inherited in an autosomal dominant manner.

Prenatal genetic testing technology for the SOD1 mutation exists. Patients and their families should discuss questions and concerns with their neurologist and genetic counselor for more information about this complex and personal matter.

Of particular note is that the majority of families with FALS (80%) will not have a change in their SOD1 gene and therefore, a normal SOD1 genetic test is not informative in a family where an SOD1 change has not been identified. Although researchers are diligently looking for other genes, at this time there is no genetic testing to offer non-SOD1 families. Therefore, the determination that an individual has FALS is typically based on family history rather than a genetic test.

Q. Does a genetic test diagnose ALS?

A. No. Since the vast majority of patients do not have the hereditary type of ALS, diagnosis of ALS is not determined by a genetic test. Instead, a neurologist makes the diagnosis after a review of a person's symptoms, a neurological exam, and results on nerve and muscle function tests. Clinically, FALS and SALS are basically identical.

Q. Who is appropriate for genetic testing?

A. Anyone who has symptoms of ALS in addition to a family history of ALS, such as a parent, grandparent, aunt or uncle, or a brother or sister. Additionally, if one's family history is unknown or a parent passed away at a young age, testing is also appropriate. However, only about 2% of all patients with ALS will have an SOD1 genetic change. Those patients with ALS without a family history can also be offered genetic testing but it is extremely important that it is offered in the context of genetic counseling or discussion with a neurologist about the implication of finding a mutation, as a mutation would mean the ALS is now hereditary in an apparently sporadic situation.

Q. What would the results of the genetic test tell me?

A. A positive test means that the genetic cause of FALS has been identified. Researchers have developed a mouse model with the same genetic change so that they can better understand how a change in the SOD1 gene can lead to the symptoms of ALS. Currently, new therapies are being tried on this animal model to slow or halt the progression of ALS. Although still in the distant future, gene therapy to correct the genetic change is also being researched. A positive test does not change medical treatment at this time and may or may not provide prognostic information. Even though the inheritance may already be established by the family history, an individual may feel furthered burdened by learning they carry a change in their SOD1 gene as concerns for children resurface. Others prefer to have this knowledge and may feel comforted that there is much research aimed specifically at ALS caused by changes in the SOD1 gene.

A negative test means only that the genetic cause of ALS has not been identified. However, this does not rule out familial ALS since there are still other unidentified genes that cause ALS in 80% of FALS families.

Q. If I have a family history of FALS, should I have a genetic test even if I don't have symptoms?

A. This situation is called presymptomatic testing. The decision to have presymptomatic genetic testing is highly personalized and often individuals in the same family will disagree whether to pursue it. However, in order for the test to be meaningful, a genetic change in the SOD1 gene needs to first be found in a family member affected with ALS. When an SOD1 change is not identified in a symptomatic person, presymptomatic genetic testing is not available for other family members, because the ALS is being caused

by an unidentified gene, thus we cannot test for it.

Benefits of presymptomatic genetic testing in ALS is limited by the absence of preventative treatment, the inability to predict the age at which someone who is a gene carrier will get ALS, or even that a gene carrier will definitely get ALS. Since both a negative or positive presymptomatic test result in a known SOD1 family can have a great emotional impact, genetic and psychological counseling is usually required before undergoing such testing (A presymptomatic genetic testing protocol is typically followed). Individuals often consider how the information that they did or did not inherit the predisposing gene would affect their lives, who they would tell about the results, and how relationships may change depending on the results.

Individuals who learn they do not carry the SOD1 change often feel great relief, although they can sometimes wonder why they escaped while another family member did not. They may regret past decisions made based on the presumed at risk status, or find it hard to let go of that part of their identity. Learning that one does carry a predisposing gene, is usually more difficult and that person may need ongoing professional support. Ambiguity is not entirely erased as the question may change from do I carry the gene to when or will I get symptoms? Commitment to friends and family may be strengthened. However, knowledge of the testing by insurance companies or employers is a concern regarding future coverage. A genetic counselor can further discuss the issues involved in presymptomatic testing.

Q. How is the genetic test done?

A. A blood sample is taken and sent to a specialized lab where the genetic material, also called DNA, is removed. Special laboratory techniques allow the SOD1 gene to be replicated and then tested. One form of testing is runnign the sample on a gel to generate a series of bands. If a genetic change is present, the bands will be in a different location compared to a control sample, which is known not to have a genetic change in the SOD1 gene. This method is called single strand conformation polymorphism or SSCP for short. Another method called sequencing may also be used to either initially test or confirm results. Sequencing is able to view the DNA on a finer scale by displaying the actual letters of the "instruction book" so that changes can be seen.

Q. How long does the genetic test take?

A. Because five different parts of the SOD1 gene need to be looked at, the testing usually takes about 2-3 months. The cost is about $300-500 depending on the clinical laboratory that is doing the testing.

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