

## Section J

### GENETIC ISSUES in ALS

About 90 percent of patients with ALS have no known family history of the disease. In these patients, the disease is called sporadic ALS, or SALS. Although genetic risk factors may yet be identified in SALS, the disease is not directly inherited in a family. The remaining 10 percent of patients with ALS have an inherited form of the disease called familial ALS, or FALS.

#### FALS

##### Genes and Chromosomes

Genes are very small units of inherited information that are found inside each of our cells. The genes provide instructions that direct the cell to make proteins, which are important in the individual's development and physical characteristics. Scientists now think that there are about 30,000 genes in the human body. The genes in the body's cells are in pairs. A child gets one copy of the gene of each pair from the mother and one from the father. If a gene changes, or mutates, the instructions in the gene are changed and genetic disorders can result. The gene no longer provides the proper instructions to the cells.

Chromosomes are the structures in a cell that carry genes. Humans have 23 pairs of chromosomes in each body cell, for a total of 46. The first 22 numbered pairs are the same in men and women, and are called autosomes. The 23rd pair of chromosomes are the sex chromosomes, which help determine if a person is male or female. In males, typically the two sex chromosomes are different, one X and one Y. Females typically have two X chromosomes.

##### How Is FALS Inherited?

The most common inheritance pattern for FALS is called *autosomal dominant*. Autosomal means the gene that carries the disease is located on one of the chromosomes that is the same in men and women. Female and male offspring are equally likely to inherit the gene for FALS. Dominant means that an offspring will be likely to have ALS even if he or she has a mutation for FALS in only one copy of the pair of genes.

Each parent randomly passes on one copy of each gene pair to the offspring. Suppose a child has one parent who has FALS and one who does not. This child has a 50 percent chance of inheriting the FALS gene and a 50 percent chance of not inheriting it. The chance is 1 out of 2, or 50 percent, because the parent who has FALS will pass on either the gene for ALS or the gene that is not for ALS. The other copy of the gene pair, from the other parent, will have the gene that is not for ALS. A child who inherits the mutation for FALS has a 90 percent chance of developing symptoms by age 70. Therefore, inheriting the gene for FALS does not guarantee that the person will develop ALS, and the severity and scope of the onset of the disease cannot be predicted. The cause of the variability of the disease progression is unknown.

## **GENETIC TESTS**

### **Can a Genetic Test Diagnose ALS?**

No, diagnosis of ALS cannot be determined by a genetic test. A neurologist makes the diagnosis after reviewing a patient's symptoms, the results of a neurologic examination, and the results of nerve and muscle function tests. Clinically, sporadic ALS and familial ALS (FALS and SALS) are identical.

### **Is There a Genetic Test for FALS?**

Changes in one gene have been identified in about 20 percent of the families with FALS. This gene is located on chromosome number 21 and is called copper-zinc superoxide dismutase, or SOD1. The SOD1 gene has five sections, called exons. 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 is made up of five different pages, one for each exon. SOD1's normal job is to affect certain substances in the body, called free radicals, that can harm cells. SOD1 normally changes the free radicals so they are no longer harmful. Researchers think that the changes, or mutations, in the SOD1 gene cause the gene to function in a new way that somehow damages or injures motor neurons, instead of preventing injury to the cell/motor neuron.

Eighty percent of the families with FALS do not have a mutation in the SOD1 gene. Therefore, families with FALS may have a mutation present, however it is not detectable through the currently available genetic testing. Researchers

are searching for other genes that might cause autosomal-dominant FALS, but at this time there is no genetic testing to help non-SOD1 families. The determination that an individual has FALS is typically based on family history, rather than on a genetic test.

### **How Is the Genetic Test Done?**

A blood sample is taken and sent to a specialized lab. There, the genetic material, called DNA, is separated and removed. DNA is the substance that makes up the chromosomes and controls a cell's activities. The SOD1 gene can then be copied and visualized by making many duplicate copies of it, separating it from the other genes and then adding a special dye to make the gene visible. Then the gene can be compared with a control. If an SOD1 gene mutation is present, the gene will look different from the control.

### **Who Should Have a Genetic Test?**

Testing is appropriate for anyone who has symptoms of ALS and a family history of ALS, such as a parent, grandparent, aunt, uncle, brother, or sister who has or had the disease. Additionally, if the family history is unknown or if a parent passed away at a young age, testing is appropriate.

A positive genetic test means that the genetic cause of a patient's FALS has been identified. However, only about 2 percent of all patients with ALS will have an SOD1 mutation. A negative test means that the genetic cause of the ALS has not been identified. This does not change the diagnosis or the chance that a family member might develop ALS. Other genes, at present unidentified, cause FALS in the majority of FALS families. Researchers might ask for samples from additional family members in order to help identify these other genes.

A person with a family history of FALS might have a genetic test even if he or she doesn't have symptoms. This is called presymptomatic testing. The test will be meaningful only if a mutation in the SOD1 gene has been found in a family member who has ALS. A negative or a positive result of a presymptomatic test in a known SOD1 family can have a great psychological impact. Therefore, genetic and psychological counseling is usually required before such testing. At this time, there isn't much advantage to presymptomatic genetic testing in ALS. There is no preventative treatment, the age at which a person with the gene will get ALS is unpredictable, and it is not even certain that a person with the gene will actually get ALS. The

Genetic Counselor at the Lois Insolia Center can discuss in detail the issues involved in presymptomatic testing.

### **LABORATORY-BASED GENETIC RESEARCH STUDIES**

Genetic research studies, unlike drug studies, do not provide a potential direct therapeutic benefit to the patient. However, by investigating the genetics of ALS, researchers hope to aid in the development of new treatments and prevention. The Les Turner ALS Research Laboratory approaches this task from several aspects:

- gene studies in familial, or hereditary, ALS (FALS)
- animal studies
- genetic studies of risk factors in sporadic, or nonhereditary, ALS (SALS)

#### **Genetic Studies in FALS**

In 1993, scientists with the Les Turner ALS Research Laboratory, working with collaborators from Massachusetts General Hospital and Duke University, identified the only gene proven to cause FALS. This gene, located on chromosome 21, is called superoxide dismutase (SOD1). The normal role of the protein produced by the SOD1 gene is involved with detoxifying free radicals. Excess amounts of free radicals can cause damage to cells and proteins. Changes, or mutations, are present within the SOD1 gene in about 20 percent of FALS families. Researchers are working to find out how the mutations in the SOD1 gene damage motor neurons.

For large nonSOD1 FALS families, linkage studies are performed to search for other genes that might cause the disease. Linkage studies involve collecting blood samples from both healthy and affected family members and then studying genetic markers to try to pinpoint an area on a chromosome where an ALS gene may lie. Once such an area is found, additional families are included in the study to help narrow the region until a single affected gene can be identified.

A second gene mutation that causes an inherited form of ALS has been identified by the Les Turner ALS Research Laboratory at Northwestern University Feinberg School of Medicine. The newly identified gene mutation is responsible for a rare, slowly progressive, early-onset form of the disease, called juvenile inherited ALS (ALS2). The ALS2 gene was discovered in

highly inbred populations in North Africa and the Middle East. The ALS2 gene is located on chromosome 2q33. In its normal form, the gene responsible for ALS2 codes for a protein called alsin that plays an integral role in cell signaling pathways, and possibly neuronal outgrowth. The gene mutations in the ALS2 gene may cause a loss of function of the alsin protein. The discovery of this gene will assist researchers in determining the effects of the deficient alsin protein on ALS and will help identify cellular pathways that may intersect with those of mutant SOD1, the ALS gene previously discovered by the Research Laboratory.

### **Genetic studies in SALS**

Because the causes of sporadic ALS are unknown, Dr. Siddique's research team is trying to determine what genetic factors may "predispose" an individual to developing sporadic ALS; therefore genetic risk factor studies are being conducted. Genetic markers in SALS patients are compared to immediate family members, either to both parents, or to siblings (preferably a brother or sister who is older than the age of the patient at the onset of symptoms). Participating in a genetic research study is voluntary and confidential. Typically, participation only requires having a blood sample drawn at a physician's office or hospital clinic and sent to the Research Laboratory, as well as answering questions regarding family history. The research program covers all costs associated with the study.

### **Animal Studies**

In 1994, researchers developed a strain of mice that have the SOD1 mutation. This animal model helps the researchers understand how a change in the SOD1 gene can lead to the symptoms of ALS and how the disease develops. It also allows them to test the effectiveness of possible drug treatments on the disease. New therapies are being tried on this animal model to slow or halt the progression of ALS. Although results are still in the distant future, gene therapy to correct the mutation is also being studied.

### **THE LOIS INSOLIA ALS TISSUE BANK**

The tissue bank located at Northwestern University Feinberg School of Medicine is an integral component of the ongoing research into the causes of ALS. Blood, brain tissue, and spinal cord tissue from ALS patients is collected and preserved for use in research at Northwestern University's Feinberg School of Medicine and other institutions. Families interested in tissue donation may contact Lisa Dellefave, MS at 312-503-0154 or

l-dellefave@northwestern.edu or Nailah Siddique RN, MSN at 312-503-2712 or nsiddique@northwestern.edu. Lisa or Nailah can provide information and help to arrange the donation process based upon the family's wishes. The arrangements could take up to a week to complete. Therefore, if possible please contact them when initially considering the gift of tissue donation. Having all procedures in place may help to reduce stress on the family at the time of death.