Section 10
Genetics of ALS
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About 90 percent of people with ALS have no known family history of the disease – they are the only affected person in their family. For these individuals, 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 people with ALS do have one or more affected family members and these individuals have an inherited form of the disease called familial ALS, or FALS.

Familial ALS

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 20,000 human genes that provide our cells with instructions on how to grow and function. Most genes are present in pairs, and a child gets one copy of the gene of each pair from the mother and one from the father. Genes are our cells’ ‘recipes’ for proteins. Therefore, if a gene contains a change, also known as a mutation, the instructions of that gene are changed and this can result in an abnormal or absent protein. Genetic mutations can lead to genetic disorders, since the gene no longer provides the instructions that the cells need to function.

Everyone has “FALS genes” – when working properly, they provide instructions for our brain and nerve cells to make proteins necessary for normal functions. However, if one of these genes has a mutation that causes it to create an abnormal protein, that can lead to the symptoms of FALS.

If we think of genes as books, we can think of chromosomes like bookshelves – they contain the genes and keep them organized. Humans have 23 pairs of chromosomes in each 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. Males typically have one X and one Y chromosome, and females typically have two X chromosomes. Egg and sperm cells each contain 23 chromosomes – one of each pair. When these two cells combine, the resulting cell contains a full 23 pairs of chromosomes.

How Is FALS Inherited?

The most common inheritance pattern for FALS is called *autosomal dominant*. Autosomal means the gene that carries the mutation that causes the disease is located on one of the autosomes – the chromosomes that are the same in men and women. If a parent is affected, then
female and male offspring are equally likely to inherit the gene copy with the mutation or gene copy without the mutation. Dominant means that only one copy of the gene pair needs to have a mutation to cause symptoms of ALS.

Each parent randomly passes on one copy of each gene pair to the offspring. If a child has one parent who has FALS and one parent who does not, that child has a 50% chance of inheriting the FALS gene mutation and a 50% chance of inheriting their affected parent’s non-mutated, working copy of the gene. The chance is 1 out of 2, or 50%, because the parent who has FALS will pass on either the mutated copy of the FALS gene (leading to an increased risk for FALS for that child) or the normal, working copy of the FALS gene (leading to no increased risk for FALS). FALS gene mutations are rare, so the unaffected parent will always pass on a working copy of the FALS gene in question.

A person who inherits a mutation for FALS can have up to a 90% chance of developing symptoms by age 70; however, each gene and mutation is different so this percentage can vary widely. 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, a diagnosis of ALS cannot be made by a genetic test. A neurologist familiar with ALS makes the diagnosis after reviewing a person’s symptoms, the results of a neurologic examination and the results of nerve and muscle function tests. Clinically, SALS and FALS are identical.

**Is there a genetic test for FALS?**

Yes, but only for specific genetic mutations that have been identified to cause FALS. Currently, about 60% of all FALS cases can be connected with an identified FALS gene. The remainder of FALS cases have genetic causes that have not yet been identified by researchers.

In 1993, Dr. Teepu Siddique, at the Les Turner ALS Research Laboratory, now part of the Les Turner ALS Research and Patient Center at Northwestern Medicine, working with collaborators from Massachusetts General Hospital and Duke University, identified the first gene that causes FALS. Changes in this gene have been identified in about 20% of the families with FALS. This gene, located on chromosome number 21, is called copper-zinc superoxide dismutase, or SOD1.

SOD1’s normal job is to interact with certain substances in the body, called free radicals, which can harm cells. Normally, SOD1 changes the free radicals so they are no longer harmful. Researchers think that 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.

Another gene called C9orf72 has been found to cause FALS in about 40% of affected families. The protein that this gene codes for is important for sending and receiving signals between neurons. The C9orf72 protein likely plays a role in many processes involving the chemical cousin of DNA, known as RNA. This protein is thought to influence the production of RNA from genes, the production of proteins from RNA, and the transport of RNA within the cell. The C9orf72 gene contains a section of repeated letters – like a word in a paragraph that has been repeated over and over. This is a normal part of this gene, and up to a certain threshold the gene functions normally. However, if the number of repeats is beyond that threshold, the protein that the gene encodes is abnormal and this puts a person at increased risk to develop symptoms. Testing for this gene ‘counts’ the number of repeats present in each of the two copies of this gene that everyone has. Mutations in this gene have also been found to cause other symptoms, including frontotemporal dementia (FTD) and Parkinson-like features.

There are approximately 20 identified genes that cause FALS, but they are much rarer than SOD1 and C9orf72. Together, all other known genes account for about 60% of all FALS.

Forty percent of families with FALS do not have a mutation in the SOD1 or C9orf72 gene or other identified genes. Therefore, FALS in these families is caused by a mutation in other genes that have not yet been identified. Because we don’t know where these genes are located, we cannot test for them in either patients or their family members. Researchers are searching for other genes that might cause FALS, but at this time we do not know the genetic cause of FALS in all FALS families. The determination that an individual has FALS is typically based on family history (more than one family member with ALS) rather than on a genetic test.

**How is the genetic test done?**

A blood sample is taken and sent to a specialized lab. Our blood cells contain DNA, and this is separated and removed for testing. DNA is the language of genes – the substance that makes up the chromosomes and controls a cell’s activities. The gene or genes being tested can then be amplified, or copied. Using a variety of methods, the sequence of the gene can be ‘proofread’ and compared with the sequence of a normal, working version of the gene.

**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 may be appropriate.
A positive genetic test means that the genetic cause of a patient’s FALS has been identified. However, not all people with ALS will have a mutation – about 60 percent of all FALS patients have a mutation in a FALS gene for which we can currently test. A negative test means that the genetic cause of the ALS has not been identified in the family and does not change the diagnosis or the chance that a family member might develop ALS. Other currently unidentified genes cause FALS in about 40% 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 pre-symptomatic testing. Testing is available only if a mutation in a known FALS gene has been found in a family member who has ALS. A negative or a positive result of a pre-symptomatic test in a FALS family can have a great psychological impact. Therefore, genetic counseling and a neurological evaluation are required before such testing. Part of the discussion with a genetic counselor will involve the benefits and limitations of getting pre-symptomatic testing for FALS. Currently, there are no preventative options, 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 mutation will definitely get ALS. However, individuals may be interested in learning their status for financial or insurance planning purposes. Additionally, there are reproductive technologies available that can greatly reduce the risk of passing on a FALS gene mutation, therefore ensuring that a person’s children will not be affected. Everyone has different reasons for choosing to test or not test, and it is a very individual decision – even siblings within the same family may feel differently about whether or not they want to be tested. Pre-symptomatic testing is a big decision, and should not be taken lightly. The Genetic Counselor at the Lois Insolia ALS Clinic at the Les Turner ALS Center at Northwestern Medicine can discuss in detail the issues involved in pre-symptomatic 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. One of the Les Turner ALS Research Laboratories, headed by Dr. Teepu Siddique, 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

For large FALS families with no identifiable genetic cause, several strategies may be used to find potential genes of interest. One strategy is a linkage study, which involves collecting blood samples from both healthy and affected family members and then studying genetic markers to try to pinpoint an area of shared inheritance amongst affected individuals 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 was also identified at the Les Turner ALS Research and Patient Center at Northwestern Medicine. The gene is responsible for a rare, slowly progressive, early-onset form of the disease, called juvenile inherited ALS (ALS2). The gene mutations in ALS2 may cause a loss of function of the alsin protein. Identification of this and other FALS genes assist researchers in determining cellular pathways that may intersect with those of mutant SOD1, and other FALS genes.

Genetic studies in SALS

Because the causes of sporadic ALS are unknown, Dr. Siddique’s research team at the Les Turner ALS Research and Patient Center at Northwestern Medicine is trying to determine what genetic factors may “predispose” an individual to developing sporadic ALS by conducting genetic risk factor studies. Genetic markers in SALS patients are compared to immediate family members, either parents or 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 a few voluntary questionnaires regarding family history and environmental exposures. 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. Mouse models exist for other FALS genes as well. These mouse models also allow researchers 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 future, gene therapy to correct mutations is also being studied.