

# Ask the Neurologist: Genetics of ALS

Spring 2004

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**The questions in this newsletter will focus on the genetics of ALS**

## **Is ALS inherited?**

Most often it is not. ALS can be divided into an inherited type (familial ALS) and a non-inherited type (sporadic ALS). About 5-10% of cases of ALS are familial. The majority of those cases show a pattern of inheritance which is called autosomal dominant. To understand inheritance, it helps to understand some basic genetic principles. All genes come in pairs, known as alleles. Individuals with a dominantly inherited disease possess one copy of a mutated gene and one copy of a "normal" gene. Because the mutated gene is dominant, the affected individual usually shows the features of the disease. When that individual has children, he or she will pass on one allele of each pair in each egg or sperm cell. Because half of the alleles code for the disease and half are normal, there is a 50-50 chance that each egg or each sperm cell will have the abnormal allele. Assuming that this individual has a child with an individual who is unaffected (has 2 normal alleles), there is a 50% chance that the child of such a union will have the genetic basis for developing the disease (one mutated allele, one normal) and a 50% chance that the child will be unaffected. Thus, the child of someone with familial ALS generally has a 50% chance of developing ALS. This probability is no different in males than in females. But, if someone with ALS has no family history of the disease in close family members, then it is highly unlikely that he or she has familial ALS. Such a person with sporadic ALS can assume that the chance of his or her children developing ALS is no greater than that of the general population.

## **What gene has been found to produce familial ALS?**

Mutations in the SOD1 gene have been found to be present in about 20% of individuals with familial ALS. The SOD1 gene codes for the enzyme superoxide dismutase. Because only 5-10% of cases of ALS are familial, and because only 20% of these familial cases have an SOD1 mutation, this means that an SOD1 mutation can be identified in only about 1-2% of all individuals with ALS. So, 98-99% of individuals with ALS do not have a known genetic basis for their disease. It gets more complicated, because many scientists and physicians who study ALS now believe that genetics may play a larger role, even though the genes responsible for ALS have not been identified. Why else should some individuals develop this disease, while others do not? The search for other genes, particularly in sporadic ALS, is being led by Dr. Robert Brown at Harvard, and Dr. Teepu Siddique at

Northwestern, who are collecting blood samples on individuals with sporadic ALS and their family members in an attempt to identify a possible genetic basis for some cases of sporadic ALS.

### **Should genetic testing be done in people with ALS?**

Not usually. Most neurologists and geneticists do not recommend genetic testing for individuals with sporadic ALS or their families, because the SOD1 mutation is virtually never found in such individuals. For those with a family history of ALS that fits the pattern of autosomal dominant inheritance described above, genetic testing is sometimes done, but a decision about whether or not to have such testing performed should be carefully considered. Is the diagnosis uncertain, so that genetic testing is being done for confirmation of diagnosis? If that is the case, then only 20% of individuals with familial ALS will have the SOD1 gene mutation, so that the genetic test will be negative 80% of the time even if dominantly inherited ALS is present! If the test is being done so that other family members can be screened for the gene, then a positive test for the mutation in the affected individual will lead to accurate screening. That is, if the person with ALS has the SOD1 mutation, then a negative blood test on his or her children rules out the possibility that they will develop familial ALS, but a positive blood test is more complex. It means that they are highly likely to develop familial ALS, but tells nothing about when. Usually the age of onset is similar, but not always. And, in rare cases, the individual may carry the gene but still not develop ALS. Also, not everyone wants to know if they are carrying the gene. For some, the stress of knowing that they are likely to develop ALS is unbearable, while in others the stress of not knowing is even worse. The bottom line is that a good understanding of genetic testing is necessary before such testing is performed. A genetic counselor or a an experienced neurologist who is an expert in ALS can and should provide such guidance.

### **Can you tell me about the “ALS mice” that are used to help scientists understand ALS?**

The mice are known as “transgenic mice.” These are mice who have the human SOD1 mutation inserted into their own genetic material, thus causing them to develop a motor neuron disease as they age. The value of transgenic mice is that they may lead to a better understanding of the disease, and they permit studies of possible treatments. If a drug looks promising, it can be given to transgenic mice, who can be studied to determine whether or not they develop ALS at the expected age, and whether the disease progresses at the usual rate. A treatment that delays the onset of the disease or slows the rate of progression eventually may be a candidate for human trials. Of course, the model is not perfect for several reasons: 1) only a small fraction of human ALS is associated with an SOD1 mutation; 2) the disease that develops in mice is not precisely the same as human ALS; and 3) we cannot treat humans before the disease develops to see if the onset of disease is delayed, so we don’t really know what it means if the treatment delays onset in mice. But, the use of transgenic mice has led to a greater understanding of human ALS, and is being actively used to test new treatments and expand our knowledge of the underlying mechanisms of the disease.