SOD….TDP….FUS.…HFE…ETC, ETC!! The Alphabet Soup of ALS Genetics

Summer 2010

Zachary Simmons, MD

Most individuals with ALS are classified as "sporadic" (no family history of ALS), but roughly 10% of persons with ALS have a family history of the disease and are classified as familial ALS (fALS). Although this percentage is small, the implications would seem to be obvious and very important: we "know" the cause of ALS in the familial subgroup. However, as with many scientific facts, and certainly with most things related to ALS, the story is more complicated.

Of individuals classified as fALS because of a clear family of the disease, approximately 20% possess a mutation in the superoxide dismutase 1 (SOD1) gene, 5% have a mutation in the TAR DNA binding protein 43 (TDP-43) gene, and another 4-5% of have a mutation in the fused in sarcoma (FUS) gene. While there are other genes which appear to cause ALS in very small numbers of individuals, this means that a gene can be identified in only about 30% of individuals who, by history, have fALS. The other 70% will have a "negative" genetic test, despite a positive family history.

There are a few additional twists. The 3 genes mentioned here usually are autosomal dominant, meaning that children of affected individuals each have a 50% chance of inheriting the mutation which will cause ALS. But, in families with an SOD1 gene mutation, which is the gene best studied to date, there are individuals who possess the mutation, yet live a long life without ever developing ALS, a trait the geneticists term "incomplete penetrance." And, in some families with SOD1 mutations, autosomal recessive inheritance is found, meaning that affected individuals must possess two copies of the mutation, and children of such individuals are unlikely to develop ALS. Usually such families have far fewer affected members.

What does this mean for patients and their families? One important question is whether everyone with ALS should undergo genetic testing, regardless of family history. Most neurologists would not recommend that, because rare individuals with sporadic ALS have one of the mutations mentioned above, and the significance of this for their children and other family members often is unclear. However, if an individual with ALS has a clear family history of the disease, there is value in a discussion of genetic testing. Individual asking for testing should have a clear understanding of the meaning of the tests. Key points are:

- If there is a family history, then a mutation in the SOD1 or TDP-43 o FUS gene will be found about 30% of the time.

- Children of individuals who possess one of these e mutations usually have a 50% probability of inheriting the mutated gene, and are likely to develop ALS. However, it is by no means a certainty that the children will develop ALS because of incomplete penetrance.
- For individuals who inherit an ALS gene mutation and go on to develop ALS, the age at which they will develop ALS and the rate of progression, while often similar among individuals in a family, is not always uniform. An example of this has been seen in our ALS center, in which one patient developed slowly progressive ALS years before her mother developed a much more rapidly progressive form. Both possessed an SOD1 mutation, but the clinical expression of this mutation was markedly different in the two individuals.
- Children and other asymptomatic relatives of an individual with ALS and a known mutation must receive detailed and clear genetic counseling regarding the issues discussed here. They may or may not wish to undergo genetic testing themselves. Many people do not wish to know whether they possess a gene mutation which is likely to produce a fatal disease at an unknown point in their future. The implications are enormous, and the emotional stresses of a positive test can be substantial.
- The meaning of a "negative" genetic test must be understood. If there is a clear family history of ALS and if the individual develops ALS and tests "negative", this does not, of course, mean that the individual does not have ALS. It simply means that he/she does not possess a gene mutation for which commercial testing is available. In such a case, testing of family members is not of any value, because they have a gene mutation which cannot at this point in time be identified. This is the case in about 70% of persons who have fALS, meaning that gene testing often does not provide the information hoped for.

There are other genes which appear to play a role in ALS as well. For example, in collaboration with Dr. James Connor, we found that mutations in the HFE gene, a gene usually associated with the iron storage disease hemochromatosis, occur more frequently in individuals with ALS than in others. Work in other labs has confirmed this, and demonstrates that the presence of a variant of the HFE gene known as H63D increases the risk of developing ALS by 4-fold. We recently found that ALS mice that possess this mutation have shorter lifespans than those who do not. We do not believe that H63D is a direct cause of ALS, because many individuals with the H63D mutation do not develop ALS. Rather, we hypothesize that H63D creates an environment that makes it more likely that an individual will develop ALS, possibly by increasing oxidative stress. We are working toward developing a better understanding of the mechanism whereby H63D contributes to ALS, in the hope that this may lead to treatments that are particularly effective in individuals with ALS who possess this mutation.

Other therapies based on ALS genetics are being explored. The compound ISIS 333611 is being tested at Massachusetts General Hospital, Johns Hopkins, and several other sites by intrachecal infusion (injection in to the spinal fluid) in individuals with SOD1 fALS in the hope that it will decrease mutant SOD1 levels in a manner similar to that achieved in rodents. Arimoclomol, a drug that is believed to act at the level of protein misfolding, is

being tested in individuals with SOD1 positive fALS at Emory University, Massachusetts General Hospital, and the University of California at Irvine.

The genetics of ALS appear to be complex, and it likely that multiple genes will be found to contribute to an increased susceptibility to ALS. It is possible that this higher susceptibility, combined with some type of environmental trigger, may underlie the pathogenesis of the disease. I do not believe that genetic research alone with result in identification of cause or cure. But I believe strongly that our progress in this field is leading to a better understanding of ALS, and will contribute to the identification of better treatments.