

SOD1 A4V familial ALS in North America

Can understanding the past lead to a better future?



Carmel Armon, MD,
MHS

Address correspondence and reprint requests to Dr. Carmel Armon, Baystate Medical Center/Tufts University School of Medicine, 759 Chestnut Street, S4648, Springfield, MA 01199
carmel.armon@bhs.org

Neurology® •••

Mutations in the gene encoding cytosolic Cu,Zn superoxide dismutase (SOD1)¹ account for 20% of cases of familial amyotrophic lateral sclerosis (ALS), which account for 5 to 10% of all cases of ALS. With one exception,² they are inherited in an autosomal dominant fashion. Of the over 100 mutations identified, one in particular—an alanine-to-valine substitution in codon 4 (A4V)—accounts for 50% of cases of SOD1-related familial ALS in the United States. This mutation causes a rapidly progressive form of pure lower motor neuron ALS with a median survival of 1 year from onset,³ compared to 3 years for patients with sporadic ALS. The mutation is rare in Europe. Understanding why the frequency of A4V SOD1 mutations is different on the two continents might provide clues as to how familial ALS originates and spreads within populations. One reason may be the age of the mutation, or the founder effect. A mutation that occurred earlier may be more prevalent because it had time to spread before the occurrence or introduction of other mutations. Alternatively, a particular mutation may confer survival advantage in one locale but not in another.

In this issue of *Neurology*®, Saeed et al.⁴ report that they identified two founders for the North American SOD1 A4V mutation. One founder, accounting for 18% of North American A4V patients, had a genetic background similar to that of European A4V patients. The other founder, accounting for 82% of the North American A4V patients, was genetically similar to Amerindians (Native Americans), who migrated from Asia into North America. Using two different methods, they estimated that the mutation was introduced into the white population about 400 to 500 years ago.

Another group of investigators⁵ performed similar analyses in North American patients with A4V

SOD1 ALS. They identified a conserved minimal haplotype 2.8 Kb in length around the A4V mutation, showed that it was statistically more similar to Asian (Chinese and Japanese) than European population DNA sets, and suggested that “the A4V mutation arose in native Asian-Americans who reached the Americas through the Bering Strait.” Saeed et al. were able to be more specific because they used an Amerindian reference group, in addition to a Chinese reference group. The principal reason Saeed et al. could identify the second, European, founder appears to be that they had discovered a new biallelic CA repeat, tightly linked to A4V, which was particularly useful in distinguishing between the two founders.

Saeed et al. did not identify any Amerindians with ALS, sporadic or familial. They consider several explanations. First is underascertainment of ALS in Amerindians. If true, I encourage readers of *Neurology*® to rectify this, with appropriate Institutional Review Board oversight, by publishing reports of patients with ALS of Amerindian descent and referring them (or their blood samples) to Saeed et al. Another explanation they consider, focusing just on the A4V mutation, is that the mutation became extinct in Amerindians. It is not unreasonable to think that the original carriers of the mutation were few in number and at a survival disadvantage compared to the white recipients.

Finally, Saeed et al. hypothesize that Amerindians may carry a protective factor against development of ALS in general, including A4V SOD1 ALS. They make reference to the D90A SOD1 mutation, which may present in dominant, recessive, and sporadic forms. Parton et al.² proposed that a protective mutation (a regulatory polymorphism close to the D90A SOD1 gene) occurred approximately 63 generations

See page XXX

e-Pub ahead of print at www.neurology.org.

From Baystate Medical Center/Tufts University School of Medicine, Springfield, MA.

Disclosure: Dr. Armon is Principal Investigator at Baystate Medical Center for a study of dextromethorphan/quinidine in patients with pseudobulbar palsy, sponsored by Avanir Pharmaceuticals; was PI at Baystate for a study of CoQ10 in ALS, sponsored by NIH (Columbia, NY, coordinating center); and is a contributor to the ALS DNA data bank, sponsored by NIH. Dr. Armon had received compensation from a group of current and former manufacturers of welding consumables for expert opinion related to risk factors and causation in ALS and from several law firms for expert opinion, in cases where medical malpractice has been alleged, and in a case in which trauma was alleged to have caused ALS. Baystate Medical Center has a contract with the Massachusetts Department for Public Health for consultative services provided by Dr. Armon in support of the Massachusetts ALS registry.

ago, resulted in amelioration of the consequences of a dominant mutation that had occurred approximately 895 generations ago, and established the autosomal recessive lineage of D90A SOD1 ALS. However, the circumstances here are different. Saeed et al. note that the size of the DNA fragment spanning the Amerindian A4V mutation introduced into the white population was long (>3 Mb). It is difficult to entertain the hypothesis that a protective polymorphism very close to the A4V SOD1 locus was different and without protective effect just in the fragment transmitted to the white population or changed during the transmission. Inferring a protective effect for Amerindian lineage against all forms of ALS would require confirmation of low incidence of ALS in this population after vigorous case-finding efforts.

The reports by Saeed et al.⁴ and Broom et al.⁵ do not explain why the Amerindian A4V mutation appears to have been more successful in spreading in North America than was the European variant in Europe and North America. It is tempting to speculate that the answer may reside in the 3 Mb of genetic material transmitted with the Amerindian A4V mutation. These reports advance our quest

for better understanding of the spread and expression of the genes producing familial ALS. The challenge for patients with familial ALS, and those who care for them, is how to apply this information.

REFERENCES

1. Rosen DR, Siddique T, Patterson D, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature* 1993;362:59–62.
2. Parton MJ, Broom W, Andersen PM, et al. D90A SOD1 ALS Consortium. D90A-SOD1 mediated amyotrophic lateral sclerosis: a single founder for all cases with evidence for a cis-acting disease modifier in the recessive haplotype. *Hum Mutat* 2002;20:473.
3. Juneja T, Pericak-Vance MA, Laing NG, Dave S, Siddique T. Prognosis in familial amyotrophic lateral sclerosis: progression and survival in patients with glu100gly and ala4val mutations in Cu,Zn superoxide dismutase. *Neurology* 1997;48:55–57.
4. Saeed M, Yang Y, Deng H-X, et al. Age and founder effect of SOD1 A4V mutation causing ALS. *Neurology* Epub ahead of print.
5. Broom WJ, Johnson DV, Auwarter KE, et al. SOD1A4V-mediated ALS: absence of a closely linked modifier gene and origination in Asia. *Neurosci Lett* 2008;430:241–245.