

SOD1 Mutations: More to Learn

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In this issue of the Canadian Journal of Neurological Sciences, Baek et al¹ report a novel *SOD1* mutation in a case of amyotrophic lateral sclerosis characterized by a slow disease progression. Interestingly the missense mutation was identified in three other asymptomatic members of the family across three generations. The affected amino acid is highly conserved across species and the substitution was predicted to be probably pathogenic by three different bioinformatics programs.

Amyotrophic lateral sclerosis (ALS), commonly named Lou Gehrig's disease or Charcot's disease, is caused by the death of both the upper and lower motor neurons. The first symptoms in ALS patients usually occur during mid-adulthood and typically progress rapidly, usually over a three to five year period, leading to death from failure of respiratory muscles. Familial cases of ALS represent 10% of all cases.² The majority of patients are considered to be sporadic cases, with no other affected family members.

The cause of neuronal death in ALS is currently unknown, and no treatment to prevent, slow down or stop neurodegeneration exists to date, with the exception of Riluzole, which at best prolongs life by a few months. Over the last decades significant efforts have been deployed to better understand the pathological mechanisms leading to ALS and to eventually develop novel therapeutics. In 1989, genetic analysis using 150 families with ALS identified two regions of possible linkage on chromosomes 11 and 21.³ Further evidence of linkage on chromosome 21q22.1-q22.2 was published in 1991, this way identifying the first ALS locus, currently known as ALS1.⁴ In 1993, an international consortium reported 11 different *SOD1* missense mutations in 13 out of 18 dominantly inherited ALS families.⁵ Since then, about 166 disease-causing mutations, 87% of which are nucleotide substitutions of the encoded protein, have been identified among the 153 amino acids of this five-exon gene. The remaining 13% of mutations are deletions, nonsense or splicing mutations, which affect the length of the protein.⁶⁻⁹ Even if most *SOD1* mutations are transmitted in an autosomal dominant manner, a few families have reduced penetrance or recessive transmission.¹⁰ Moreover, compound heterozygotes have also been reported, with two different heterozygote *SOD1* mutations in the same patient.¹¹ An intriguing report recently described a patient affected with both familial ALS and cerebellar ataxia and an *SOD1* mutation.¹² Rare *SOD1* mutated cases with frontotemporal dementia, cognitive impairment, or autonomic dysfunction have also been reported.¹³⁻¹⁵ Interestingly, some substitutions affecting particular *SOD1* amino acids are associated with slow disease progression, while other amino acid substitutions, sometimes located in the same region of the gene, are found in patients with a very fast progression.¹⁶⁻¹⁸ The effect on rate of progression is thought to be related to the fact that some mutants lead to a stable protein while others are highly unstable.^{9,19-22} Approximately 42 mutations have been reported in SALS cases, representing 25% of the total *SOD1* variation. Fifteen to 20% of familial cases

result from *SOD1* mutations, hence variations in this gene explain about 1-2% of all ALS cases.⁵

The superoxide dismutase 1 protein (SOD1) is ubiquitously expressed and is mainly located in the cytosol of cells, catalyzing the reduction of the superoxide anion to O₂ and H₂O. Most mutations reduce dismutation,²³ but some have normal or only slightly reduced dismutase activity.^{20,21} Based on the dominant inheritance and the fact that *SOD1* knock out mice have no motor neuron phenotype while overexpression of mutant *SOD1* does, it is agreed that mutant *SOD1* acquires a novel cytotoxic function which promotes neurodegeneration.^{24,25} This toxic gain-of-function has been proposed to involve different mechanisms including protein aggregation and misfolding, oxidative stress, mitochondrial dysfunction, microglia activation, glutamate excitotoxicity, and defects in axonal transport.²⁶ Specifically, the presence of protein misfolding and aggregation is a recurrent observation in cells of ALS patients, which may inactivate or impair normal processes such as proteasomal degradation or chaperone function.²⁷ Some observations also suggest that *SOD1* might be involved in RNA processing.²⁸ In addition, *SOD1* toxicity has been found to modify wild type SOD1 by inducing it to misfold.²⁹ Though extensive research has been conducted to understand the specific pathways involved, it is still unclear how mutant *SOD1* leads to the ALS phenotype.

It is intriguing that mutations in the same gene could lead to significantly different disease progression. The missense mutation reported here is located in exon three of the *SOD1* gene, where only a small number of variants have been reported. The affected member of the reported family had slow progression of disease, similar to the ALS phenotype previously associated with another mutation in the same region.³⁰ While previous exon three mutations have been mainly associated with a lower motor neuron phenotype, the reported mutation presented here was identified in a patient with mainly upper motor neuron involvement. In addition, the fact that there is currently only one affected individual in this pedigree, no family history and three unaffected mutation carriers, one possibility that must be considered is that this is a non-causative variant. Additional work needs to be done to establish with certainty that the P66S is a disease causing *SOD1* mutation. Mutation reports such as this one are essential to better understand the role of genetic variations and understand the pathological pathways involved in the hope to eventually develop effective therapeutics for ALS.

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