Amyotrophic lateral sclerosis pathogenesis: recent insights from genetics

Sandra D'Alfonso

Department of Medical Sciences, University of Eastern Piedmont A. Avogadro, Novara, Italy
Tel: 39 321 660684
Email: sandra.dalfonso@med.unipmn.it

Amyotrophic Lateral Sclerosis (ALS) is a progressive and ultimately fatal adult-onset disorder characterized by motor neuron (MN) degeneration both in the brain and spinal cord. The disease is predominantly sporadic although 5-10% of ALS cases are familial (FALS), mostly inherited as autosomal dominant. Besides the Cu,Zn superoxide dismutase gene (*SOD1)*, which is involved in a small number of sporadic cases (SALS) (1-3%) and a larger component of familial ones (20%), at least nine disease loci and pathogenic mutations in five other genes (*ALS2, SETX, VAPB, DNCT1*, and *ANG*) have been described in isolated families or atypical form of the disease. Mutations in two genes with related functions were recently reported in patients with familial and sporadic ALS: the *FUS/TLS* gene and the *TARDBP* gene. Altogether, considering the three genes more commonly mutated in ALS (*SOD1*, *TARDBP* and *FUS*), mutations have been reported in approximately 25% of FALS patients and, with lower frequencies (1-4%), also in apparently sporadic patients.

In addition, several genome-wide association studies in ALS has been published. These studies clearly show that there is no definitive and common highly penetrant allele that causes ALS. Although many additional ALS genes remain to be identified, the accumulated genetic evidence has already provided new insights into ALS pathogenesis and thus in the motor neuron degeneration, which adds to the well-established involvement of *SOD1* mutations. The pathways that have been recently implicated include those that affect RNA processing, axonal transport and mitochondrial function. The functional classes of ALS genes identified so far are likely to aid the selection of high-priority candidate genes for future investigation, including those for the sporadic cases.