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SHORT ARTICLE

Genetics of amyotrophic lateral sclerosis: more than twenty years of studies

Letizia Mazzini[1]*, Fabiola De Marchi[1], Lucia Corrado[2] and Sandra D'Alfonso[2]

Abstract

Amyotrophic lateral sclerosis, also known as motor neuron disease or Lou Gehrig's disease, is an adult-onset neurodegenerative disease that targets motor neurons in the spinal cord, cortex and brain stem. Selective degeneration of corticospinal (upper) and spinal (lower) motor neurons manifests as a linear decline in muscular function, eventually resulting in paralysis, speech and swallowing deficits and death, usually from impaired respiratory function, over a time course of approximately 3–5 years.

Keywords: ALS, genetics, Lou Gehrig's disease

[1]ALS Centre Department of Neurology, Eastern Piedmont University, University Hospital "Maggiore della Carità", Novara, Italy

[2]Interdisciplinary Research Center of Autoimmune Disease (IRCAD), Eastern Piedmont University, Novara, Italy

*Corresponding author: L. Mazzini
E-mail: letizia.mazzini@uniupo.it

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In Europe and the United States there are one or two new cases of amyotrophic lateral sclerosis (ALS) per year per 100,000 people; the total number of cases is approximately 3 to 5 per 100,000 (1). These statistics are globally fairly uniform, although there are rare foci where ALS is more common. The incidence and prevalence of ALS increase with age. About 10 to 20% of all cases of ALS are familial cases (fALS), while the majority (~90%) are sporadic (sALS), without any family history of the disease.

Advances in gene mapping and DNA analysis have facilitated identification of many ALS genes. SOD1 was the first ALS gene identified in 1993 (2). Since then, more than 30 genes have been described, four of which explain >50% of familial cases. Mutations in the FUS and TARDBP genes (encoding TDP-43 protein) were the next discoveries (3, 4). Both gene products belong to the RNA/DNA binding protein family, and are involved in the pathological protein aggregation pathway of ALS (5).

Other mutations discovered include the optineurin (OPTN) mutation, described as a cause of autosomal recessive ALS in Japanese families in 2010 (6). It was subsequently observed that heterozygous mutations in this gene rarely caused familial ALS in persons of European ancestry (7). Again in 2010, Johnson reported mutations in valosin-containing protein (VCP) responsible for 1–2% of familial cases of ALS (8).

Neuropathological analysis led to identification of insoluble cytoplasmic phosphorylated protein deposits in the brain and spinal cord, as in other forms of brain neurodegeneration, such as fronto-temporal dementia (FTD). In 2011, hexanucleotide expansion mutations (GGGGCC) were discovered in a gene called C9ORF72 located in a region of chromosome 9, previously identified in linkage studies in families with FTD, ALS or both (9). This was the first time that a large intronic repeat expansion was implicated in ALS. The form of ALS linked to this gene may account for up to one third of cases with European ancestry (9, 10).

Together, the major genes described above (SOD1, FUS, TARDBP and C9ORF72) account for 60–80% of familial cases of ALS (11). In particular, C9ORF72 expansions are about 50% of the mutations found in familial forms manifesting after 40 years of age; (12) mutations in FUS account for 35% of cases manifesting before 40 years and are respon-

sible for the youngest case described (13). All gene mutations described in ALS can be found in the following online databases: http://alsod.iop.kcl.ac.uk and http://www.alsgene.org (14).

More recently, thanks to next generation sequencing of large series of ALS samples, several new ALS genes were identified, including TUBA4A and TBK1, each of which accounts for a few ALS cases (15, 16).

The contribution of common genetic polymorphisms as genetic risk factors for ALS has also been investigated in large genome-wide association studies (17, 18). The genetic risk factors identified confer disease susceptibility but are presumably insufficient to trigger onset of ALS; rather, exposure to certain environmental agents is thought to render genetic variant carriers susceptible to ALS.

Intermediate repeats in the ATXN2 gene are an example of gene risk factor. This repeat mutation shows higher occurrence of intermediate CAG (coding for glutamine) repeats (polyglutamine, polyQ) in the 5' terminal of the ATXN2 gene in ALS patients (19). Several authors found that an intermediate CAG expansion with a range of 30–33 repeats was associated with an increased risk of ALS. Currently this is the only genetic risk factor for ALS (20).

There is also immense interest in genetic variants that modify the clinical phenotype of the disease (for example genetic variation in the KIFAP3, EPHA4 and CAMTA1 loci), although these variants themselves do not cause ALS.

As described above, the genetic spectrum of ALS, both familial and sporadic, is heterogeneous. Several genes in ALS are known to cause many other neurodegenerative diseases, for example the relation between C9Orf72 and FTD, and the presence of two different phenotypes in the same family raise the question whether genetic and environmental factors interact to trigger disease onset. Classical genetic analysis, such as linkage analysis, candidate gene studies and genome-wide association studies have revealed the causative genes in about one third of fALS and only a small number of sALS cases. With advanced methods, such as whole genome sequencing, we can expect that the number of genes involved in the pathogenesis of ALS, whether as novel genes or gene modifiers, will continue to increase.

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