REVIEW ARTICLE

Genetic approach in amyotrophic lateral sclerosis

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Abstract

The superoxide dismutase type 1 (SOD1) gene is the first responsible gene mapped in amyotrophic lateral sclerosis type 1 (ALS1), and it codes for the enzyme SOD1, the function of which is to protect against damage mediated by free radicals deriving from oxygen. Its pathophysiological mechanism in ALS1 is related to ischemia. Several molecular studies of the SOD1 gene show that point mutations are the most frequent. The most common mutations in familial cases are p.A4V, p.I113Y, p.G37R, p.D90A and p.E100G, which account for more than 80% of cases, although intronic mutations have also been described as responsible for ALS1. Sporadic cases are explained by mutations in other genes such as SETX and C9orf72. ALS1 is a complex disease with genetic heterogeneity. On the other hand, familial and sporadic cases have a different etiology, which is explained by molecular heterogeneity and multiple pathogenic mechanisms that lead to ALS1; oxidative stress and ischemia are not the only cause. In Mexico, ALS molecular genetics studies are scarce. Clinical studies show an increase in cytokines such as adipsin in cerebrospinal fluid.

KEY WORDS: *Familial motor neuron disease. Muscle atrophy. Superoxide dismutase 1.*

Introduction

Amyotrophic lateral sclerosis (ALS) is a lethal, progressive neurodegenerative disease that affects upper and lower motor neurons.[1-2] Its prevalence in Mexico ranges from 5000 to 7000 patients according to Martínez et al. In France, it is estimated at 2.5 per 100,000 population.[3] The age of onset is approximately 47.5 years, with survival of up to 58.9 months after diagnosis. Otero et al. reported that ALS accounts for more than 90 % of cases of motor neuron diseases in Mexico, with the phenotype including signs of upper or lower motor neuron.[1]

Genetic and molecular epidemiology

ALS occurs sporadically (SALS) in 90 to 95 % of cases and family-wise (FALS) in 5 to 10 %. Sporadic forms are more often observed outside the European continent.[1-3] FALS forms are associated with a large number of pleiotropic genes (Table 1), which results in clinical and pathological phenotypes overlap. Different inheritance patterns have also been described.[3] The genes most frequently associated with FALS are *SOD1 Tau*.[4,5] Mutations in the *SOD1* gene explain 2 % of cases affected by SALS, out of which approximately 10 % are inherited as a dominant autosomal pattern with high penetrance after the sixth decade. Clinical phenotype is similar in FALS and SALS cases.[6-9] It should be noted that Scandinavians' p.D90A mutation is transmitted with a recessive pattern[10] (Table 1).

SOD1 classical mutations in ALS are p.G37T, p.L38V, p.G41S, p.G41D, p.H43R, p.G85R, p.G93C, p.G93A, p.E100G, p.L106V and p. I113Y, which produce changes in *SOD1*, thus decreasing enzymatic activity.[7] In an Italian population, the p.G12R, p.G41S,

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Table 1. Types of ALS according to the involved gene and its inheritance pattern

Type	Symbol	Gene	Locus	FALS	SALS	Inheritance
ALS 1	*SOD1*	Cu/Zn superoxide dismutase 1	21q22.11	Yes	Yes	AD and AR
ALS 2	*ALS2*	Alsin 2	2q33.2	Yes	No	AR
ALS 3	*ALS3*	Alsin 3	18q21	Yes	No	AD
ALS 4	*SETX*	Senataxin	9q34.13	Yes	Yes	AD
ALS 5	*SPAST*	Spastin	2p24	Yes	Yes	AR
ALS 6	*FUS*	t-derived gene (12;16)	16p11.2	Yes	Yes	AD
ALS 7	*ALS7*	Alsin 7	20p13	Yes	No	AD
ALS 8	*VAPB*	B-protein associated with vesicle membrane-associated protein	20q13.33	Yes	No	AD
ALS 9	*ANG*	Angiogenin	14q11.1	Yes	Yes	AD
ALS 10	*TARDBP*	TAR DNA-binding protein	1p36.22	Yes	Yes	AD
ALS 11	*FIG4*	Homologous to FIG4, SCA1 lipid phosphatase-containing domain	6q21	Yes	Yes	AD
ALS 12	*OPTN*	Optineurin	10p13	Yes	Yes	AD and AR
ALS 13	*ATXN2*	Ataxin 2	12q23-24.1	No	Yes	---
ALS 14	*VCP*	Valiosin-containing protein	9p13	Yes	No	AD
ALS 15	*UBQLN2*	Ubiquitin 2	Xp11.21	Yes	No	Dominant X-linked
ALS 16	*SIGMAR1*	Non-opioid sigma 1 intracellular receptor	9p13	Yes	No	AR
ALS 17	*CHMP28*	---	3p11.2	No	Yes	---
ALS 18	*PFN1*	Profilin 1	17p13.3	No	Yes	---
ALS 19	*ERBB4*	Viral avian erythroblastic leukemia oncogene homolog	2q34	Yes	No	AD
ALS 20	*HNRNPA1*	Heterogeneous nuclear ribonucleoprotein A1	12q13.13	Yes	Yes	AD and AR
ALS 21	*MATR3*	Matrin 3	5q31.2	Yes	No	AD
ALS-DFT2	*CHCHD10*	Coiled-Coil-Helix-Coiled-Coil-Helix Domain-Containing Protein 10	9q21-q22	Yes	No	AD
ALS-DFT1	*C9orf7 2*	Chromosome 9 open reading framework 72	9p21.2	Yes	Yes	AD
Risk	*UNC13A*	*Caenorhabditis eleganss A* homolog	19p13.11	No	Yes	
---	*DAO*	D-amino acid oxidase	12q24	Yes	No	AD
---	*DCTN1*	Dinactin	2p13	Yes	Yes	AD
---	*NEFH*	Neurofilament constitutive 200-kDA heavy chain	22q12.1	Yes	Yes	AD
---	*PRPH*	Peripherin	12q12	No	Yes	---
---	*SQSTM1*	Sequestrosome 1	5q35	Yes	Yes	AD
---	*TAF15*	TATA box binding protein-associated factor	17q11.1-q11.2	Yes	No	AD
---	*SPAST*	Spastin	2p24	No	Yes	---
---	*ELP3*	Homolog elongation protein 3 (*Saccharomyces cerevisiae*)	8p21.1	No	Yes	---
---	*LMNB1*	Laminin B1	5q23.2	Yes	No	AD

ALS = amyotrophic lateral sclerosis, SALS = sporadic amyotrophic lateral sclerosis, FALS = familial amyotrophic lateral sclerosis, AD = autosomal dominant, AR = autosomal recessive. --- Is used in the type column when, despite the fact that the gene was associated, it has not had a sufficient number of reports to assign a specific name to the disease associated with it; in the inheritance column it is used to note that a specific inheritance form has not been determined. Table created based on OMIM data and http://alsod.iop.kcl.ac.uk/

p.L114F and p.D90A mutations were found in seven out of 39 patients with atypical-phenotype FALS. In addition, a synonymous p.S59S variant was identified in a patient with ALS.[7]

In another case series, nt34A> C intron 3 polymorphism was found in 17 out of 264 patients (6.4 %), and the IVS3 + 62 T> C variant was identified in one FALS patient. Total frequency of *SOD1* gene mutations (17.9 %) in FALS cases was comparable to that found in other studies, with a similar sample size of ALS cases. Among the FALS cases, the most common mutation was p.G41S.[11]

In another cross-sectional Italian population cohort, eight out of 38 patients (21 %) with FALS and five out of 175 (3 %) with SALS had nonsense mutations in the *SOD1* gene. Two additional mutations were identified, one in exon 4 (p.L84F) in a familial case and the second in exon 3 (p.G72S) in a sporadic patient.[12]

The role of the *SOD1* enzyme

The *SOD1* gene has its locus at 21q22.11, it has a length of 9310 base pairs (bp) and is composed of five exons; it encodes the superoxide dismutase (SOD1) enzyme. This protein has 153 amino acid residues with a weight of 16 kDa[13] and oxidoreductase and peroxidase activities. Its quaternary structure is formed by barrel-shaped beta strands arranged in a Greek key motif.[14] Each homodimer constitutes a unit called A, B, C, D or E and has the capacity to associate with four other units, reaching a configuration similar to a “dog femoral bone”; in turn, these structures tend to group forming asymmetric units, which generate a structure that resembles a honeycomb.[14]

The SOD1 enzyme is cytoplasmic, and catalyzes the conversion of superoxide with nitric oxide (NO) to the peroxidized anion (ONOO-) form, which generates HO and NO_2 toxic radicals.[14-16] This mechanism might induce neurodegeneration due to free radical accumulation, causing cell death.[7]

Through immunohistochemistry, SOD1 has been shown to be abundantly distributed in motor neurons, interneurons and sensory neurons in the spinal cord,[17] with a punctate pattern in the motor and sensory portions of the cranial nerve nuclei, the soma, as well as in proximal dendrites and terminal axons in unaffected individuals;[18] it has been diffusely found in the cortex, hippocampus and amygdala.[19] On the other hand, a more abundant expression of *SOD1* has been demonstrated in patients affected by ALS. These evidences strongly support the gain-of-function hypothesis with toxic effect rather than haploinsufficiency.[18,20]

Mutations in the *SOD1* gene

Most mutations reported in *SOD1* are nucleotide changes with sense or intron reading frame shifts.[1-3] The effect of enzyme activity percentage is a poorly studied field, which limits genotype-phenotype correlation determination. Among the largest studies that have reported the frequency of mutations in the *SOD1* gene is the cohort of 2045 non-Hispanic white patients with FALS and SALS, among which *SOD1* mutations were found in 148 cases. The most prevalent mutations associated with the disease in the *SOD1* gene were p.A4V, in 41 % of patients, p.Ile113Tre in 16 % and intron mutations in 11 %. Sixteen exon mutations were found (p.K8V, p.F20C, p.Q22L, p.H48R, p.T54R, p.S59I, p.V87A, T88DTAD, p.A89T, p.V97M, p.S105DSL, p. V118L, p.D124G, p.G141X, p.G147R and p.I151S, which correspond to a frequency of 10.81 %. In 2.7 % of cases with SALS, four patients were detected with the following mutations: p.G37R, p. D90A and p.E100G.[21]

In another cohort of non-Hispanic white subjects with FALS, the p.A4V mutation in exon 1 was the most common (32 %). On the other hand, the p.G37R p.G93A, p.E100G and p.I113Y mutations had a frequency of 8 %. The study of molecular coupling (docking) of these variants reveals the alteration of the interactions for the contact of the doublets and the beta barrel dimer. The red blood cells of the heterozygous index cases had less than 50 % activity, which consistent with a structurally defective SOD dimer.[22]

In clinical practice, genotype-phenotype correlation studies are important (Table 2); for example, in a FALS cohort in an Asian Japanese population, four different sense mutations were reported in exons 2, 4 and 5 of the *SOD1* gene in five families: p.H46R, p.L84V, p.I104F and p.V148I. Patients with the p.H46R mutation showed a benign clinical course and stereotyped progression of muscle weakness and leg atrophy. p.L84V carriers have a very similar clinical course of disease, with the age of onset being earlier in males than in females. Patients with p.I104F showed wide ranges of age of onset and duration, with ophthalmoparesis and sensory involvement in one patient. Those with the p.V148I mutation showed an earlier age at onset and first variable symptoms within the family. Although the LMN sign was evident in all cases, hyperreflexia varied between patients with different

Table 2. **Genotype-phenotype correlation for mutations in *SOD1***

Type	Type of mutation	Frequency (%)	Affected (n)	Clinical phenotype	Enzyme activity %	Population	Reference
SALS	p.E21K	1.5	1/67	Definitive diagnosis	Not reported	European, Scottish	6
SALS	p.I113Y	87	20/23	Definitive diagnosis	Not reported	Non-Hispanic White	8
SALS	IVS3+34 A > C	5.3	14/264	Definitive diagnosis	Not reported	European, Italian	11
SALS	p.S59S	0.4	1/264	Definitive diagnosis	Not reported	European, Italian	11
SALS	p.G72S	2.6	1/38	Definitive diagnosis	Not reported	European, English	12
SALS	p.G37R	1.4	2/148	Definitive diagnosis	Not reported	Non-Hispanic White	22
SALS	p.D90A	0.7	1/148	Definitive diagnosis	Not reported	Non-Hispanic White	22
SALS	p.A4V	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
SALS	p.G72C	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
SALS	p.D76Y	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
SALS	p.D90A	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
FALS	p.D90A	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
FALS	p.D90A	7.7	1/39	Atypical phenotype	Not reported	European, Italian	11
SALS	p.C111Y	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
SALS	p.I113Y	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
FALS	p.I113Y	13	9/67	Definitive diagnosis	Not reported	European, Scottish	6
FALS	p.I113Y	8	2/25	Severe progressive neurogenic muscular atrophy	Lower than 50%	Non-Hispanic White	22
FALS	p.I113Y	16	24/148	Definitive diagnosis	Not reported	Non-Hispanic White	21
FALS	p.G93R	1.5	1/67	Definitive diagnosis	Not reported	European, Scottish	6
FALS	p.E100G	1.5	1/67	Definitive diagnosis	Not reported	European, Scottish	6
FALS	p.G12R	7.7	1/39	Slowly progressive disease course	Not reported	European, Italian	11
FALS	p.L114F	7.7	1/39	Slowly progressive course	Not reported	European, Italian	11
FALS	IVS3+62 T	0.4	1/14	Definitive diagnosis	Not reported	European, Italian	11
FALS	p.G72C	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24

(Continúes)

Table 2. **Genotype-phenotype correlation for mutations in *SOD1* (*Continued*)**

Type	Type of mutation	Frequency (%)	Affected (n)	Clinical phenotype	Enzyme activity %	Population	Reference
FALS	p.D76Y	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
FALS	p.C111Y	7.7	1/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
FALS	p.G37R	8	2/25	Severe progressive neurogenic muscular atrophy	Lower than 50%	Non-Hispanic White	22
FALS	p.G93A	8	2/25	Severe progressive neurogenic muscular atrophy	Lower than 50%	Non-Hispanic White	22
FALS	p.E100G	8	2/25	Severe progressive neurogenic muscular atrophy	Lower than 50%	Non-Hispanic White	22
FALS	p.L84V	10	3/30	Early age of onset	Lower than 50%	Asian Japanese	23
FALS	p.H46R	6.7	2/30	Benign clinical course	Lower than 50%	Asian Japanese	23
FALS	p.I104F	6.7	2/30	Ophthalmoparesis and sensorial involvement	Severe reduction, lower than 10%	Asian Japanese	23
FALS	p.A4V	15.28	2/13	Definitive diagnosis	Not reported	Caucasian, Canadian	24
FALS	p.I113Y	13	3/23	Definitive diagnosis	Not reported	Non-Hispanic White	8
FALS	IVS3+34 A > C	1.14	3/264	Definitive diagnosis	Not reported	European, Italian	11
FALS	p.G41S	30.8	4/39	Rapidly progressive course with severe cognitive impairment	Not reported	European, Italian	11
FALS	p.V148I	13.3	4/30	Early onset	Lower than 10%	Asian Japanese	23
FALS	p.A4V	32	8/25	Severe progressive neurogenic muscular atrophy	Lower than 50%	Non-Hispanic White	22
FALS	p.G41S	100	9/9	Severe phenotype, rapidly progressive	Not reported	European, Italian	26
FALS	p.D90A	38.5	12/60	Definitive diagnosis	Not reported	Asian, Iranian	25
FALS	p.L84F	2.6	1/38	Definitive diagnosis	Not reported	European, English	12
FALS	p.A4V	41	61/148	Definitive diagnosis	Lower than 10%	Non-Hispanic White	21

SALS = sporadic amyotrophic lateral sclerosis, FALS = familial amyotrophic lateral sclerosis.

mutations.[23] Bulbar paralysis was common in p.I104F carriers, but not in those with p.H46R. Red blood cell SOD1 activity was severely reduced with p.I104F and p.V148I, but slightly reduced with p.H46R.[24]

Another study with this approach in 254 patients with FALS and SALS in the province of British Columbia, Canada, showed, in 13 patients (5.1 %), the p.A4V, p.G72C, p.D76Y, p.D90A, p.C111Y and p.I113T mutations in *SOD1*, both in FALS and SALS. There were clinical discordances even between patients with the same mutation. This supports the hypothesis that ALS is a heterogeneous disorder where genetics, the environment and aging interrelate to form the final clinical phenotype.[24]

In an Asian Iranian cohort of 60 patients with ALS (four families), *SOD1* mutations were found in 11.7 %, 38.5 % of FALS subjects and in 4.25 % of SALS cases; the screening identified p.D90A homozygous in all related families. Haplotype analysis suggests that Iranian patients might share a common founder with the famous recessive Scandinavian p.D90A allele. Other mutations identified were p.L84F, p.A4Y and p.I113Y.[25] In an Italian

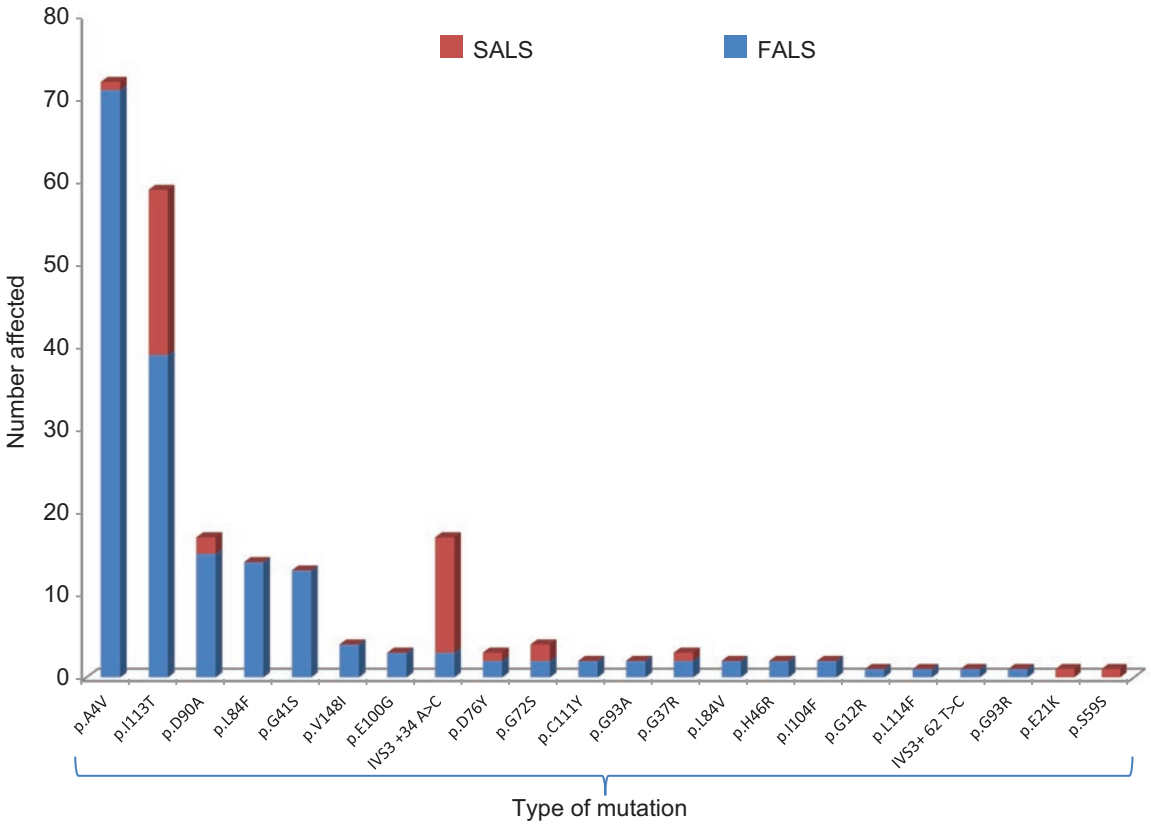

Figure 1. *Proportion of mutations found in the SOD1 gene in patients with amyotrophic lateral sclerosis type 1. SALS = sporadic amyotrophic lateral sclerosis, FALS = familial amyotrophic lateral sclerosis.*

population, one case of FALS was found to bear the heterozygous mutation p.L106, whose clinical presentation was characterized by relatively early age of onset, and bulbar and spinal involvement.[25] SOD1 pathogenic mechanism in neuronal death varies; lines of evidence suggest poor protein folding. p.G10R mutation docking showed strong destabilization, which influences the strength of the dimer interface, generating toxic intracellular aggregates, which supports this theory.[25]

In a case report of two Italian patients with ALS, apparently sporadic, heterozygous for the p.D90A mutation in *SOD1*, one patient experienced early sensory involvement.[26] In six families with ALS, the p.G41S mutation was detected by direct sequencing. Clinical pattern of these patients was characterized for the spinal appearance of upper and lower motor neurons with early involvement, the appearance of bulbar signs in one year and death a few months later; average age at onset was 49.3 years and average duration of the disease was 0.9 years; a common haplotype was found for carriers of the mutation, which demonstrates a founding effect in Italy. Indeed, the p.G41S mutation is constantly related to a severe, rapidly progressive phenotype.[26]

The following data were obtained from the aforementioned studies: total number of individuals affected by ALS was 2553, out of which 46 were FALS; in these cases, the most common mutations were p.I113T in 45.67 % and IVS3+34 A>C in 30.44 % (Fig. 1). In the FALS cases, the p.A4V, p.I113Y, p. D90A, p.L84F and p.G41S mutations were detected in 39.01, 21.43, 8.24, 7.69 and 7.14 %, respectively. Only two of the reviewed studies analyze the enzyme function with the mutations found in the affected population.[22-23]

ALS is a complex disease

Genetic studies show that ALS is a complex disease due to molecular heterogeneity, there are more than 23 responsible genes that have a direct effect on the phenotype, as described in Table 1. More than 140 different mutations distributed in the five exons and introns of the *SOD1* gene have been reported, with p.A4V being the most common mutation in familial cases, while in sporadic cases it is the p.I113T mutation.[10] This supports ALS high polygenic component, as well as its molecular and allelic heterogeneity.

Disease presentation varies, with sporadic forms and familial variants that are transmitted with an autosomal dominant inheritance pattern;[6-10] however, there are mutations that are transmitted with a recessive pattern.[12,26,27] Even 85-year-old, completely asymptomatic individuals have been reported to be carriers of the p. D90A mutation, with this adding to the hypothesis on the existence of a complementary mechanism responsible for neurological damage in ALS.[26]

It should be noted that the phenotype can differ depending on the region of the gene the mutations affect. There is not a clear genotype-phenotype correlation, due to differences in the presentation between familial and sporadic cases, as well as in intra-familial cases with the same mutation,[22-26] which is attributed to variable expressivity or to modifier genes.[10]

ALS has been postulated to be a conformational disease, since mutations in *SOD1* lead to changes in the structure of the enzyme and affect its catalytic activity (activity lower than 50 %), as well as to haploinsufficiency.[22-23] On the other hand, accumulation of this protein with folding defects is related to mutations, which translates into gain-of-function with a toxic effect, known as negative dominant effect.[26-27]

Studies of targeted mutagenesis analyzing haploinsufficiency and the negative dominant effect are limited; in future works, it will be important to investigate them in order to identify the clinical effect of the amino acid change in the structure of the active site, the allosteric region and other *SOD1* functional domains.

Advances in ALS genetics

Through new generation sequencing, 20 % of familial cases were found in the French population, with a frequency of 50 % for *SOD1* mutations,[28] while in the English population the following mutations were found: p.C256G, p.G229T, p.A272C, p.A305G, p.C310T, p. G335A p.T341C and p.A403G.[29] Recently, a new c.791A> G mutation was found in the *SETX* gene in a woman with ALs of Hungarian ancestry.[30] In a population with that same ancestry, new mutations in the *SOD1* gene have been reported in sporadic cases, including p.K91R/X, p.V14M, p.D90A, p.L144F and p.L91R/X8.[31] Abnormal expansion of (GGGGCC)n of the C9ORF72 gene has also been found in up to 30 % of SALS cases.[31-32] The *SOD1* and *C9orf72* genes have the most important contribution in the pathogenesis of the disease. Currently, the new targets in ALS therapy are focused on protein homeostasis disruption, alterations in the biology of proteins that bind to RNA, as well as cytoskeleton dynamics defects.[33]

Frontiers in ALS research

The new challenges in the study of ALS are the effect of epigenetic modifications, which might shed light on the age of onset, familial presentation or severity, to facilitate the identification of efficacious therapies, early diagnosis and potential therapeutic interventions at early stages.[34] In Latin America, there is no research with information on ALS genetics. At the immune system level, the role of 19 cytokines has been explored, including adipsin, adiponectin, IL-4 and IL-6 in relation to clinical severity and disease duration. Adipsin was found to be elevated in cerebrospinal fluid; adiponectin showed a tendency towards higher concentrations.[35-36] Certainly, more epidemiological studies on these interleukins are necessary in order to establish their prognostic value. This evidence may suggest that variants in the genes that code for these proteins can modify ALS clinical expression. Relevant clinical studies include a report of four cases of juvenile familial ALS and prolonged survival.[37-39] Recently, our working group reported a case of ALS in Mexico, which was positive for a mutation in the MT-CYTB gene.[40]

Conclusions

ALS is a complex genetic disease, which is reflected on its different inheritance patterns, mutational component, high penetrance, variable age of onset, and simultaneously-altered multiple metabolic pathways in patients with this disease. On the other hand, most mutations found in *SOD1* are mainly responsible for FALS and one third of SALS cases. There are other genes that should be explored as a cause, especially in FALS: *C9orf72* and *SETX*. At the clinical level in Mexico, proinflammatory cytokines could be prognostic markers, although it will be necessary to validate them.

Conflict of interest

There were no conflicts of interest by the authors.

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