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VIEW AND REVIEW

Clinical and genetic basis of familial amyotrophic lateral sclerosis

Bases clínicas e genéticas da esclerose lateral amiotrófica familiar

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ABSTRACT

Amyotrophic lateral sclerosis represents the most common neurodegenerative disease leading to upper and lower motor neuron compromise. Although the vast majority of cases are sporadic, substantial gain has been observed in the knowledge of the genetic forms of the disease, especially of familial forms. There is a direct correlation between the profile of the mutated genes in sporadic and familial forms, highlighting the main role of *C9orf72* gene in the clinical forms associated with frontotemporal dementia spectrum. The different genes related to familial and sporadic forms represent an important advance on the pathophysiology of the disease and genetic therapeutic perspectives, such as antisense therapy. The objective of this review is to signal and summarize clinical and genetic data related to familial forms of amyotrophic lateral sclerosis.

Keywords: amyotrophic lateral sclerosis, motor neuron disease, neurogenetics, neurodegeneration, C9orf72 gene.

RESUMO

A esclerose lateral amiotrófica representa a forma mais comum de doença neurodegenerativa com comprometimento do neurônio motor superior e inferior. Embora a maioria dos casos seja esporádica, ganho impressionante referente ao conhecimento das formas genética da doença foi observado, em especial das formas familiares. Há uma correlação direta entre o perfil de genes mutados nas formas familiares e esporádicas, destacando-se o papel principal do gene *C9orf72* nas formas clínicas associadas com espectro da demência frontotemporal. Os diferentes genes relacionados às formas familiares e esporádicas representam um importante avanço na fisiopatologia da doença e perespectivas terapêuticas genéticas, como a terapia antisense. O objetivo desta revisão é apontar e resumir os principais dados clínicos e genéticos relacionados às formas familiares da esclerose lateral amiotrófica.

Palavras-chave: esclerose lateral amiotrófica, doença do neurônio motor, neurogenética, neurodegeneração, gene C9orf72.

Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's disease is the main progressive adult-onset neurodegenerative motor neuron disease (MND), affecting primarily upper (UMN) and lower motor neurons (LMN) giving rise to its typical neurological manifestations. Overall prevalence of ALS is around two to seven cases per 100000 inhabitants[1,2], and incidence around one to two new cases per 100000 inhabitants per year[2,3,4].

ALS arises as a consequence of multiple pathophysiological mechanisms and cellular dysfunctions (Figure 1), including protein misfolding and aggregation, altered RNA processing (mainly disturbed mRNA splicing and signaling), defects in axonal transport, abnormal metabolism and accumulation of reactive oxygen species, mitochondrial dysfunctions, microglial neuroinflammatory mechanisms, direct glutamate excitotoxicity by astrocytes, abnormal modulatory effects from other glial cells, disturbances of autophagy, ubiquitine-proteosome system abnormalities and primary and secondary ion channel defects[5,6,7,8]. Environmental and toxic factors also represent major factors, including traumatic sports mechanisms and toxic causes (including the ALS-parkinsonism/dementia of Guam)[9].

Typical electrodiagnostic and clinical signs arise from a complex network of neuropathological changes including upper motor neuron degeneration in the frontal lobe (mainly Betz giant cells in the motor cortex), corticospinal and corticobulbar tracts (in the spinal cord, internal capsule and cerebral peduncles pathways), lower motor neurons in brainstem nuclei (motor nuclei of cranial nerves VII, X, XI and XII) and in anterior horn motoneurons of the spinal cord. Onufrowicz-Mannen's nucleus and some cranial nerve motoneurons (motor nuclei of cranial nerves III, IV and VI) are generally spared, correlating with exceptionally

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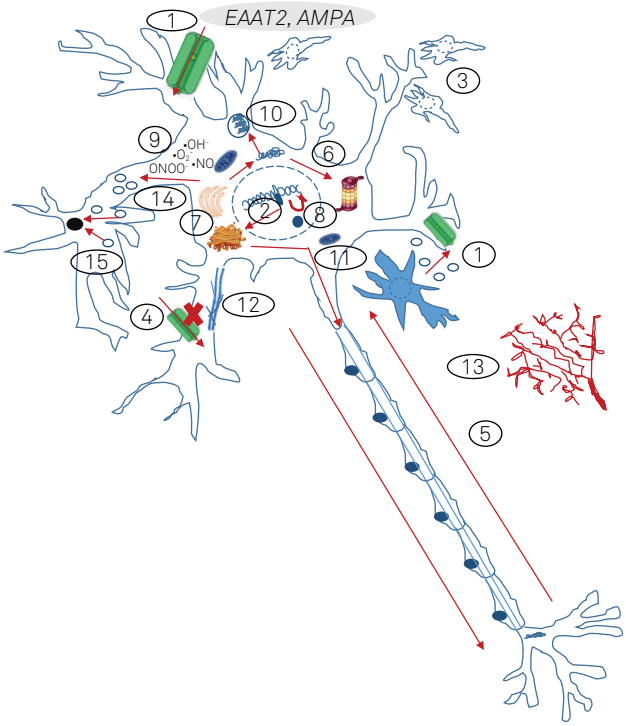

1. Direct glutamate astrocyte excitotoxicity (i.e. *DAO, ALS2, HFE*)
2. Altered RNA processing and metabolism (i.e. *C9orf72, TARDBP, FUS, EWSR1, TAF15, ATXN2, HNRNPA1, SETX, ANG, SMN1, ELP3, MATR3*)
3. Microglial neuroinflammatory activation (i.e. *SOD1*)
4. Secondary ion channel defects and transmembrane receptors (i.e. *C9orf72, SIGMAR1, ERBB4, TRPM7, HFE*)
5. Anterograde/retrograde axonal transport (i.e. *SOD1, DCTN1, PRPH, SPG11, PRPH, CHMP2B, PFN1, KIFAP3*)
6. Ubiquitin-proteosome system dysfunction (i.e. *VCP, UBQLN2, SQSTM1, OPTN, FIG4*)
7. Golgi-endosomal reticulum trafficking (i.e. *OPTN, FIG4, SIGMAR1, VAPB, VCP*)
8. Direct DNA lesion repair (i.e. *SPG11, SETX, FUS, APEX1*)
9. Abnormal accumulation of reactive oxygen species (i.e. *SOD1, ALS2, APEX1, HFE, PON*)
10. Toxic protein aggregates and misfolding (i.e. *SOD1, VCP, UBQLN2, DAO, OPTN, SQSTM1*)
11. Mitochondrial dysfunctions (i.e. *CHCHD10, CYP27A1, COX1, IARS2*)
12. Cytoskeleton dynamics and architecture (i.e. *TUBA4A, PFN1, DCTN1, NEFH, PRPH*)
13. Angiogenesis (i.e. *ANG, VEGF*)
14. Endosomal and vesicular trafficking (i.e. *ALS2, VAPB, C9orf72, CHMP2B, OPTN, DCTN1, ATXN2, FIG4, VCP, UNC13A*)
15. Disturbances of autophagy (i.e. *FIG4, VCP, UBQLN2, SQSTM1*)

Figure 1. Schematic representation of the main pathophysiological mechanisms involved in familial amyotrophic lateral sclerosis and the genetic changes involved in each case[5,6,7,8].

rare compromises of facial and extrinsec ocular movements and sphincteral disturbances[1,2]. In microscopic evaluation, cytoplasmic Bunina bodies and Lewy body-like are motor neuron neuropathological hallmarks of ALS, although each genetic subtype commonly presents with their signatures. Neuropathological remarks include neurofilamentous swelling of proximal axons with reduced calibre of distal axons and axonal wallerian degeneration, accumulation of neurofilament and peripherin in axons and perikarium, reactive glyosis, Lewy body-like cytoplasmic neuronal inclusions, perikarial inclusions with phosphorylated neurofilament and ubiquitin immunoreactivity and positive immunoreactivity for other biochemical markers depending on genetic basis of the disease, mainly ubiquinated protein inclusions with positivity for TAR (Transactive response) DNA-binding protein 43 (TDP-43)[2]. Furthermore, different authors believe there is a regional spreading of intracellular misfolded pathogenic proteins SOD1 and TDP-43 involved in ALS in a prion-like propagation in an intercellular contiguous spreading fashion[2,6,10].

Most cases of ALS present with asymmetric focal apendicular weakness progressing with bulbar dysfunction, quadriparesis and respiratory insufficiency leading to death in about two to three years after onset[1]. The combination of upper motor neuron and lower motor neuron signs of compromise is classically described with variable degrees of each component during disease progression[1]. Association with cognitive and behavioural disturbances is common and sometimes present with the classical phenotype of behavioral variant (bv) frontotemporal dementia (FTD). Although lability of affect commonly occurs, bvFTD, executive dysfunction and mood disorders occurs more frequently in some specific clinical and genetic conditions. A FTD clinical suspection can be properly analyzed applying specific criteria, including the Hodge's and Neary criteria[11]. Other cognitive compromise patterns also occurs including primary progressive nonfluent aphasia, logopenic progressive aphasia and semantic dementia. Around 5% of sporadic and familial ALS cases fullfill properly diagnostic criteria for FTD[11].

There are no specific clinical, neuroimaging and serum and cerebrospinal fluid biochemical markers to provide the definite diagnosis of ALS and clinicians must be aware about differential diagnosis and red-flags[1]. Clinical and electrodiagnostic findings are essential to guide the diagnosis process using both the revised El Escorial criteria and the Awaji-shima electrodiagnostic criteria. Although causative genes and susceptibility loci are well-established in sporadic and familial ALS (Table 1), presymptomatic testing does not represent a reliable and available diagnostic method in most neurological centers[2,6].

Most cases of ALS are sporadic (90 to 95% of ALS cases) and generally occurs in patients between the fifth and seventh decades of life. Familial ALS cases are defined when there is a context of more than one affected family member (relative) from first or second generation from the index or propositum case with the same disease presentation (despite the frequent occurence of intrafamilial clinical variability) and generally associates with: (i) earlier age at disease onset; (ii) more commonly symptom onset starts in the lower extremities; and (iii) longer or shorter disease duration, life expectancy and clinical progression, depending on particular genetic subtypes[2,12,13]. Familial cases can occur in an autosomal recessive or dominant or dominant X-linked inheritance patterns. Most adult-onset cases of familial ALS have autosomal dominant inheritance pattern, while juvenile-onset cases have autosomal recessive pattern, in a similar way to the observed with autosomal recessive cerebellar ataxias and autosomal dominant spinocerebellar ataxias. Overall penetrance is age and gene-dependent

Table 1. Genetic causes of amyotrophic lateral sclerosis, year of description, pattern of inheritance and allelic conditions[2,8,12,59].

Gene involved (locus) – year of description	Inheritance	Allelic disorders
SOD1 (Superoxide dismutase 1; 21q22.11) – 1993	AD/AR	ALS1
C9orf72 (Chromosome 9 Open Reading Frame 72; 9p21.2) – 2011	AD	FTD-ALS type 1, FTD, ALS, HD-like, atypical parkinsonism (PSP-like, CBD-like, MSA-like), CJD-like, AZD-like
FUS (Fused in Sarcoma; 16p11.2) – 2009	AD/AR	ALS6, Hereditary essential tremor type 4
CHMP2B (Chromatin-modifying protein member 2B; 3p11.2) – 2006	AD	ALS17, Chromosome 3-linked FTD
ALS2 (Alsin; 2q33.1) – 2001	AR	ALS2, Juvenile Primary Lateral Sclerosis, Infantile-onset Ascending Spastic Paralysis
UBQLN2 (Ubiquilin 2; Xp11.21) – 2011	XD	ALS15
PFN1 (Profilin 1; 17p13.2) – 2012	AD	ALS18
OPTN (Optineurin; 10p13) – 2009/2010	AR/AD	ALS12, primary open angle glaucoma type 1, Paget disease of bone
TARDBP (TAR DNA-binding protein; 1p36.22) – 2008	AD	ALS10, FTD
SQSTM1 (Sequestosome 1; 5q35.3) – 2011	AD	ALS, Paget disease of bone
PRPH (Peripherin; 12q13.12) – 2004	AD?	ALS
HNRNPA1 (Heterogeneous Nuclear Ribonucleoprotein A1; 12q13.13) – 2013	AD	ALS20, IBM with early-onset Paget disease without FTD type 3
DCTN1 (Dynactin 1; 2p13.1) – 2003	AD	ALS, Perry syndrome, Distal hereditary motor neuronopathy with vocal paresis (type VIIB)
ANG (Angiogenin; 14q11.2) – 2006	AD	ALS9
FIG4 (FIG4, S. cerevisiae, homolog of SAC1 lipid phosphatase domain containing; 6q21) – 2009	AD	ALS11, Charcot-Marie-Tooth disease type 4J, Yunis-Varon syndrome, Bilateral Temporooccipital Polymicrogyria, Primary Lateral Sclerosis
NEFH (Neurofilament protein, Heavy Polypeptide; 22q12.2) – 1999	AD	ALS
VCP (Valosin-containing Protein; 9p13.3) – 2010	AD	ALS14, IBM with early-onset Paget disease and FTD type 1
SETX (Senataxin; 9q34.13) – 2004	AD	ALS4, ataxia with oculomotor apraxia type 2 (AOA2)
ERBB4 (V-Erb-B2 avian erythroblastic leucemia viral oncogene homolog 4; 2q34) – 2013	AD	ALS19, schizophrenia, melanoma
SIGMAR1 (Sigma Nonopioid Intracellular Receptor 1; 9p13.3) – 2011	AR	ALS16
VAPB (Vesicle-associated Membrane Protein-associated Protein B; 20q13.32) – 2004	AD	ALS8, late-onset Spinal Muscular Atrophy Finkel type
MATR3 (Matrin-3; 5q31.2) – 2014	AD	ALS21
CHCHD10 (Coiled-coil-helix-coiled-coil-helix-domain-containing protein 10; 22q11.23) – 2014	AD	FTD-ALS type 2
DAO (D-amino acid oxidase; 12q24) – 2010	AD	ALS, Schizophrenia
ATXN2 (ataxin 2; 12q24.12) – 2010	AD	ALS13, Spinocerebellar ataxia type 2
SMN1 (Survival of Motor Neuron 1; 5q13.2) – 2012	AD	ALS, Spinal muscular atrophy (types 1-4)
EWSR1 (Ewing sarcoma breakpoint region 1; 22q12.2) – 2012	AD	ALS, Ewing sarcoma, Neuroepithelioma
TAF15 (TAF15 RNA polymerase II, TATA box-binding protein-associated factor, 68-kD; 17q12) – 2011	AD	ALS, Extraskeletal myxoid chondrosarcoma
SPG11 (SPG11 gene/spatacsin; 15q21.1) – 2010	AR	ALS5, Hereditary Spastic Paraplegia type 11 (SPG11)
TUBA4A (Tubulin, alpha-4A; 2q35) – 2014	AD	ALS
TRPM7 (Transient Receptor Potential Cation Channel, Subfamily M, Member 7; 15q21.2) – 2005	AD?	ALS-Parkinsonism/Dementia complex type 1
VEGF (Vascular Endothelial Growth Factor; 6p21.1)	AD?	ALS, Microvascular complications of diabetes 1

AD: autosomal dominant; AR: autosomal recessive; XD: X-linked dominant; ALS: Amyotrophic Lateral Sclerosis; FTD: frontotemporal dementia; HD-like: Huntington's disease-like phenotype; PSP-like: Progressive Supranuclear Palsy-like; CBD-like: corticobasal dementia syndrome-like; MSA-like: Multiple System Atrophy-like; CJD-like: Creutzfeldt-Jakob disease like; AZD-like: Alzheimer's disease-like; IBM: inclusion body myopathy.

in familial ALS, as nearly half of patients with *SOD1* and *FUS* genes mutations become symptomatic at their fifties and 90% at their seventies[12]. There is also a good correlation between genetic subtypes and general age at onset (Figure 2). Genetic anticipation is exceptionally seen. There is also a tendency to progress with more prominent bulbar symptoms in familial ALS than in sporadic cases with the same age. It is important to reiterate that no specific clinical, cerebrospinal and neuroimaging parameters can rightly and reliably differentiate familial from sporadic ALS in cases without a significant familial history of neurodegeneration[2,12,13,14].

There are two other clinical situations which should be remembered in the context of familial and sporadic ALS: young-onset and juvenile ALS. Young-onset ALS starts before 45 years old, corresponds to 10% of all ALS cases and tends to present less commonly with bulbar-onset symptoms. Most cases arise in the context of sporadic ALS[15]. Juvenile ALS represents cases starting very early before 25 years of age with slowly progressive ALS, serving as a guide and key-element for clinical suspicion of autosomal recessive familial cases[6,15]. Juvenile forms are frequently described in ALS2, ALS4, ALS5, ALS6 (rarely), ALS15 and ALS16[6].

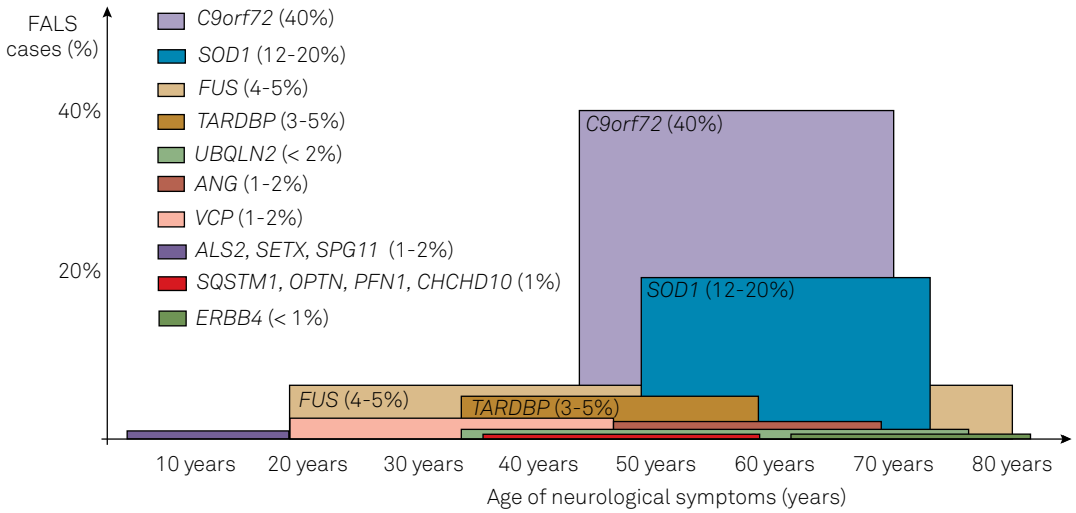

Figure 2. Distribution of the most important genetic causes of familial ALS according to the age of onset of neurological signs and symptoms. The proportion of each gene in relation to all familial cases is also represented[4,8].

CLINICAL AND GENETIC FORMS OF FAMILIAL ALS

From a historical perspective, Horton classified familial forms of motor neuron disease in three main clinico-pathological phenotypes: (i) the first with early-onset motor symptoms, before five years of age, with a rapidly progressive and lower motor neuron dominant ALS phenotype, with degeneration of corticospinal tracts and anterior horn motoneurons; (ii) the second form clinically similar, but also with posterior column and spinocerebellar tract degenerations; and (iii) a third form similar to the second, but with prolonged survival period of up to two decades[16].

The genetic history of familial ALS can be summed up by the outstanding roles of *SOD1* and *C9orf72* genes. By 2011, the year of the initial description of the hexanucleotide repeat expansion of *C9orf72* gene, only 30% of familial cases had established their genetic etiology[5,8,17,18,19]. In the last decade, more than 20 different loci were related to familial ALS.

Despite the marked heterogeneity of familial ALS, it can be said that most cases relate to *C9orf72*, *SOD1*, *FUS*, *TARDBP* and *UBQLN2* genes[6,8]. Thus, it is also possible to set specific genetic test batteries for recessive and autosomal dominant and X-linked forms, according to inheritance patterns, clinical comorbitidities, natural history and clinical evolution, and population epidemiology. However, up to 32% of familial cases and up to 11% of sporadic cases still do not have a definite genetic diagnosis of ALS[2,7,8,19].

Establishing a definite diagnosis of familial ALS is complex. In an Italian study with 53 families, genetic screening for seven of the most important genes (*SOD1, C9orf72, TARDBP, FUS, ANG, ATXN2, OPTN*) disclosed only 25% of definite genetic diagnosis with 75% of them with two family members clinically affected and 17% with only one affected family member first and second degrees away[14].

There is a lot of controversy regarding the role of most genes discovered nowadays in relation to ALS, as some of them do not have a unique causative mechanism (i.e. *SOD1, C9ORF72, SETX, ANG, SPG11, FUS, TARDBP, VAPB, VCP, UBQLN2, OPTN*, among others) but a disease-modifying function or susceptibility loci (i.e. *PGRN, HFE, NEFH, UNC13A, VEGF*, among others)[4,13]. Further discussions regarding genetic and clinical basis of familial ALS types will be provided forth (Tables 1 and 2).

ALS1

ALS1 (MIM #105400) represents the second most common form of familial ALS, giving rise to up to 20% of cases with an autosomal dominant or recessive inheritance. *SOD1* gene (*superoxide dysmutase-1*; 21q22.11) mutations give rise to abnormal function of copper/zinc superoxide dysmutase 1, responsible for converting superoxide free radical species from cytoplasm and inner intermembrane mitochondrial space into molecular oxygen and hydrogen peroxide. Secondary dysfunction of tyrosine phosphatases with phosphorilation inhibition by EGF (epidermal growth factor), IGF-1 (insulin-like growth factor 1) and FGF-2 (fibroblast growth factor-2) by MAPK (mitogen-activated protein kinase) pathway[7,20].

By 2011, *SOD1*-associated ALS (formerly the 21q-associated ALS) represented the most common form of familial and sporadic ALS. Most cases present with adult-onset ALS without cognitive compromise and variable clinical outcomes depending on the genetic background involved in each case[4,7,20]. Rapidly progressive forms of *SOD1* familial ALS occur in USA with p.Ala4Val mutation. Slowly progressive cases correlate to p.Asp90Ala mutation in Scandinavia and p.His46Arg in Japan. A LMN dominant ALS variant linked to *SOD1* was described in cases of p.Ala4Val e p.Val148Gly mutations. A

Table 2. Diagnostic cues and hallmarks of each type of familial ALS[2,8,58].

ALS type (gene involved; locus)	Hallmarks
ALS1 (*SOD1*; 21q22.11)	No specific clinical milestones
ALS2 (*ALS2*; 2q33.1)	Juvenile (< 10 years); AR; UMN-ALS, PS; facial spasticity
ALS3 (18q21)	No specific clinical milestones
ALS4 (*SETX*; 9q34.13)	Juvenile (< 20 years); AD; no bulbar/respiratory compromise; SMA-like phenotype with pyramidal signs
ALS5 (*SPG11*; 15q21.1)	Juvenile (< 25 years); AR; slowly progressive
ALS6 (*FUS/TLS*; 16p11.2)	Wide; Rapidly progressive juvenile variant (20-30 years)
ALS7 (20p13)	No specific clinical milestones
ALS8 (*VAPB*; 20q13.32)	Brazilian/Portuguese ascendancy; rapidly progressive, postural tremor, late-onset SMA, LMN-ALS
ALS9 (*ANG*; 14q11.2)	Bulbar-onset, parkinsonism, late-onset FTD; LMN-ALS
ALS10 (*TARDBP*; 1p36.22)	No cognitive compromise; slowly progressive
ALS11 (*FIG4*; 6q21)	AR; prominent pyramidal signs
ALS12 (*OPTN*; 10p13)	Japanese/Italian ascendancy; slowly progressive; glaucoma, Paget's disease of bone
ALS13 (*ATXN2*; 12q24.12)	SCA2 and late-onset parkinsonism family history
ALS14 (*VCP*; 9p13.3)	Early-onset Paget disease, FTD, inclusion body myopathy
ALS15 (*UBQLN2*; Xp11.21)	XD; early bulbar symptoms; young-onset ALS, dystonia, athetosis; variable brain iron accumulation
ALS16 (*SIGMAR1*; 9p13.3)	Saudi Arabia; AR; starts with spastic paraparesis; no bulbar/respiratory/cognitive signs
ALS17 (*CHMP2B*; 3p11.2)	LMN-ALS; FTD
ALS18 (*PFN1*; 17p13.2)	No bulbar-onset symptoms; young-onset ALS
ALS19 (*ERBB4*; 2q34)	Japan; late-onset, no cognitive signs
ALS20 (*HNRNPA1*; 12q13.13)	Inclusion body myopathy, early-onset Paget disease; no cognitive signs
ALS21 (*MATR3*; 5q31.2)	Vocal cord palsy, inclusion body myopathy; cognition
FTD-ALS type 1 (*C9orf72*; 9p21.2)	Complex familial history; broader neurological phenotype
FTD-ALS type 2 (*CHCHD10*; 22q11.23)	French/Spanish; FTD, parkinsonism, sensorineural deafness, ataxia, myopathy with ragged-red fibers
ALS-Parkinsonism/Dementia complex type 1 (*TRPM7*; 15q21.2)	Parkinsonism; FTD; Chamorro population (Guam Island)
TUBA4A-linked ALS (*TUBA4A*; 2q35)	No specific clinical milestones; FTD
DCTN1-linked ALS (*DCTN1*; 2p13.1)	Perry syndrome; FTD; parkinsonism; vocal cord palsy
NEFH-linked ALS (*NEFH*; 22q12.2)	Scandinavian; monomelic ALS, FTD, severe dysphagia
EWSR1-linked ALS (*EWSR1*; 22q12.2)	No specific clinical milestones
TAF15-linked ALS (*TAF15*; 17q12)	No specific clinical milestones
DAO-linked ALS (*DAO*; 12q24.11)	No specific clinical milestones
SMN1-linked ALS (*SMN1*; 5q13.2)	LMN-ALS
PRPH-linked ALS (*PRPH*; 12q13.12)	No specific clinical milestones; neuroaxonal spheroids
SQSTM1-linked ALS (*SQSTM1*; 5q35.3)	Paget's disease of bone
VEGF-linked ALS (*VEGF*; 6p21.1)	2578AA genotype in males
Juvenile ALS with Dementia	Dutch, Juvenile (< 10 years); AR, dementia
Utah Juvenile ALS Cluster	Utah/USA, Juvenile (< 10 years); AR, UMN-ALS, ptosis, gynecomastia, hypopalesthesia

AR: autosomal recessive; AD: autosomal dominant; XD: X-linked dominant; ALS: Amyotrophic Lateral Sclerosis; FTD: frontotemporal dementia; UMN-ALS: upper motor neuron-dominant ALS; LMN-ALS: lower motor neuron-dominant ALS; SMA: spinal muscular atrophy; PS: pseudobulbar syndrome; SCA2: spinocerebellar ataxia type 2.

cerebellar ataxia variant with slow progression was described in Scandinavia in cases of p.Asp90Ala mutation[7,20].

ALS2

ALS2 (MIM #205100) represents a rare autosomal recessive slowly progressive UMN-dominant juvenile ALS as a consequence of homozigosity mutations in *ALS2* gene (2q33.1), coding alsin, involved in the membrane and endosomal intracellular trafficking as guanine nucleotide exchange factor for Rac1 and Rab5 GTPases, in neurite outgrowth in hippocampus mediated by Rac1 activation and in prevention of glutamartegic excitoxicity mediated by Glur2 subunit of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors[15,21]. It begins in preschool child until the young adult ages (up to third decade) and has been described in japanese, turkish, tunisian, kuwaitian, saudi arabian, cypriot and Amish population. ALS2 starts with lower limb and facial spasticity, moderate muscular atrophy, pseudobulbar signs, spastic dysathrophonia and bladder dysfunction evolving statically after two decades. Important clinical overlap with allelic forms of Juvenile primary lateral sclerosis and infantile ascending hereditary spastic paralysis occurs[13,15,21].

ALS3

ALS3 (MIM %606640) represents a rare autosomal dominant adult-onset familial ALS with lower limb onset associated with 18q21 locus. Classicaly evolves to respiratory failure and death five years after onset[22].

ALS4

ALS4 (MIM #602433) represents a rare autosomal dominant slowly progressive juvenile ALS associated with mutations in *SETX* gene (9q34.13), coding the protein senataxin, a DNA/RNA helicase domain involved in RNA processing and metabolism, in DNA repair mechanisms and in RNA polymerase II-dependent transcription. A toxic gain of function generally arises[4,23]. Very early-onset (generally before 6 years up to adolescence) with prominent distal muscular atrophy and eventually cerebellar ataxia are clues to diagnosis, mimicking spinal muscular atrophy with pyramidal signs and some forms of hereditary distal motor neuropathy. Corticospinal tract and dorsal column changes may be seen in neuroimaging. Ataxia with oculomotor apraxia type 2 is an allelic condition[4,23].

ALS5

ALS5 (MIM %602099) represents a rare autosomal recessive slowly progressive juvenile ALS, arising from missense and frameshift mutations or deletions in *SPG11* gene (15q21.1), coding spatacsin, involved in axonal outgrowth and intracellular trafficking. ALS5 represents solely the most important cause of autosomal recessive juvenile ALS[4,24,25]. Prominent tongue fasciculations and amyotrophy in the first two decades evolve in up to three decades with upper motor neuron signs and spastic dysarthrophonia. Faster clinical courses were described in late-onset cases[24,25]. Allelic condition to Hereditary Spastic Paraplegia type 11[25].

ALS6

ALS6 (MIM #608030) represents an autosomal recessive or dominant adult or late-onset LMN-dominant familial ALS associated with heterozygous mutations in the *FUS/TLS* gene (*fused in sarcoma, translated in liposarcoma*; 16p11.2), coding the FUS nucleoprotein, involved with DNA repair, transcription activation, and with RNA splicing and transport to the cytoplasm. FUS associates with TDP-43 protein during the formation of SMN complex in spliceosome maintenance[6,26,27]. Up to 4% of familial and 1% of sporadic ALS arise from mutations in *FUS* gene, most commonly in USA, Cape Verdean and Europe (Germany, Italy, France, French-Canadian, United Kingdom). A rare juvenile variant with basophilic inclusions has also been described with a rapidly progressive motor phenotype starting during the second to third decade. Clinic and genetic correlations links p.Lys525Pro mutation with an aggressive rapidly progressive phenotype. Allelic disorders include hereditary essential tremor type 4 and *FUS*-related FTD[6,26,27].

ALS7

ALS7 (MIM %608031) represents a rare autosomal dominant adult-onset familial ALS, occurring in USA in association with ALS7 locus (20p13) without FTD or other systemic signs[28].

ALS8

ALS8 (MIM #608627) represents a rare autosomal dominant slowly progressive LMN-dominant familial ALS, related to heterozygous mutation in *VAPB* gene (*vesicle-associated membrane protein-associated protein B, synaptobrevin-associated membrane protein B*; 20q13.32), coding the VAPB protein lnked to the response supression to unfolded protein accumulation in endoplasmic reticulum and microtubule-associated membrane transport, presynaptic neuronal terminal formation and vesicular trafficking[29].

A complex spectrum of neurological emerges, including: (i) a rapidly progreressive adult-onset severe LMN-dominant ALS; (ii) atypical slowly progressive ALS with postural tremor; and (iii) late-onset spinal muscular atrophy type Finkel. Cases were described mainly in Brazilian families and portuguese and United Kingdom ascending patients[29].

ALS9

ALS9 (MIM #611895) represents a rare bulbar-onset autosomal dominant familial ALS linked to heterozygous mutation in *ANG* gene (*angiogenin*; 14q11.2), coding angiogenin protein (pancreatic ribonuclease A, superfamily 5), involved with angiogenic activity in motoneurons acting as a neovascularization inducer, ribosomal RNA formation and inducing cellular proliferation by VEGF (vascular endothelial growth factor). Cases were reported in Ireland, Scotland, Italy, USA, northeastern Europe and France. *ANG*-related ALS represents near 2% of familial cases. Atypical parkinsonism with late-onset frontotemporal dementia, rapidly progressive variants and LMN-dominant ALS with parkinsonism and FTD have also been described[4,30].

ALS10

ALS10 (MIM #612069) represents a rare early-onset autosomal LMN-dominant familial ALS, linked to heterozygous missense mutations in *TARDBP* gene (*TDP-43, transactive response DNA binding protein 43 kDa*; 1p36.22), coding the RNA-ligand TDP-43 (TAR DNA-binding protein 43-kD) ribonucleoprotein, involved in regulation of protein expression, transcription and translation, pre-mensager RNA alternative splicing and microRNA biogenesis[6,20,31]. ALS10 represent up to 5% of familial ALS cases and 2% of sporadic cases, being described in Italy (Sardinia), France, Germany, Japan, England, Australia and China. *TARDBP*-associated ALS also occur as long-standing symptoms in the upper limbs and with bulbar-onset in Asian patients. Clinical and genetical correlations are well-established: G298S mutations with rapidly progressive course, A315T and M337V mutations with longer survival periods[6,20,31].

ALS11

ALS11 (MIM #612577) represents a rare autosomal dominant adult-onset ALS or PLS, related to heterozigous missense mutations in *FIG4* gene (*phosphatidylinositol 3,5-bisphophate*

5-phosphatase, Sac domain-containing inositol phosphatase 3; 6q21), coding the FIG4 protein, a 5-phosphatase acting on phosphatidyl-inositol-3,5-biphosphate involved in dynamic changes in endosomal membranes during fission and fusion processes in intracellular transport from lysossomes and late endosomes to the trans-Golgi system, giving rise to autophagia dysfunction and motorneuron vacuolization in anterior horn. FIG4-related disorders include a broader spectrum including Yunis-Varon syndrome, Charcot-Marie-Tooth type 4J and bilateral temporooccipital polimicrogyria[6,32].

ALS12

ALS12 (MIM #613435) represents a rare autosomal recessive or dominant slowly progressive familial ALS sith dominant UMN signs, resulting from homozygous or heterozygous mutations in *OPTN* gene (*optineurin*; 10p13), coding optineurin protein related to nuclear factor-kappa B (NF-κB) inhibition or activation by TNF-α pathways, Golgi complex manteinance, autophagy induction and interacting with huntingtin, Rab8 and transcription factor IIIA[6,33]. Cases were described in japanese and italian families starting in the third or fifth decades with bulbar compromise at early and moderate disease stages. Allelic disorders include Paget disease of bone and primary open-angle glaucoma type 1[4,6,33].

ALS13

ALS13 (MIM #183090) represents an autosomal dominant form of familial ALS in families with spinocerebellar ataxia phenotypes, related to intermediate repeat lengths of CAG trinucleotide (27-33 repeats, generally more than 31) in the 5-prime end of the coding region in the exon 1 of the *ATXN2* gene (*ataxin 2*; 12q24.12), coding ataxin-2, involved with EGF receptor trafficking as a negative regulator of endocytosis by interactions with endophilins A1 and A3, forms a RNA-dependent complex with TDP-43, and interacts with PABP protein (poly-A-binding-protein 1) in motoneurons[6,34]. Cases were described in Belgium, Netherlands, France and Canada. Intermediate repeat lengths also correlated with late-onset Parkinson's disease and Progressive Supranuclear Palsy. More than 33 repeats are described in spinocerebellar ataxia type 2 (SCA2)[6,34].

ALS14

ALS14 (MIM #613954) forms a rare autosomal dominant form of familial ALS resulting from heterozygous mutations in *VCP* gene (*valosin-containing protein*; 9p13.3), coding the AAA+-ATPase valosin-containing protein, involved in substrate extraction in ubiquitin-proteosome systems, in Golgi complex biogenesis, in chlatrin-mediated membrane trafficking in endocytosis and Golgi complex, regulates protein degradation at the outer mitochondrial membrane, peroxysomal assembly, autophagosome maturation, and regulates cell cycle[4,35]. Up to 2% of familial ALS are *VCP*-related, occur in italian and north-american families and starts in the fourth to sixth decades with spine-onset ALS. Allelic disturbances include inclusion body myopathy, early-onset Paget disease, and frontotemporal dementia type 1, and distal myopathy[4,35].

ALS15

ALS15 (MIM #300857) represents the rare dominant X-linked form of familial ALS with incomplete penetrance related to mutations in *UBQLN2* gene (*ubiquilin* 2; Xp11.21), coding ubiquilin-2, linked to ubiquilin regulator family of ubiquitin-proteosome system and autophagy[6,36]. Up to 2% of familial ALS cases have a X-linked pattern of inheritance, most commonly in the first third to fifth decades, and starts with bulbar-onset disease evolving with FTD, dystonia, athetosis and spastic tetraparesis. Neuroimaging unveils cortical and basal ganglia atrophy, rarely with brain iron accumulation in basal ganglia[6,36].

ALS16

ALS16 (MIM #614373) represents an autosomal recessive UMN-dominant juvenile ALS (starting in preschool and early infancy), linked to homozygous E102Q mutations in the *SIGMAR1* gene (*sigma nonopioid intracellular receptor 1*; 9p13.3) in Saudi Arabia, coding the S1R receptor, an endoplasmic reticulum chaperone of the cholinergic post-synaptic membrane, which binds neurosteroids, psychostimulants and involved in potassium chanell regulation and calcium signaling by IP3 receptors in cortical and spinal cord motoneurons. Ubiquitin-proteosome system abnormalities and abnormal motoneuron apoptosis have also been described[6,37].

ALS17

ALS17 (MIM #614696) represents an autosomal dominant form of lower motor neuron dominant familial ALS (sometimes associated with FTD) related to missense heterozygous mutations in the *CHMP2B* gene (*Chromatin-modifying protein 2B or charged multivesicular body protein 2B*; 3p11.2), coding the VPS2B protein (vacuolar protein sorting 2), involved with the endosomal sorting complex ESCRT-III linked to degradation of surface receptors to the trans-Golgi and lysosomal networks, formation of multivesicular endocytic bodies, axonal transport, protein translation and MAPK intracellular pathways[38].

ALS18

ALS18 (MIM #614808) represents a rare autosomal dominant form of spinal-onset familial ALS linked to heterozygous *missense* mutations in the *PFN1* gene (*profilin 1*; 17p13.2), coding the profilin-1 protein, which inhibits actin polymerization and regulates the outgrowth of the filamentous portion of (F)-actin by binding to monomeric (G)-actin. It represents up to 2% of familial cases starting in the fourth and fifth decades in caucasian and Sephardic Jewish populations without severe cognitive compromise[2,6,39].

ALS19

ALS19 (MIM #615515) represents a rare autosomal dominant form of late-onset slowly progressive familial ALS described in japanese and canadian families, resulting from heterozygous missense mutations in *ERBB4* gene (*V-ERB-B2 avian erythroblastic leucemia viral oncogene homolog 4*; 2q34), coding the HER4 protein ligand for NDF/heregulin and neurregulin-ERBB4 pathways, involved in synaptic plasticity, cell proliferation and differentiation, glutamatergic hypofunction, and inhibition of NMDA currents and raise of AMPA currents[40].

ALS20

ALS20 (MIM #615426) represents an extremely rare autosomal dominant form of ALS with late-onset motor symptoms linked to heterozygous missense mutations in the *HNRNPA1* gene (*heterogeneous nuclear ribonucleoprotein A1*; 12q13.13), coding the heterogeneous nuclear ribonucleoprotein A1, involved with splicing and processing of pre-messenger RNA and further metabolism and associates with core proteins of the protein moiety of the nuclear 40S ribonucleoprotein particle with RNA polymerase II transcripts. Allelic disorders are represented by inclusion body myopathy with early-onset Paget's disease without frontotemporal dementia type 3[41].

ALS21

ALS21 (MIM #606070) represents a rare slowly-progressive autosomal dominant familial ALS linked to heterozygous missense mutations in the *MATR3* gene (*matrin3*; 5q31.2), coding the matrin-3 protein, an internal matrix nuclear protein which interacts with TDP-43 participating in the aberrant processing of RNA and stabilizing messenger RNA[42,43].

ALS21 (formerly the vocal cord and pharyngeal dysfunction with distal myopathy type 2) presents with adult-onset dystal myopathy with inclusion body myopathy-like features and vocal cord and pharyngeal weakness, occasionally with lower limbs brisk reflexes and tongue fasciculations and death after 15 years of symptom-onset. Other European cases were described in assocation with dementia and MND. Other Indian patient presented with adult-onset ALS and hyper-CKemia[42,43].

ALS22

ALS22 (MIM #616208), a recently described rare form of adult-onset familial ALS, correlates with *TUBA4A* gene (*Tubulin, Alpha-4A*; 2q35), coding the tubulin-alpha-4A protein, involved with microtubule network stabilization and reducing repolimerization dynamics. This form presents with late-onset familial spinal-dominant ALS with or without FTD[44].

FTD-ALS type 1

FTD-ALS type 1 (MIM #105550) represents the most common form of familial ALS. It occurs in an autosomal dominant inherited pattern in association with FTD and is associated with hexanucleotide repeat expansion (GGGGCC) in the non-conding intronic region of 5' regulatory region of *C9orf72* gene (*chromosome 9 open reading frame 72*; 9p21.2), coding the C9orf72 protein, involved in multiple intracellular mechanisms[45,46].

Loss of function by happloinsufficiency and toxic gain-of-function mechanisms are both present. *C9orf72*-related disorders result from abnormal membrane and endosomal trafficking (related to ubiquilin-2, HNRNPA1 and HNRNPA2B1 proteins), abnormal RNA processing and metabolism (with toxic RNA foci and gain-of-function), abnormal functions of ubiquitin-proteosome system, abnormal regulation of Rab guanine-nucleotide exchange factors involved with autophagia, and secondary axonal transport disturbances. Abnormal expansion repeats form RNA G-quadruplexes with distinct structures and promote formation of DNA/RNA hybrid R-loops with linkage of aborted transcripts to the expanded regions in ribonucleoproteins leading to nucleolar stress and neuronal apoptosis. Another mechanism involves the translation of expansion transcripts without the ATG start codon, the so-called RAN process (repeat-associated non-ATG translation), generating polipeptides with poli-glycine-arginine and poli-proline-arginine (also called dipeptide repeat proteins), which leads to neutoxicity by direct effects to DNA and binding to HNRNPA2 and changing RNA biogenesis[8,46,47,48,49].

Some neuropathological and molecular signatures from *C9orf72*-related disorders differentiate them from other ALS and FTD genetic forms. Spinal motor neurons and glial cells may present with TDP-43 positive cytoplasmic inclusions in association with cortical and spinal cord intraneuronal cytoplasmic ubiquitin-positive, Tau-negative inclusions, FUS-negative and Ubiquilin 2 positive inclusions[12]. The same way, a nearly pathognomonic neuromolecular marker of *C9orf72*-related disorder is the presence of TDP-43 negative and p62-positive intraneuronal intracytoplasmic inclusions with dipeptide repeat proteins in extraspinal regions (dentate gyrus granule cells in the CA4 pyramidal cells of the hippocampus, frontal neocortex, and granule cells of the cerebellum). These dipeptide repeat proteins result from sense and antisense repeat associated non ATG-initiated translation of the expanded repeat noncoding region, previously described. Furthermore, the loss of dopaminergic neurons in substantia nigra has also been described in *C9orf72*-related ALS with parkinsonism, p62-positive inclusions and α-synuclein-negative Lewy bodies[12].

C9orf72-associated ALS represents the main discovery in neuromuscular genetics since 2011 (former chromosome 9p-linked FTD with ALS)[48,49] and the major cause of ALS ranging from one third up to 46% of familial cases and from 6% up to 21% of sporadic cases[20]. There is a clear tendency of low prevalence in cases from Asian countries and Pacific islands. On the other hand, high sporadic prevalences are

detected in Finland (with a founder effect), Sweden, United Kingdom, Netherlands, Greece and USA, and high familial rates in Belgium, Sweden, Greece, Finland, Ireland, France and United Kingdom[46,47].

Neurological symptomatic cases arise with 250 up to 1600 expansion repeats, as healthy people most commonly present with 2 to 19 repeats[46,47]. The clinical picture of *C9orf72*-related disorders is expanding its phenotypical spectrum. Family history of FTD-ALS patients may unveil dementia (with FTD, dementia with diffuse Lewy bodies or Alzheimer's disease), atypical parkinsonism (with rapidly progressive progressive supranuclear palsy and corticobasal degeneration), complex movement disorders (Huntington's disease-like), and psychiatric disorders (mainly late-onset psychosis). Intense intrafamilial clinical variability makes difficult the recognition of this neurodegenerative complex[46,47].

Thus, *C9orf72*-related ALS must be investigated in cases of adult-onset familial ALS, mainly in non-Asian patient cases with FTD phenotype, or in cases with a complex familial network of neurodegenerative disorders, including adult and late-onset chorea, atypical parkinsonism or isolated psychiatric syndromes.

FTD-ALS type 2

FTD-ALS type 2 (MIM #615911) represents a rare autosomal dominant form of familial ALS with frontotemporal dementia, resulting from heterozygous mutations in the *CHCHD10* gene (*Coiled-coil-helix-coiled-coil-helix domain-containing protein 10*; 22q11.23), coding the CHCHD10 protein, involved in oxidative phosphorylation and maintenance of cristae morphology in the inner intermembranous mitochondrial space. In France and Spain patients around the fifth decade of life present with complex neurological phenotypes involving frontotemporal dementia, cerebellar ataxia, myopathy with ragged-red fibers and COX-negative fibers, motor neuron disease with progressive bulbar dysfunction, and rarely with akinetic-rigid parkinsonism and sensorineural deafness[50].

UNCLASSIFIED FORMS OF FAMILIAL ALS

Several genetic forms of familial ALS, well-recognized by specialists, are not characterized as a single familial ALS form in the Monogenic Muscle Gene Table classification (World Muscle Society)[51]. The most distinguished forms are discussed here.

Familial forms associated to *NEFH* gene (*neurofilament, heavy polypepeptide*; 22q12.2) are involved in monomelic ALS with dementia and severe dysphagia in Scandinavia. *NEFH* gene codes the heavy polypeptide neurofilament, the most important neuron-specific intermediate filament of cytoskeleton in myelinated axons, involved in maintenance of cytoskeleton and axonal architecture in proximal axonal region of spinal motoneurons[51,52].

PRPH-associated familial ALS represents an adult-onset ALS with Lewy body-like inclusions and neuroaxonal spheroids in proximal axonal region of spinal motoneurons. It is associated with mutations in *PRPH* gene (*peripherin*; 12q13.12), coding peripherin, an intermediate filament type 3 neuronal cytoskeleton similar to neurofilament[51,53].

DCTN1-related disorders are involved in a complex spectrum of neurodegenerative allelic disorders, including hereditary distal motor neuropathy type VIIB, FTD-like phenotypes and atypical parkinsonism, like PSP and Perry syndrome. A lower motor neuron dominant slowly progressive ALS with vocal cord and facial palsy arises as a consequence of G59S heterozygous mutation in *DCTN1* (*dynactin 1*; 2p13.1), coding dynactin-1, involved with dynactin complex connection with microtubules and cytoplasm dynein for axonal transport[54].

DAO (*D-aminoacid oxidase*; 12q24.11) gene mutations are also involved with very rare adult-onset familial ALS. Dysfunction of D-aminoacid oxidase gives rise to abnormal downregulation of D-serine, a normal co-agonist of excitatory NMDA glutamate receptors, as a consequence of abnormal cerebellar and spinal oxidative deamination of D-aminoacids. There is association with schizophrenia in canadian patients[6,55].

SQSTM1-associated ALS correlates with adult-onset autosomal dominant familial ALS associated with Paget disease of bone, representing up to 1% of familial cases. *SQSTM1* gene (*Sequestosome 1*; 5q35.3) mutations are involved with abnormal coding of p62 protein, involved in ubiquitination and authophagy by activation of NF-κB pathway[4,6].

TAF15 (*TATA Box-binding protein-associated factor RNA polymerase II*; 17q12) and *EWSR1* (*Ewing sarcoma breakpoint region 1*; 22q12.2) genes are involved with extremely rare adult-onset familial ALS, both participating directly in transcription processes with other activators or repressors: the former coding RBP56 protein (RNA-binding protein 56), allelic to extraskeletal mixoid condrosarcoma; and the last coding EWS protein, allelic to neuroepithelioma and Ewing sarcoma[4,6].

A rare autosomal recessive juvenile ALS form (MIM %20 5200) has been described in Dutch and Amish patients with early juvenile-onset dementia during the first decade with distal muscular atrophy and death after up to two decades of symptom-onset[56].

Another recently described familial ALS form has been described in Utah, USA, involving autosomal recessive inheritance and clinically manifest with upper motor neuron dominant juvenile ALS, with slowly progressive motor symptoms starting in the lower limbs and bulbar region in the first decade of life and evolving with partial eyelid ptosis, gynecomastia and mild distal hypopalesthesia[2,3].

Amyotrophic lateral sclerosis-parkinsonism/dementia complex type 1 results from mutations in the *TRPM7* gene (*Transient receptor potential cation channel,*

subfamily M, member 7; 15q21.2), coding the transient receptor potential cation channel subfamily M member 7, involved in regulation of oxidative stress metabolism and in the phosphorylation of different intracellular substrates. Susceptibility from direct exposure to neurotoxic effects β-methylamino-L-alanine found in local Guam species of flying fox (*Pteropus tokudae*) was described in patients from the Chamorro population from Guam Island in USA which posteriorly become called the Lytico-bodig disease[57]. Most authors do not include Lytico-bodig disease as familial ALS. However, this apparently narrowed distribution of this ALS form has also been linked to another form of ALS described in the Kii Peninsula of Japan, also known as Muro disease with a complex neurological phenotype with dementia and movement disorders (including parkinsonism, dystonia and myoclonus), in which *TRPM7*, *C9orf72* and *SOD1*-related mechanisms have been described[58].

FAMILIAL AND SPORADIC FORMS ASSOCIATED WITH OTHER SUSCEPTIBILITY LOCI

In many of the so-called sporadic cases, there is an important role of genetic factors usually associated with incomplete penetrance and the complex stochastic predisposing events and the individual and environmental risk factors[59]. Much data on susceptibility loci results from linkage analysis studies, candidate-gene association studies, genome-wide association studies and methylation analysis, copy number variants and chromosomal rearrangements studies, and whole-exome or genome-sequencing studies[2,3,59]. Most clinical descriptions are related to single nucleotide polymorphisms (SNPs), polyglutamine repeats, missense mutations, abnormal copy number of genes, gene promoter SNPs, and insertions and deletions[7]. More than 20 different gene loci have been described so far.

CYP27A1 gene (*Cytochrome P450, Subfamily XXVIIA, Polypeptide 1*; 2q35) mutations have been described in cerebrotendinous xanthomatosis (CTX) (MIM #213700) and as a susceptibility loci for sporadic ALS[60]. In our experience, CTX may present with an early-onset lower motor dominant juvenile ALS phenotype in two Brazilian sisters with severe bulbar compromise, orofacial dyskinesia and generalized epilepsy. One of them presented also with typical systemic signs of CTX, including chronic diarrhea, juvenile bilateral cataracts and early-onset premenopausal osteopenia (unpublished data). Other gene loci are also involved with sporadic forms described as susceptibility loci (most as SNP associations or demonstrated by genome-wide association studies) for which there is some degree of suspicion related to familial cases (Table 3)[2,4,7,12,13,59].

Table 3. Summary of the main gene loci involved with sporadic forms and with high suspicion of involvement in familial cases[2,4,7,12,13,59].

Gene involved and locus	Distribution and allelic disorders
APEX1 gene (*apurinic endonuclease 1, multifunctional DNA repair enzyme*; 14q11.2)	Ireland and Scotland; no allelic disorders
SS18-like gene 1 (*Calcium-responsive Transactivator*; 20q13.33)	No allelic disorders
CAMK1G gene (*Calcium/Calmodulin-dependent Protein Kinase I-Gamma*; 1q32.2)	No allelic disorders
ARHGEF28 gene (*Rho Guanine Nucleotide Exchange Factor 28*; 5q13.2)	No allelic disorders
HFE gene (*hemochromatosis*; 6p22.2)	USA, Ireland, United Kingdom, Italy, China and Netherlands; hemochromatosis; susceptibility to porphyria variegata and cutanea tarda
VEGF gene (*Vascular Endothelial Growth Factor A*; 6p21.1)	Sweden, Belgium, Germany and England
ITPR2 gene (*inositol 1,4,5-triphosphate receptor type 2*; 12p12.1-p11.2)	No allelic disorders
DPP6 gene (*dipeptidyl-peptidase VI*; 7q36.2)	No allelic disorders
KIFAP3 gene (*kinesin-associated protein 3*; 1q24.2)	No allelic disorders
PLCD1 gene (*Phospholipase C, Delta-1*; 3p22.2)	Nonsyndromic congenital nail disorders (leukonychia) type 3
Telomeric *SMN1* gene (*survival of motor neuron 1*; 5q13.2) duplications	Spinal muscular atrophy types 1-4
Centromeric *SMN2* gene (*survival of motor neuron 2*; 5q13.2) deletions	Spinal muscular atrophy type 3
COX1 (*Complex IV, Cytochrome c Oxidase subunit I, MT-CO1*) gene	Leber optic atrophy, Acquired idiopathic sideroblastic anemia, cytochrome c oxidase deficiency, recurrent myoglobinuria, colorectal cancer
IARS2 (*mitochondrial Isoleucyl-tRNA synthetase*; 1q41) gene	Cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysplasia
PON1 gene (*paraoxonase, arylesterase A*; 7q21.3)	Alzheimer's disease, idiopathic Parkinson's disease; sensitivity to organophosphate; susceptibility to coronary artery disease

Other gene *loci*: *FGGY* (*FLJ10986*) gene; 7p13.3 locus; *SPG17/BSCL2* gene (11q13); *SPG39/PNPLA6* gene (*Patatin-like phospholipase domain-containing protein 6*; 19p13.2); *UNC13A* gene (*KIAA1031*; 19p13.11); *PGRN* gene (*granulin precursor*; 17q21.31); *ELP3* gene (*Elongator Acetyltransferase Complex, Subunit 3*; 8p21.1); *SUSD2* gene (*Sushi Domain-Containing Protein 2*; 22q11.23); *EPHA4* gene (*Ephrin receptor EphA4*); *CHGB* gene (*chromogranin B, secretogranin I*; 20p12.3), *C19orf12* gene (*Mitocondrial Membrane Protein Associated Neurodegeneration*-MPAN/NBIA4;19q12); *GLE1* gene (*GLE1, S. cerevisae, Homolog-like*; 9q34.11)

CONCLUSION

Although most cases of ALS are sporadic, familial ALS cases represent important clinical, genetic and neuropathological keys to understand the natural history of different genetic forms, clinical and genetic correlations, and allow new genetic targeted therapies for ALS. Despite the current trend of ALS diagnoses are limited to syndromic clinical descriptions, in the near future it will be essential to establish the genetic types associated with the different clinical subtypes and presentations, especially in familial cases and in complex neurological phenotypes.

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