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Genetics of ALS and Correlations Between Genotype and Phenotype in ALS – A Focus on Italian Population

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1. Introduction

Amyotrophic Lateral Sclerosis, generally known as ALS, is a lethal neurodegenerative disease that gradually affects the motor neurons (nerve cells) which control muscle movement. The causes of the disease are as yet unknown and the substantial amount of research currently under way has found that the causes of ALS are multifactorial, such as genetic predisposition. In fact, about the involvement of genetic, ALS is a multigenic disease result from mutations in more than one gene (Table 1). The annual incidence of ALS is 0,4-1,76 per 100000 [1]. The majority of cases of ALS are sporadic (90-95%), called SALS. Around 5-10% of cases are considered to be familial (FALS), where the disease is present in both a proband and first-degree or second-degree relative [2-3]. FALS is usually inherited in an autosomal dominant manner, though there are rare cases of autosomal recessive disease. FALS is genetically heterogeneous, including 15 mapped loci, of which the causative genes are identified for 11. Mutations in several of the known FALS genes have also been described in apparently sporadic cases of ALS at low frequencies. Genetic changes detected in sporadic cases arise both from new mutations and also lack of evidence of inheritance due to the difficulty in recognizing a genetic component to rapidly lethal late-onset disease. The systematic, detailed diagnosis of neurological disease in older people is a modern, and still incomplete, medical phenomenon. For any late-onset disorder both incomplete penetrance and premature death of earlier generations due to other causes attenuates the expression of disease within a family so that in many examples where apparently sporadic ALS is associated with genetic mutation there is limited information about the family rather than a clear demonstration of unequivocally de novo genetic change [4].

ALS type	Onset	Inheritance	Locus	Gene	Protein
ALS1	Adult	AD	21q22.1	<i>SOD1</i>	Cu/Zn superoxide dismutase
ALS2	Juvenile	AR	2q33-35	<i>ALS2</i>	Alsin
ALS3	Adult	AD	18q21	Unknown	
ALS4	Juvenile	AD	9q34	<i>SETX</i>	Senataxin
ALS5	Juvenile	AR	15q15-21	<i>SPG11</i>	Spatacsin
ALS6	Adult	AD	16p11.2	<i>FUS</i>	Fused in sarcoma
ALS7	Adult	AD	20p13	Unknown	
ALS8	Adult	AD	20q13.33	<i>VAPB</i>	VAMP-associated protein B
ALS9	Adult	AD	14q11	<i>ANG</i>	Angiogenin
ALS10	Adult	AD	1q36	<i>TARDBP</i>	TAR DNA-binding protein
ALS11	Adult	AD	6q21	<i>FIG4</i>	PI(3,5)P(2)5-phosphatase
ALS12	Adult	AR/AD	10p15p14	<i>OPTN</i>	Optineurin
ALS-FTD1	Adult	AD	9q21-22	Unknown	
ALS-FTD2	Juvenile	AD	9p13.2-21.3	Unknown	
ALS-FTD3	Adult	AD	9p21	<i>C9orf72</i>	C9orf72

Table 1. Genes and loci associated with ALS.

Discoveries in the clinical genetics of ALS in particular offer opportunities to deepen understanding of various disease phenotypes that appear to share aspects of pathogenesis, confirm previous hypothesis around the concept of disease spectra, in terms of linkage to a specific proteinopathy, and increase the scope of pathological studies of human motor system disease.

Genetic factors may play a role in determining the range of ALS phenotypes although to date no genes have been shown to have a definite effect on phenotype [4]. In fact the genetic alteration is not the only factor that determines the clinical course of the disease, other factors must also contribute to phenotype and it is not yet possible to predict the evolution of patients based solely on presence of the mutation or rate of progression in other family members.

The diagnosis of ALS is based on the original El Escorial diagnostic criteria, revised from 2000 [5-6].

It is a generally accepted notion that the clinical spectrum of ALS includes different phenotypes marked by a varying involvement of spinal and bulbar upper and lower motor neurons. Accordingly, eight distinctive clinical phenotypes are recognised in the literature: classic, bulbar, flail arm, flail leg, pyramidal, respiratory, pure lower motor neuron, pure upper motor neuron.

- a. Classic ALS phenotype is characterised by onset of symptoms in the upper or lower limbs, with clear but not predominant pyramidal signs. It is the commonest phenotype in men and the second in women, with a peak of incidence rate in the seventh decade in both

genders. 0-5% of cases have frontotemporal dementia. Median survival time is 2,5 years [4].

- b. Bulbar phenotype starts with dysarthria, dysphagia, tongue wasting, fasciculation and no peripheral spinal involvement for the first 6 months after symptoms onset; pyramidal signs aren't required to be evident in the first period but needs to be evident thereafter. This subtype has the same incidence in the two genders, with peak of incidence in the eighth decade. It is the commonest phenotype associated with frontotemporal dementia (10%). Median survival time is 2 years [4]. It is now accepted that FTD and MND are part of the same clinicopathological spectrum. Frontotemporal dementia is characterised clinically by progressive behavioural changes and frontal executive deficits and/or selective language difficulties. The presence of FTD is determined using a screening test, such as FAB (frontal assessment battery), and is based on Neary criteria [7-8]. Frontotemporal dementia is present in about 5-10% of patients, however many ALS patients have evidence of FTD behavioural dysfunction that may not satisfy Neary criteria for FTD. Patients often have bulbar phenotype with muscle atrophy, weakness and fasciculations prominent in the tongue and also in the upper extremities.
- c. Flail arm phenotype is characterised by progressive, predominantly proximal, weakness and wasting in the upper limbs and functional involvement has to be confined in this parts for at least 12 months after symptoms onset. This phenotype is relatively rare and more common in men, often benign with a median survival time of 4 years. Frontotemporal dementia is rare in this phenotype [4].
- d. Flail leg begins with progressive distal onset of symptoms in lower limbs. Patients with symptoms beginning proximally in the legs without distal involvement at onset are classified as classic ALS. This type of disease has the same incidence in two genders. Mean age of onset is about 65 years and the peak of incidence rate is in the eighth decade. Median survival time is 3 years [4].

In two last categories there are forms with pathological deep tendon reflexes or Hoffmann and Babinski sign but without hypertonia or clonus.

- e. Patients with pyramidal phenotype have manifestations dominated by severe spastic para/tertaparesis associated with Babinski or Hoffmann sign, hyperactive reflexes, clonic jaw jerk, dysarthric speech and pseudobulbar affect. Spastic paresis could be present at the beginning or in the fully developed stage of the disease. These patients show at the same time clear-cut signs of lower motor neuron impairment from onset of the disease, as indicated by muscle weakness and wasting and by the presence of chronic and active denervation at the EMG examination in at least two different sites. Patients have a quite young age at onset, under 60 years. Both genders are equally represented. FTD is uncommon and median survival time is 6 years [4].
- f. There is a particular and the rarest phenotype with respiratory impairment at onset, defined as orthopnoea or dyspnoea at rest or during exertion, with only mild spinal or bulbar signs in the first 6 months after onset. These patients show signs of upper motor neuron involvement. Median survival time is 1,5 years, with the worst prognosis [4].

- g.** Pure lower motor neuron phenotype is characterised by clinical and electrophysiological evidence of progressive LMN involvement. Patients with family history of inherited spinal muscular atrophy are excluded. It has a low incidence rate and is twice as frequent in men. Patients with this form are younger than those with any other ALS phenotype, with a peak of incidence rate in the seventh decade among men and in the sixth decade among women. Nobody has FTD and mean survival is the longest (7 years) [4].
- h.** Patients with pure upper motor neuron have signs of UMN involvement (severe spastic para/tertaparesis associated with Babinski or Hoffmann sign, hyperactive reflexes, clonic jaw jerk, dysarthric speech and pseudobulbar affect). Patients with clinical or EMG signs of LMN involvement or with history of spastic para/tetraparesis in family such as hereditary spastic paraplegia are excluded. It has a low incidence rate with peak in the sixth decade in both genders, Median survival time is the longest among ALS phenotype (more than 10 years) [4].

Phenotype	No of cases (%)	Age at onset (years) (mean (SD))	Age at onset (years) (median (IQR)) [‡]	Diagnostic delay (months) (mean (SD))	Diagnostic delay (months) (median (IQR)) [‡]	Cases with FTD (%)
Classic	404 (30.3)	62.8 (11.3)	64.6 (56.1–70.6)	10.9 (9.6)	8 (5–13)	16 (4.0)
Bulbar	456 (34.2)	68.8 (9.7)	69.9 (62.9–75.0)	9.8 (7.0)	8 (5–12)	41 (9.0)
Flail arm	74 (5.5)	62.6 (11.8)	63.3 (54.8–72.2)	12.8 (11.0)	9 (5–15)	1 (1.4)
Flail leg	173 (13.0)	65.0 (9.6)	65.6 (58.5–71.2)	13.1 (10.1)	11 (7–17)	7 (4.1)
Pyramidal	120 (9.1)	58.3 (13.5)	60.1 (49.2–68.3)	15.9 (13.4)	12 (6–22)	3 (2.5)
Respiratory	14 (1.1)	62.2 (8.6)	62.0 (58.3–65.3)	6.4 (4.3)	5 (3–9)	–
PLMN	38 (2.9)	56.2 (11.3)	55.2 (45.7–61.3)	15.5 (12.4)	14 (10–19)	–
PUMN	53 (4.0)	58.9 (10.9)	56.5 (48.3–62.6)	15.9 (14.3)	15 (10–19)	2 (3.8%)
Overall ALS	1332	64.3 (11.3)	65.3 (59.7–71.8)	10.8 (10.4)	9 (5–14)	70 (5.4%)
		p=0.0001*		p=0.0001*		p=0.0001†

*ANOVA.

† χ^2 test.

‡Q1–Q3.

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; PLMN, pure lower motor neuron phenotype; PUMN, pure upper motor neuron phenotype.

Table 2. Mean age at onset, mean time delay from onset to diagnosis and frequency of frontotemporal dementia [4].

Phenotype	Overall, incidence rate (95% CI)	Men, incidence rate (95% CI)	Women, incidence rate (95% CI)	Men to women incidence rate ratio
Classic	0.94 (0.85 to 1.04)	1.17 (1.03 to 1.32)	0.71 (0.61 to 0.83)	1.65:1
Bulbar	1.05 (0.96 to 1.15)	1.04 (0.91 to 1.19)	1.06 (0.94 to 1.20)	0.98:1
Flail arm	0.17 (0.13 to 0.21)	0.28 (0.21 to 0.36)	0.07 (0.04 to 0.12)	4.00:1
Flail leg	0.40 (0.34 to 0.47)	0.40 (0.32 to 0.50)	0.39 (0.31 to 0.48)	1.03:1
Pyramidal	0.28 (0.23 to 0.34)	0.28 (0.21 to 0.36)	0.27 (0.21 to 0.35)	1.04:1
Respiratory	0.03 (0.02 to 0.05)	0.06 (0.03 to 0.10)	0.01 (0 to 0.03)	6.00:1
PLMN	0.08 (0.06 to 0.11)	0.11 (0.07 to 0.17)	0.05 (0.03 to 0.08)	2.04:1
PUMN	0.12 (0.09 to 0.16)	0.12 (0.08 to 0.18)	0.12 (0.08 to 0.17)	0.98:1
Overall ALS	3.07 (2.89 to 3.25)	3.46 (3.23 to 3.71)	2.68 (2.44 to 2.90)	1.29:1

ALS, amyotrophic lateral sclerosis; PLMN, pure lower motor neuron phenotype; PUMN, pure upper motor neuron phenotype.

Table 3. Amyotrophic lateral sclerosis phenotypes. Overall and men versus women mean annual crude incidence rates (/100000 population), 95% CIs and gender incidence rate ratios [4].

In this chapter we would deep investigate the correlation between genetic and clinical features in the ALS population that we better know, the Italian one. However, heterogeneity between and among families implies that other environmental and genetic influences contribute to not only the rate of evolution and which signs predominate but also whether the disease will appear at all during life. Considerable work lies ahead in determining the genetic and environmental factors that most contribute to ALS. Altogether one determinant of ALS phenotype is the underlying causative mutation.

We will focus this book section on the correlation between genotype and phenotype in Italian ALS disease population. This chapter will be organized in different paragraphs about the genes mostly mutated in Italian ALS patients, *SOD1*, *FUS*, *TARDBP*, *ANG*, *C9orf72* and *OPTN* genes (Table 2), and each paragraphs will be subdivided in two parts about genotype and phenotype. Moreover we will try to define and understand particular connection between phenotype and genotype in Italian population and in our experience in Pavia to characterize the Italian ALS population in relation to the genetic aspects.

Obviously in literature different mutations are known for every genes and many other ones will be discovered in future.

In this chapter we cannot deepen the importance of every mutation in relation to the phenotypic characteristic of ALS patients.

For this reason in this book section we will develop speech on more frequent alterations and on which we have met during our daily activity in Pavia or in our collaborations with other groups.

2. Cu/Zn Superoxide Dismutase (SOD1 gene)

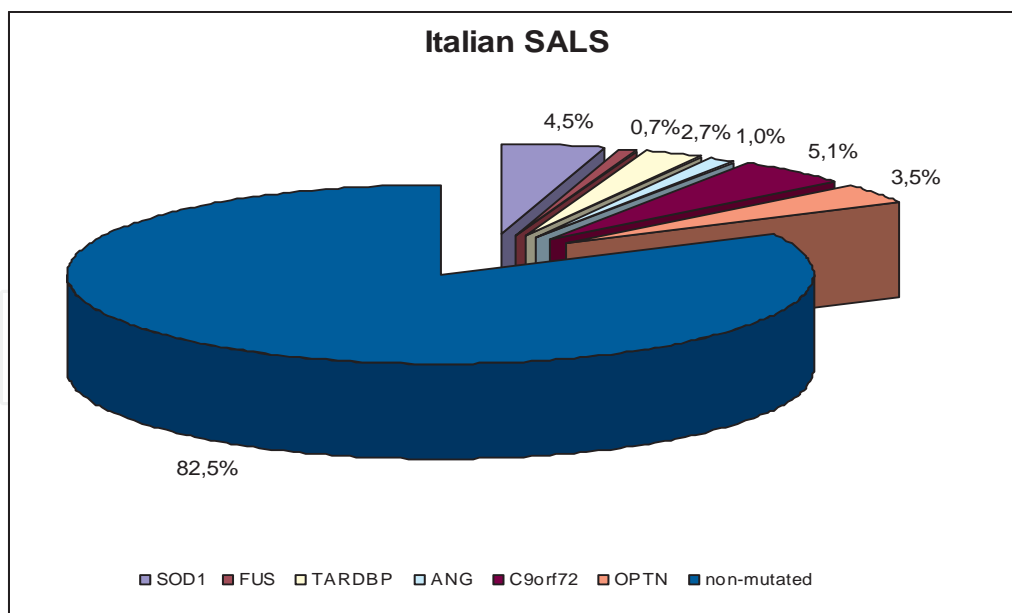
Superoxide dismutase [Cu-Zn] also known as superoxide dismutase 1 or SOD1 is a soluble protein acting as a 32 kDa homodimeric enzyme. SOD1 is one of three human superoxide dismutases.

Its main function is the conversion, naturally occurring, but harmful, superoxide radicals to molecular oxygen and hydrogen peroxide.

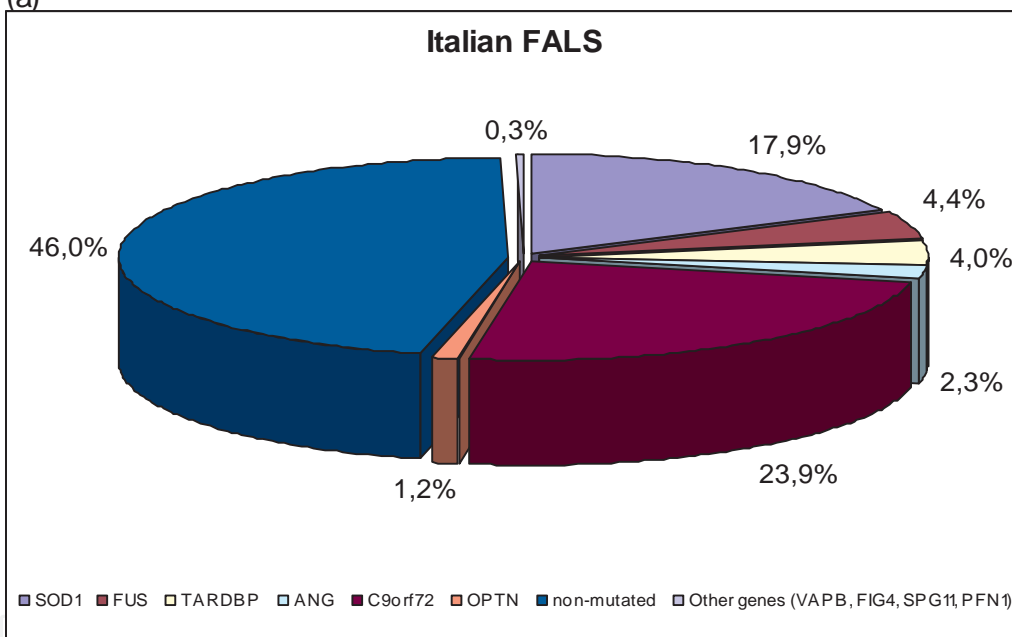
SOD1 binds copper and zinc ions and is one of three superoxide dismutases responsible for destroying free superoxide radicals in the body. The encoded isozyme is a soluble cytoplasmic and mitochondrial inter-membrane space protein, acting as a homodimer to convert naturally occurring, but harmful, superoxide radicals to molecular oxygen and hydrogen peroxide

2.1. Genotype

The human *SOD1* gene (Entrez Gene ID 6647) is located on chromosome 21q22.11, and it codes for the monomeric SOD1 polypeptide (153 amino acids, molecular weight 16 kDa).



(a)



(b)

Figure 1. Summarize the percentage of mutations in Italian ALS patients, (a) SALS, (b) FALS [2, 9, 10, 11, 12, 13, 14].

In 1991, Siddique and collaborators [15] identified a linkage between familial ALS and the *SOD1* locus on chromosome 21q22 and demonstrated genetic locus heterogeneity in FALS studying 23 ALS families.

In 1993, Rosen and collaborators [16] have reported tight genetic linkage between ALS and *SOD1* gene, establishing *SOD1* as the first causative gene for ALS. More than 150 *SOD1* mutations have been reported in 68 of the 153 codons, spread over all five exons (ALS Online Genetic Database, ALSOD: <http://alsod.iop.kcl.ac.uk/>).

The vast majority of which are missense substitutions distributed throughout the five exons of the gene. Also frame-shift deletions and insertions, all clustered in exons 4 and 5, which lead to a premature truncation of the protein have been described (Figure 2).

Collectively, SOD1 mutations are found in ~20% of all FALS patients, and in ~3% of SALS cases [17].

In Italian ALS population, different screening have been performed [2, 18] and both confirmed that the percentage of mutation in SOD1 gene in Italian SALS was 4.5%.

About FALS the percentage of SOD1-mutated FALS patients was 14.7% [18]. In the most recent screening of 480 SALS patients in 48 FALS has been found that the percentage of mutations was totally 2.1% [19].

Novel mutations are continuous discovered, the last one in Italian patient has been described in January 2012 [20].

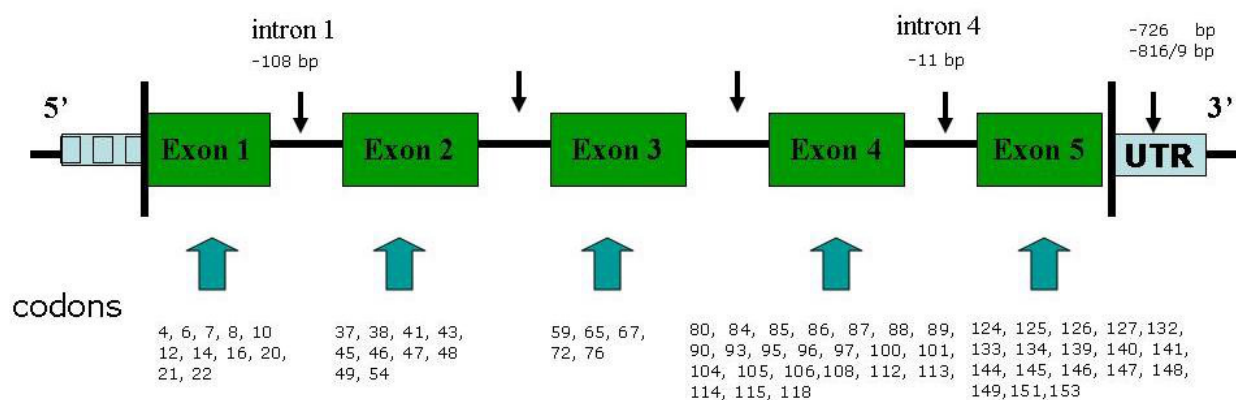


Figure 2. Distribution of *SOD1* mutations detected in sporadic ALS patients.

2.2. Phenotype

Patients with SOD1 mutations, FALS and SALS, show a phenotypic heterogeneity even within the same mutation although some sporadic missense mutations carry a consistently worse or better prognosis. A lot of mutations have been described during the time, we have focused in this paragraph on the most interesting in the Italian population for eventually presence of correlation between genotype and phenotype, both for FALS and SALS.

Patients with FALS and G41S mutations have similar clinical phenotype with early upper and lower motor neuron involvement in one or both lower limbs, rapidly spreading to upper limbs, appearance of bulbar signs within 1 years and death a few months later [21].

In 2010 Battistini et al. [22] described a family with 9 members ALS affected, in which there was evidence of a missense mutation in exon 4 (L106F) in SOD1 gene. In this family there was autosomal dominant inheritance. The clinical presentation was characterized by relatively

early age of onset, spinal onset with proximal distribution weakness, bulbar involvement and a rapid disease course about two years.

Another mutation, L106P, has been found in a patient who presented similar clinical pattern with spinal onset with weakness mainly in proximal areas; however in this patient, 30 months after disease onset, weakness remained restricted to the upper limbs without pyramidal signs and it was consistent with brachial amyotrophic diplegia, a relatively slowly progressive variant of motor neuron disease [23].

Corrado et al. [2] suggested that the nonsense mutation in exon 5 was present in SALS patients with severe and rapid clinical course, analogous to what found for most SOD1 mutations leading to a truncated protein. Conversely, N65S and A95T are both associated to a slowly progressive course of the disease, similarly to other mutations (H46R, D76V, H13T, L144P, G93V, I151T, D90A, A89T) detected in patients with a disease duration >10 years. In addition N65S seems to be strictly correlated to a prevalent involvement of the lower motor neurons and only at the spinal cord.

In 2011 in their article, Del Grande et al. [3] showed a similar phenotype in three unrelated patients with sporadic SOD1 mutation D11Y: slow progression, initial distal limbs muscles involvement and predominant lower motor neurons signs. The topographic distribution in distal muscles was a constant feature over many years, with only late impairment of proximal or bulbar muscles (respiratory muscles involvement after 7-10 years). All three patients had slight pyramidal signs (hyperactive reflexes, Babinski sign without increase of muscular tone).

In 2011 Luigetti et al. [24] described a strange case report of a sporadic patient with SOD1 G93D mutation disclosing a rapid progression of the disease. The beginning of symptoms was weakness in upper limbs, without involvement of lower limbs or bulbar functions. Over a 2-year-follow up the patient showed a rapidly progressive course with involvement of lower limbs, bulbar and respiratory muscles and the patient died after 30 months since the onset.

This case is in contrast with literature data [25-27]: other patients with SOD1 mutation (FALS) presented a slowly progressive disease with a long-lasting paucisymptomatic phase. The authors discovered a novel heterozygous ANG missense mutation (c. 433 C>T, p.R145C), so they hypothesised a role in pathogenesis and clinical phenotype [24].

Penco et al. [28] described a family with same mutation of SOD1, in which there was wide variability of disease expression among family members. The ANG IVS1+27 variant in the heterozygous state was found in the proband that disclosed an aggressive clinical course. Though this variant occurred in noncoding region and no prediction of splicing alteration was made, the authors speculated that this variant contributed to the clinical phenotype.

These findings support a possible pathogenetic role of ANG mutation with influence on clinical manifestations in patient with SOD1 mutation.

Often bulbar onset is associated with older age of disease presentation without significant difference of distribution between FALS and SALS [21].

These data are confirmed by international literature [29-32].

3. TAR DNA-Binding Protein 43 (TARDBP gene)

TAR DNA-binding protein 43 is homologous to the heterogeneous nuclear ribonucleoproteins (hnRNPs) [33], which are involved in RNA processing, and its abnormal cellular distribution is one of the key features of ALS and frontotemporal lobar degeneration (FTLD) [34].

The protein is highly conserved, widely expressed and predominantly localized to the nucleus with a very small amount being present in the cytoplasm [34-35].

3.1. Genotype

The human *TARDBP* gene (Entrez Gene ID 23435) is located on chromosome 1p36.22, and it codes for a protein of 414 amino acids.

Mutations in *TARDBP* gene associated with ALS disease have been discovered for the first time in 2008 [34, 36].

The proposed mutational frequency is ~5% for FALS and 0.5-2% for SALS. To date, more than 30 different TARDBP mutations have been described, all of which are missense substitutions. With a single exception, all of them are clustered in the C-terminal glycine-rich region encoded by exon 6. The most common mutation is A382T.

Mutations in *TARDBP* gene associated with ALS disease have been discovered for the first time in 2009 and in the same year a Italian screening has been performed [9]. The Italian results showed a higher frequency of *TARDBP* mutations in SALS Italian patients compared to individuals of mainly Northern European origin (2.7% vs. 1%).

The frequency of mutations in *TARDBP* gene in Italian patients (4.4%) are similar to other population studies (about 3 to 4% of FALS cases) [37, 38].

Most *TARDBP* mutations are missense changes in exon 6, encoding for Gly-rich C-terminal region that allows to bind single-stranded DNA, RNA and proteins [39, 40] (Figure 3).

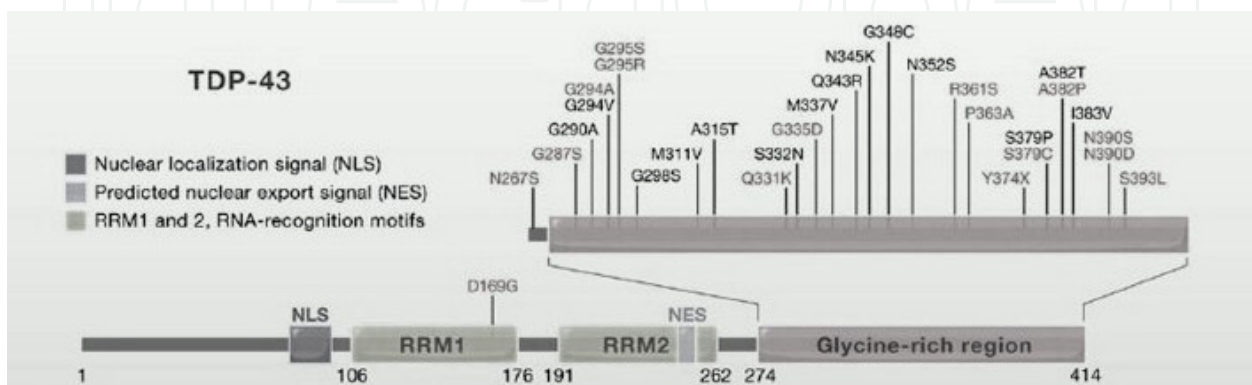


Figure 3. Distribution of TDP-43 mutations detected in sporadic ALS patients [41].

3.2. Phenotype

Many individuals who present with a pure ALS phenotype also develop pathological features of FTD and vice versa. Recently TDP-43 is identified as the major protein of inclusions in FTD and ALS brain tissues, suggesting that both degenerative diseases belong to a clinico-pathological spectrum of overlapping central nervous system disorders. Dominant mutations in the gene encoding the deposited protein account for at least some cases of these diseases.

Corrado et al. [9] described 12 different missense mutations in TARDBP, all located in exon 6, in 18 patients with ALS, both FALS and SALS. Patients don't share a homogeneous clinical phenotype: the average age at onset is 53,2 +/- 14,5 years, the site of onset is mainly spinal (88%), disease duration varies from 17 to 87 months. But in contrast to what is expected from the similarity of TDP-43 pathological deposits in ALS and FTD, none of patients tested worldwide with FTD carried TARDBP mutations. On the contrary, a TARDBP mutation (p.G294V) is discovered in patients with ALS and dementia of Alzheimer type. He developed dementia 3 years before the onset of MND. It is possible that the concurrence of the two diseases is only by chance.

Piaceri et al. [42] described clinical heterogeneity in patients with ALS and mutations in TARDBP. Age at onset is between 49 and 62 years, site of onset is both spinal and bulbar with different involvement of upper or lower motor neuron, disease duration varies from 9 to 85 years. Nobody has FTD. One patient has p.ALA382Thr mutation in exon 6.

In literature also [9, 36] this mutation is associated with some differences in phenotype, that are in site of onset (bulbar-spinal in France and spinal in Italy), disease duration (28-73 months in France, 17-60 months in Italy) and age at onset (50 years in France, 32-69 years in Italy). Italian and French patients shared a common haplotype with allele D1S2667 and D1S489, so there was a common founder for the mutation.

Literature datas [43] suggested that in TARDBP patients site of onset is in the upper limbs, with both upper and lower motor neuron signs but with disease progression lower signs became predominant. Age at onset is mean of 54 years, disease duration mean of 58 months. Some patients presented cognitive impairment that met criteria for FTD.

4. Fused in Sarcoma, Translocated in LipoSarcoma (FUS/TLS gene)

Fused in Sarcoma, Translocated in LipoSarcoma (FUS/TLS) is a heterogeneous ribonucleoprotein (hnRNP) that is involved, as TARDBP, in RNA splicing, transportation and stabilization [38, 44]. FUS/TLS (fused in sarcoma/translocated in liposarcoma) was initially identified by investigators as a component of fusion proteins found in a variety of cancers such as myxoid liposarcoma, acute myeloid leukemia, and Ewing's tumour. More recently, researchers have found several mutations of FUS/TLS in ALS and FTL D (frontotemporal lobar degeneration) patients that causes cytoplasmic mislocalization of FUS/TLS.

4.1. Genotype

The human *FUS/TLS* gene (Entrez Gene ID 2521) is located on chromosome 16p11.2, and it codes for a protein of 525 amino acids.

Mutations in *FUS/TLS* gene in ALS patients have been discovered for the first time in 2009 [37, 45], as *TARDBP*.

Following the original reports [37, 45], several other groups identified additional variants in ALS cohorts of different ethnicities, proposing an overall mutational frequency of ~4% in FALS and ~1% in SALS [46, 47, 48].

To date more than 30 different mutations have been described, the vast majority of which are missense substitutions and the rest are frameshift or nonsense mutations (Figure 3).

In the next year a Italian screening has been performed [10]. The results of the Italian screening are in accord with the interanation screening. The Italian data showed that the percentage of *FUS* missense mutations is 0.7% of Italian SALS cases, 4.4% in FALS.

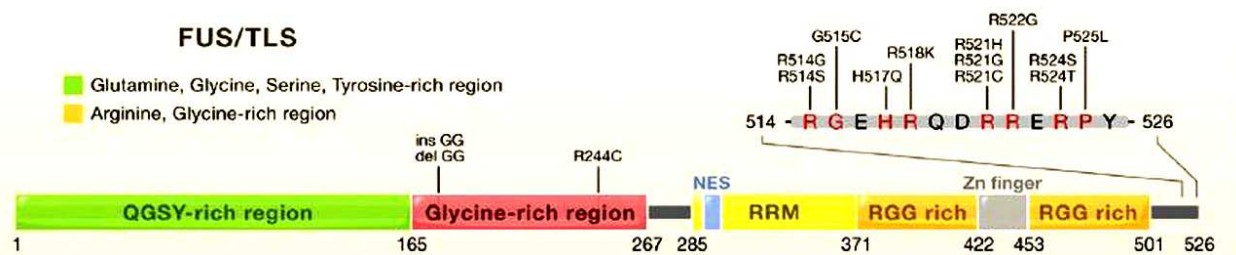


Figure 4. Distribution of *FUS* mutations detected in sporadic ALS patients [41].

4.2. Phenotype

In 2010 Corrado et al. [10] identified 9 SALS or FALS patients carrying *FUS* missense mutations. Site of onset was both in upper and lower limbs, age at onset was lower (median 50 years). One of these patients with sporadic ALS and *FUS* mutation presented, at the age of 34, bilateral scapular girdle muscle weakness with unusual neck flexor/extensor muscle weakness with cramps and fasciculations, no weakness in the lower limbs has been demonstrated. Another patient with FALS and *FUS* mutation, at the age of 54, slowly developed weakness of the neck flexor/extensor muscles and bilateral scapular girdle and proximal upper limb muscle weakness, with subsequent impairment of the pelvic girdle, no bulbar involvement has been shown but slight proximal weakness in the lower limbs; one year after onset, the symptoms extended to the bulbar region. So these two patients developed an unusual proximal symmetrical upper limbs onset and axial involvement.

Ticozzi N et al. in 2009 [49] described two patients with FALS and mutation of *FUS* that presented the same clinical phenotype.

In 2011 Lai SL et al. [50] described 4 Italian patients with sporadic ALS and FUS mutations (p.Y66Y, p.G507D, p.R521C, p.R521H). All of these cases initially manifested limb weakness and symptoms onset was before 50 years of age in more cases.

In 2009 Chiò et al. [51] described a patient with mutation in FUS and a very young age at onset (<30 years) with a bulbar presentation and a short duration.

In literature [37, 45] confirmed this correlations between genotype and phenotype in FUS mutations in ALS both FALS and SALS patients.

Millecamps S et al. [43] suggested that FUS patients had a shorter lifespan, more rapid disease, younger onset than other mutations.

5. Angiogenin (ANG)

Angiogenin is a angiogenic ribonuclease whose activity is related to its ability in regulating ribosomal RNA (rRNA) transcription. ANG induces angiogenesis by activating vessel endothelial and smooth muscle cells and triggering a number of biological processes, including cell migration, invasion, proliferation, and formation of tubular structures [52].

5.1. Genotype

The human *ANG* gene (Entrez Gene ID 283) is located on chromosome 14q11.1-q11.2, and it codes for a protein of 147 amino acids.

ANG, encoding a 14 kDa angiogenic ribonuclease, is the first loss-of-function gene identified in ALS. Since original discovery of *ANG* as an ALS candidate gene, a total of 15 missense mutations in the coding region of *ANG* have been identified in 37 of the 4,193 ALS patients. Among them, 10 have been characterized in detail and shown to be loss-of-function mutations. *ANG* gene has been found mutated in 2.3% of FALS and 1% of SALS patients [53].

The percentage of *ANG* gene mutations has been confirmed in the Italian ALS population [11].

5.2. Phenotype

Gellera et al. [11] identified 9 patients with new *ANG* mutation, 6 SALS and 3 FALS. Two patients presented bulbar onset, while 7 patients spinal onset. Patients with P-4S mutation presented signs of LMN involvement in both legs at age of 55 years and subsequently a rapidly progressive course with signs of UMN and LMN involvement. Two patients had G20G mutation but two different clinical course: first patient had slowly progressive lower limb onset MND at age 62 with prevalence of LMN signs and 3 years later manifested cognitive dysfunction of frontal lobe type, second patient presented distal weakness of upper limb at age 21 with a slowly progressive course characterized by prevalence of LMN signs. SALS Patient with V113I mutation developed spasticity of the right arm and atrophy of the right hand muscles at age 51, one year later the same symptoms appeared in the controlateral upper limb with prevalence of UMN signs. Patient with H114R mutation started with bulbar signs at age of 68.

Patients with previously described I46V mutation presented distal weakness of lower limbs, predominance of LMN signs, slow course of disease (only in one case more rapid with bulbar involvement). Age at onset was between 50-60 years.

So there was a wide phenotypic variability in these patients, for both district of onset and involvement of UMN/LMN.

Greenway et al. [53] reported that bulbar onset was more frequent in patients with ANG mutations.

6. Chromosome 9 open reading frame 72 (C9orf72)

Chromosome 9 open reading frame 72 is a protein localized on plasma membrane and cytoskeleton. There are two isoforms of C9orf72 that are produced as a result of alternative splicing events and the molecular weight of C9orf72 isoforms is 54/25 kDa. Normally, it is nuclear protein, even if the mutated form has been described in the cytoplasm [54].

6.1. Genotype

The human C9orf72 gene (Entrez Gene ID 203228) is located on chromosome 9p21.2, and it codes for a protein of 481 amino acids.

Recently, a hexanucleotide repeat expansion within the C9orf72 gene was identified as the cause of chromosome 9p21-linked ALS-FTD [54, 55].

About the Italian population, a screening C9orf72 in a large cohort of 259 familial ALS, 1275 sporadic ALS, and 862 control individuals has been performed [12]. It has been found RE in 23.9% familial ALS, 5.1% sporadic ALS, and 0.2% controls. Two cases carried the RE together with mutations in other ALS-associated genes.

Genotype data revealed that 95% of RE carriers shared a restricted 10-single nucleotide polymorphism haplotype within the previously reported 20-single nucleotide polymorphism risk haplotype, detectable in only 27% of nonexpanded ALS cases and in 28% of controls, suggesting a common founder with cohorts of North European ancestry. Although C9orf72 RE segregates with disease, the identification of RE both in controls and in patients carrying additional pathogenic mutations suggests that penetrance and phenotypic expression of C9orf72 RE may depend on additional genetic risk factors.

6.2. Phenotype

Ratti et al. [12] observed that the phenotype of RE carriers was characterized in higher proportion by bulbar-onset compared with nonexpanded patients, while in individuals with spinal onset expanded patients displayed an early involvement of the upper limbs less frequently than other patients, with predominance of upper motor neuron signs. RE carriers had a shorter survival compared with noncarriers. There was a correlation between more frequent bulbar onset in expanded patients and shorter survival time. The concurrence of FTD

was significantly higher in expanded cases compared with wild type individuals and also ALS-FTD patients with RE manifested cognitive behaviour before the onset of motor symptoms. In most cases the phenotype was compatible with a behavioural variant of FTD and frequently dominated by psychiatric symptoms, such as visual hallucination, paranoid behaviour with persecutory delusions, aggressive behaviour and/or suicidal thoughts.

Reports in literature were in according [56-59].

Extrapyramidal and cerebellar signs were also observed in two patients, while a patients presented continuous lingual myoclonus at disease onset. These cases suggested that clinical phenotype associated with RE in C9orf72 may be broader than originally thought, possibly involving extramotoneuronal structures such as the basal ganglia, cerebellum, brainstem nuclei.

Sabatelli et al. and Chiò et al. [60, 61, 62] studied clinical phenotype of patients with repeat expansion in large population and also two Sardinian families with neurodegenerative diseases (FTD-ALS) in which mutations in different genes (TARDBP p.A382T mutation and repeat expansion GGGGCC C9orf72) co-existed as pathogenetic causes, giving varied phenotypes.

7. Optineurin

Optineurin is an inhibitor protein that play an important role in the maintenance of the Golgi complex, in membrane trafficking and in exocytosis. Alternative splicing results in multiple transcript variants encoding the same protein., three different isoforms are known.

7.1. Genotype

The human *OPTN* gene (Entrez Gene ID 10133) is located on chromosome 10p13, and it codes for a protein of 577 amino acids. In 2010 *OPTN* mutations have been described, for the first time, in ALS patients [63]. In the first paper about *OPTN* mutation three type of mutation have been found, two point mutation and one deletion. In 2011, a screening in the Caucasian population in SALS and FALS patients showed that *OPTN* mutations causing ALS are rare, especially in mainly Caucasian ALS subjects [64]. About Italian population, Del Bo and collaborators screened 274 ALS patients, 161 FALS and 113 SALS and the results showed six novel variants in both FALS and SALS patients, all occurring in an heterozygous state [13]. This data support the involvement of *OPTN* in ALS, especially in FALS patients, due to the 1.2% cases found mutated [13].

7.2. Phenotype

Del Bo et al. [13] suggested that ALS patients carrying *OPTN* mutations showed a prevalent lower-limb onset, with large variable age of onset (from 24 to 71 years of age) and progression (very aggressive forms with survival time < 1 year and very slow disease course over 10 years)

with no differences between SALS and FALS patients. Many patients were characterized by a prevalence of upper motor neuron signs.

8. Conclusions

Amyotrophic Lateral Sclerosis is a multifactorial and multigenic disease with still unknown aetiology and pathogenesis. We know many causative mutations in particular genes, both in familial and sporadic patients, and different clinical presentation of ALS. Genetic factors may play a role in determining the range of ALS phenotypes although in this moment no genes have been demonstrated to have a definite effect on phenotype (Chiò et al., 2011) [4]. Heterogeneity between and among families and patients with same mutation suggests that environmental and other influences contribute to not only the rate of evolution and which signs predominate but also whether the disease will appear at all during life.

In this chapter we have identified cases in which connection between phenotype and genotype is possible and relevant.

We started from the ALS patients part of the recruitment of our Institute to define the possible clinical features that may be related to specific genes alteration.

For ALS patients with mutations in some genes, such as *SOD1*, there are an important clinical phenotypic heterogeneity at onset and during evolution of disease, different time of survival and velocity of progression with rapidly or slowly involvement of bulbar functions.

TARDBP is involved both in pathogenesis of frontotemporal dementia and ALS, but it's not sure that all patients with ALS will develop FTD and they don't demonstrated an homogenous clinical pattern.

In particular we will focus attention on connection between *FUS* mutations, and clinical presentation with upper limbs onset, developed weakness of the neck flexor/extensor muscles and bilateral scapular girdle and proximal muscle. In many cases this phenotype is correlated with rapidly bulbar evolution and frontotemporal behaviour alterations, with negative prognosis in short time. This focus is in particular due to the presence of *FUS* mutated patients in our cohort and the "poverty" of the literature about *FUS* and clinical features.

Another interesting suggestion is that sometimes mutated patients (i.e. *SOD1*) can have particular clinical course modulated by other causative or associated modified genes (*ANG*). It is an important issue that maybe indicates a central role of genotype in developing phenotype.

For other genes it's difficult discovering association between genotype and phenotype for rarity of manifestation compared with more frequent mutations.

In conclusion, at this time, in front of a patient with ALS, a neurologist should has some "milestones" considering clinical phenotype:

- if patient's history suggests a familial form, it is important to perform a screening of four principal genes (SOD1, TARDBP, FUS, C9ORF) because they cover more than 50% of FALS;
- if onset of disease is in early age, the probability of a mutation is high and four principal genes are still first candidates in SALS;
- if patient presents frontotemporal characters or premature respiratory involvement, TARDBP, FUS, C9ORF are essential in screening;
- if clinical phenotype is characterized by proximal muscles involvement in upper and/or lower limbs, FUS has to be suspected.

Our idea is that a specific mutation can cause a particular clinical onset, involvement and evolution of ALS, with a pathogenetic mechanism still unknown.

On the other side, now we have some ideas for type of disease correlated with particular mutations (i.e. FUS and TARDBP give a early onset, short duration of disease for early bulbar involvement) but it's impossible predict exactly what kind of phenotype can be developed by patient.

Different genes are involved in ALS disease, the importance of a good clinical characterization may help in choosing the genetic approach. We hypothesized that in the future, the symptoms observation may became more specific to indicate which gene is the most probably mutated. This idea may proceed in the same time of a better collaboration between clinicians and biologist to create a direct link from bed to bench.

This approach may be relevant for diagnostic use, so starting from neurological exam, that remains the essential element, and we can formulate diagnostic hypothesis that it can be surely confirmed by genetic test.

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