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Motor neuron diseases

Genetics of amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease characterized by upper and lower motor neuron damage in the bulbar and spinal territories. Although the pathophysiology of ALS is still unknown, the involvement of genetic factors is no longer a subject of debate. Familial ALS (fALS) accounts for 10–20% of cases. Since the identification of the *SOD1* gene, more than 20 genes have been described, of which four can explain >50% of familial cases. This review is an update focused on major aspects of the field of ALS genetics concerning both causative and susceptibility factors.

1. Introduction

Amyotrophic lateral sclerosis (ALS) may be considered the most frequent of the rare diseases. The neurodegenerative condition is characterized by progressive and diffuse paralysis, leading to death by respiratory failure after a median survival of 36 months from first symptoms [1]. ALS is clinically a combination of upper motor neuron (UMN) and lower motor neuron (LMN) signs in the bulbar and spinal territories.

Despite the vast literature on ALS, its pathophysiology remains poorly understood, although the involvement of genetic factors has been clearly demonstrated, especially for familial ALS (fALS) patients [2]. fALS, which accounts for 10–20% of cases, is classically transmitted within families through dominant inheritance of the pathological trait. Sporadic ALS (SALS), which accounts for the remaining 80–90% of cases, also involves genetic factors through an increased risk of the disease with certain haplotypes [3].

Our knowledge of the genetics of ALS has strongly profited from the progress made in sequencing and molecular biological technologies, which has allowed the identification of around 20 genes over the past 10 years (Table 1) [2].

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Table 1 – Genes and loci linked with familial amyotrophic lateral sclerosis (fALS).

fALS	Locus	Gene	Abbreviation	Inheritance	Clinical features	Hot spot
ALS1	21q22.1	Superoxide dismutase 1	SOD1	AD, AR	fALS	>150 mutations: A4V, D90A, G93C, I113T (most studies)
ALS2	2q33	Alsin		AR	Juvenile ALS	Rare mutations
ALS3	18q21	Unknown		AD	fALS	
ALS4	9q34	Senataxin	SETX	AD	Juvenile ALS	Main mutations: L389S, R2136H, T3I
ALS5	15q15-21.1	Spatacsin	SPG11	AR	Juvenile ALS	Multiple spots
ALS6	16q12	Fusion, derived from 12 to 16 translocation, malignant liposarcoma	FUS/TLS	AD–AR	fALS	Codon 521
ALS7	20p13	Unknown		AD	fALS	
ALS8	20q13.33	Vesicle-associated membrane protein B	VAPB	AD	fALS	Main mutation: Pro56Ser
ALS9	14q11	Angiogenin	ANG	AD	fALS	Missense mutations: K17I, K17E
ALS10	1p36.22	TAR DNA-binding protein 43	TARDBP	AD	fALS	Main mutations: A315, G348C, A382T
ALS11	6q21	FIG4 phosphoinositide 5-phosphatase	FIG4	AD	fALS	Rare mutations
ALS12	10p15	Optineurin	OPTN	AD, AR	fALS	Codons 398, 478
ALS13		Ataxin-2	ATXN2	AD	fALS	CAG repeats 27–33
ALS 14	9p13	Valosin-containing protein	VCP	AD	fALS	Codons 151, 155, 159, 191, 592
ALS15	Xp11	Ubiquilin 2	UBQLN2	X-linked	fALS	Main mutations: Pro497His, Pro497Ser, P506T, P509S, P525S
ALS16	9p13.3	Sigma-1 receptor	SIGMAR1	AR	fALS	Codon 102
ALS 17	3p11	Charged multivesicular body Protein 2B	CHMP2B	AD	fALS	Codons 29, 104, 206s
ALS18	17p13	Profilin 1	PFN1	AD	fALS	Rare mutations
ALS 19	2q34	Chorion protein gene ErB.4	ERBB4	AD	fALS	Codons 927, 1275
ALS 20	12q13	Heterogeneous nuclear ribonucleoprotein A1	HNRNPA1	AD	fALS	Rare mutations
ALS 21	5q31	Matrin 3	MATR3	AD	fALS	Codons 622, 154, 85
ALS 22	2q35	Tubulin alpha-4A	TUBA4A	AD	fALS	Rare mutations
ALS	12q24	D-Amino acid oxidase	ADO	AD	fALS	Rare mutations
ALS	9q34		GLE1	AR	fALS	Rare mutations
ALS	20q13	Synovial sarcoma translocation gene on chromosome 18-like 1	SS18L1		fALS	Rare mutations
FTD–ALS1	9p21	Chromosome 9 open reading frame 72	C9ORF72	AD	ALS, FTLD, ALS–FTD	GGGGCC repeats >30
FTD–ALS2	22q11	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10	CHCHD10	AD	ALS, FTLD, ALS–FTD	Codons 12, 15, 59, 66, 80
FTD–ALS3	5q35.3	Sequestosome 1	SQSMT1	AD	ALS, FTLD, ALS–FTD	Codons linked to ALS: 53, 259, 348, 439
FTD–ALS4	12q14.2	TANK-binding kinase 1	TBK1	AD	ALS, FTLD, ALS–FTD	Rare mutations

AD: autosomal-dominant; AR: autosomal-recessive; FTD: frontotemporal dementia; FTLD: frontotemporal lobar degeneration.

Genes linked to ALS can be divided into causative genes, which are pathogenic, and susceptibility genetic factors, which increase the risk of ALS. Genetic technologies have seen dramatic progress over the last few decades, with the evolution from linkage and polymorphism studies to whole-exome sequencing, genome-wide association studies and next-generation sequencing [4–6].

This updated review focuses on the major genetic findings thus far in the study of genetic factors linked to and associated with ALS, and presents, in succession, the major genes linked with ALS, the genes that need confirmation, the genes linked to ALS and frontotemporal dementia (FTD) and, finally, the recent susceptibility factors described in SALS.

2. Genes related to adult fALS

This involves family pedigrees with at least two ALS cases. Currently, the classification of fALS relies on either history or genetics and proposes three levels of certainty: definite, probable or possible [7]. Possible fALS is supported by ALS in a family member along with confirmed FTD [7].