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REVIEW ARTICLE

Genetics of primary lateral sclerosis

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Abstract

With the exception of rare, juvenile-onset, autosomal recessive cases, primary lateral sclerosis (PLS) has long been considered an exclusively sporadic motor neuron disease. However, the identification of PLS cases within pedigrees with familial amyotrophic lateral sclerosis (ALS), together with the clinical and neuropathological overlap with other neurodegenerative disease with strong genetic component such as ALS and hereditary spastic paraparesis (HSP), suggest the existence of a genetic component in PLS as well. Here we will review the genetics of juvenile PLS-like syndromes and the contribution of mutations in ALS and HSP-associated genes to PLS pathogenesis.

Keywords: *Genetics, PLS, neuropathology*

Introduction

Primary lateral sclerosis (PLS) is an adult-onset, neurodegenerative disorder primarily affecting the upper motor neurons (UMN) that originate the corticospinal and corticobulbar tracts, thus leading to widespread spasticity and bulbar involvement. Although previous diagnostic criteria required the absence of family history (1), mainly to differentiate PLS from the partially overlapping hereditary spastic paraparesis (HSP), rare pedigrees with multiple individuals affected with PLS have been described (2–6). This observation, together with the shared clinical and pathological features with other motor neuron disorders with high genetic component, mainly amyotrophic lateral sclerosis (ALS), raises the question whether there are genetic factors associated to PLS susceptibility as well. We will first examine the contribution of ALS-associated genes in PLS, then we will evaluate the genetic overlap between PLS and other diseases characterized by corticospinal tract degeneration such as HSP, and lastly we will describe the genetics of juvenile PLS-like syndromes (JPLS) (Table 1). To account for the possibility that any observed genetic overlap between PLS, UMN-predominant ALS and HSP may in fact be due to misdiagnosis of these three conditions, whenever feasible we applied the novel consensus criteria for the diagnosis of PLS to critically review available literature (7).

ALS-associated genes in PLS

The occurrence of ALS and PLS phenotypes within the same pedigrees, although extremely rare, suggests the existence of a common genetic background between the two diseases; however, genetic studies have demonstrated only a minimal degree of genetic overlap so far. In fact, among major ALS-associated genes (*SOD1*, *TARDBP*, *FUS* and *c9orf72*), only the $(G_4C_2)_n$ hexanucleotide repeat expansion in *c9orf72* has been rarely observed in PLS patients (8,9,15). The screening a Dutch cohort of 110 individuals with PLS revealed a single mutated case, accounting for a mutational

Table 1. Genes associated to primary lateral sclerosis.

Locus	Gene	Protein	Mutation type	Zygosity	Inheritance	No. cases	Phenotype	Atypical features	Allelic diseases	References
9p21.2	*c9orf72*	C9ORF72	$(G_4C_2)_n$ repeat	het	sporadic	3	PLS	PLS-CBS in 1 case	FTDALS1	(7–9)
6q21	*FIG4*	Phosphoinositide 5-phosphatase	MS	het	sporadic	2	PLS		ALS11, CMT4J	(10)
10p13	*OPTN*	optineurin	MS	het	sporadic	1	PLS		ALS12	(11)
Xp11.21	*UBQLN2*	ubiquilin 2	MS	hem	XD	1	PLS	ALS/PLS pedigree	ALS15	(12)
16q24.3	*SPG7*	paraplegin	MS	het	sporadic	1	PLS		SPG7	(13)
				comp het	AR	5				(14)
4ptel-4p16.1	*unknown*	unknown	unknown	unknown	AD	8	PLS			(3,4)
2p13.1	*DCTN1*	dynactin 1	MS	Het	sporadic	1	PLS		ALS, HMN VIIB, Perry syndrome	(13)
6q26	*PARK2*	parkin	MS	het	sporadic	1	PLS		PARK2	(13)
14q23.2	*SYNE2*	synaptic nuclear envelope protein 2	MS	het	sporadic	1	PLS		EDMD5	(13)
2q33.1	*ALS2*	alsin	NS, FS, MS	hom comp het	AR	>20	JPLS	saccadic gaze paresis	ALS2, IAHSP	(15–18)
8p11.23	*ERLIN2*	endoplasmic reticulum lipid raft-associated protein 2	intronic	hom	AR	4	JPLS	smooth pursuit disruption, skeletal deformities	ALS, SPG18	(19)

MS: missense; NS: nonsense; FS: frame-shift; het: heterozygous; hem: hemyzygous; comp het: compound heterozygous; hom: homozygous; XD: X-linked dominant; AD: autosomal dominant; AR: autosomal recessive; PLS: primary lateral sclerosis; JPLS: juvenile PLS; CBS: corticobasal syndrome; ALS: amyotrophic lateral sclerosis; FTD: frontotemporal dementia; SPG7: spastic paraplegia type 7; HMN VIIB: hereditary motor neuropathy type VIIB; PARK2: autosomal recessive Parkinson's disease type 2; EDMD5: Emery-Dreyfuss muscular dystrophy type 5; IAHSP: infantile-onset ascending spastic paralysis; SPG18: spastic paraplegia type 18.

frequency of 0.9% (8). Similar results were observed by Mitsumoto et al. which identified *c9orf72* repeat expansion in 1/41 PLS patients (2.3%) (9). Both patients were sporadic and fulfilled the novel consensus diagnostic criteria for definite PLS; one did present cognitive and behavioral impairment (9). The $(G_4C_2)_n$ expansion in *c9orf72* has also been described in an Italian patient with probable PLS which, three years after the onset of UMN signs, also developed dementia of frontal type, alien limb phenomenon and extrapyramidal features suggestive of a concurrent corticobasal syndrome (15).

Notwithstanding the general scarcity of information on genotype-phenotype correlation, several minor ALS-associated genes such as *ALS2*, *SETX*, *FIG4*, *OPTN*, *UBQLN2* and *SPG11* have been associated with UMN-predominant ALS phenotypes, although pathogenic mutations in adult-onset PLS cases have been reported only for a handful of them (10,16,20–24). Mutations in *FIG4*, a gene encoding for a phosphoinositide phosphatase involved in the phosphatidylinositol 3,5-bisphosphate signaling pathway, are associated to at least two neurological disorders: in compound heterozygous state they are responsible for CMT4J (OMIM #611228), a severe, recessively inherited sensorimotor neuropathy (25), while in heterozygous state they have been associated to the dominantly inherited ALS11 phenotype (OMIM #612577) (21). Interestingly, *FIG4* mutations have been described in two PLS patients with lower limbs onset at age 27 and 42, and at least one variant (p.R388G) appears to disrupt protein function in a yeast model (21). It must be noticed, however, that while presented clinical data appear to be consistent with a diagnosis of probable PLS for the patient carrying the p.R388G mutation in *FIG4*, no information on disease duration were reported for the other individual for which a diagnosis of UMN-predominant ALS cannot be ruled out in principle. In addition to this, other findings suggest an association between *FIG4* and corticospinal tract degeneration, such as the prominent UMN involvement in ALS mutated patients and the earlier and more extensive degeneration in the motor cortex compared to the spinal motor neurons in the pale tremor mouse (25).

Homozygous and heterozygous *OPTN* mutations have been observed in ALS12 (OMIM #613435), a phenotype characterized by a relatively slow progression (24). Del Bo et al. reported the occurrence of a p.T282P heterozygous variant in *OPTN* in an Italian patient with pure UMN involvement of the four limbs and the bulbar region, without neurophysiological evidence of lower motor neuron signs. The clinical phenotype and a disease duration >3 years were consistent with a diagnosis of probable PLS. Although absent from control databases, p.T282P shows a low level of conservation and was scored as neutral by *in silico* prediction tools (11). As such, it should be considered at present as a variant of uncertain significance.

Mutations in *UBQLN2* have been found in ALS15, an X-linked ALS type with or without associated frontotemporal dementia (OMIM #300857) (22). The clinical phenotype is characterized by an early age at onset and by the presence of widespread UMN signs. Gellera et al. observed a hemizygous p.P506S *UBQLN2* mutation in a familial patient with definite PLS which developed at age 30 a slowly progressive ascending paresis without clinical or neurophysiological signs of lower motor neuron involvement. The patient's mother had classic ALS, while a sibling presented with an early-onset, slowly progressive ALS, thus highlighting the phenotypic heterogeneity within FALS pedigrees (12).

HSP-associated genes and PLS

HSP are a group of highly heterogeneous neurodegenerative disorders characterized by progressive spasticity of the lower limbs associated with corticospinal tract dysfunction and degeneration. Although HSP are characterized by little to no involvement of the upper limbs and the bulbar region, the clinical overlap with PLS is often considerable. To date, more than 70 loci and genes have been associated to HSP, often displaying a striking phenotypic heterogeneity spanning the whole spectrum of neurodegenerative diseases, including motor neuron disorders (26). Network analysis also suggest the existence of considerable overlap between the genetic background of HSP and ALS (27).

For example, mutations in *SPG11* cause two recessively inherited motor neuron diseases, HSP11 (OMIM #604360) and ALS5 (OMIM #602099) (23,28). Similarly, *KIFA5*, originally associated to HSP10 (OMIM #604187) (29) is also responsible for the allelic disorder ALS25 (OMIM #617921) (30). Mutations in the HSP-associated genes *BSCL2* and *REEP1* can be observed in patients presenting with a combination of upper and lower motor neuron signs indistinguishable from ALS (31,32). The occasional finding of ALS patients carrying mutations in the *SPAST* and *SPG7* genes, which are respectively associated with the most frequently observed autosomal dominant and recessive types of HSP, further strengthen the genetic link between the two disorders (33–36).

Given these data, several groups have attempted to assess the genetic overlap between HSP and PLS as well. A screening of a small cohort of 8 PLS individuals from the UK did not

find any candidate mutation in the *SPAST* and *SPG7* genes (37). Conversely, a next generation sequencing study on 41 cases identified a p.A510V heterozygous mutation in *SPG7* in a single patient with definite PLS (9). Although *SPG7* mutations have been traditionally observed in patients with recessively inherited HSP, there is evidence that carriers of p.A501V may be at an increased risk of developing the disease, thus suggesting a pathogenic dominant effect for this variant (38). *SPG7* mutations have also been described to be associated with adult-onset, recessively inherited, familial PLS. By performing exome sequencing, Yang et al. identified compound heterozygous missense variants p.L695P and p.I743T in *SPG7* cosegregating with the disease in a PLS pedigree with 5 affected siblings (13). Although all patients had lower limb onset, the subsequent appearance of upper limb and bulbar symptoms and the absence of extramotor features clearly ruled out a diagnosis of complicated or uncomplicated HSP. Functional studies on the identified variants suggest that the mutant protein affect mitochondrial function when glucose is reduced.

Notwithstanding these isolated reports, available literature suggests that mutations in major HSP-associated occur very rarely in PLS patients.

Other PLS-associated genes

Given the rarity of the disease, and the exceptional occurrence of familial clusters, very few studies have attempted to identify novel PLS-associated genes. Dupré et al. described a large French Canadian family with adult-onset, progressive upper motor neuron disease consistent with a PLS phenotype and an autosomal dominant inheritance pattern (3). Genome wide linkage analysis revealed an association with a region on chromosome 4 (4ptel–4p16.1) with a maximum LOD score of 3.01 at marker D4S2936 (4). The sequencing of selected candidate genes within this locus, however, did not identify any pathogenic mutation.

To date, only a single study systematically screened a relatively large cohort of patients with definite PLS for disease-associated mutations using next generation sequencing technologies (9). In addition to the above mentioned finding of pathogenic mutations in *c9orf72* and *SPG7* in two sporadic patients, the study identified other variants of clinical interest, such as p.T1249I in *DCTN1*, previously observed in sporadic ALS (14), and p.R275W in *PARK2*, responsible for the most common type of autosomal recessive Parkinson's disease (PD) (OMIM #600116). A predicted pathogenic mutation was also observed in *SYNE2*, associated with Emery-Dreyfuss muscular dystrophy type 5 (OMIM #612999), as well as variants of uncertain significance in *VEGFA*, *CLN6*,

BTD and *LRKK2* genes. Collectively, these results suggest that the genetic background of PLS may overlap not only with other motor neuron diseases, but also with other neurodegenerative disorders.

Genetics of JPLS

Although PLS is traditionally considered to be a sporadic disease of adult middle age, a pure UMN syndrome has also been observed in children belonging to families with patterns consistent with autosomal recessive inheritance (39–41). The clinical phenotype is characterized by progressive degeneration of the corticospinal and corticobulbar tracts, which begins in the first two decades of life and slowly progresses to spastic tetraparesis with bulbar involvement. Cognition is spared, but gaze paresis is often observed in JPLS patients (39,42).

Following the mapping of a candidate locus to chromosome 2q33 (17), homozygous mutations in the *ALS2* gene were found to segregate with the disease in two large JPLS families from Saudi Arabia and Kuwait (16,20). Subsequent reports confirmed the association of *ALS2* mutations with the JPLS phenotype also in other ethnicities (42,43). The *ALS2* gene, encoding for the protein alsin, is composed of 34 exons. Through alternative splicing after exon 4, it generates two different transcripts of 6.5 and 2.6 kb, respectively resulting in a 1657-residue (long form) and 396-residue (short form) protein. The majority of *ALS2* mutations described so far are frameshift indels resulting in a prematurely truncated protein, or nonsense mutations. Interestingly, mutations disrupting both transcripts of alsin cause ALS2, a juvenile-onset ALS phenotype which combines upper and lower motor neuron degeneration (16,18,20,44–46), while those altering only the long form are responsible for an isolated involvement of the pyramidal tracts, resulting in the milder, allelic phenotypes of JPLS and infantile-onset ascending hereditary spastic paraparesis (47–55). Notwithstanding their causative role in juvenile-onset motor neuron disorders, *ALS2* mutations have not been observed so far in adult PLS patients (3,4,56).

Alsin putative function is to act as a guanine exchange factor for small GTPases at the cytosolic face of endosomal membranes (57), thus playing a role in vesicular trafficking, cytoskeletal organization and endosomal dynamics. Interestingly, it appears that corticospinal motor neurons present a selective vulnerability to *ALS2* loss-of-function mutations, through mitochondria and Golgi apparatus dysfunction (58).

A second gene associated to JPLS, *ERLIN2*, was identified in 2012 by performing autozygosisty mapping followed by DNA sequencing in a consanguineous family from Saudi Arabia with four

affected siblings (59). The first symptoms appeared in all patients in the first months of life and progressed to complete loss of speech and articulation by the age of 2 and of ambulation by the age of 12. Cognition was apparently normal, but ocular movement abnormalities with disruption of smooth pursuit could be observed. Skeletal deformities were also part of the phenotype. The observed mutation causes the activation of a cryptic splice acceptor site in intron 7 of *ERLIN2*, and the inclusion of a sequence of intronic nucleotides containing a stop codon, leading in turn to loss of protein function through nonsense-mediated mRNA decay (59). Similarly to *ALS2*, mutations in *ERLIN2* also display a degree of phenotypic heterogeneity spanning different motor neuron disorders, having also been observed in juvenile ALS (19), and a complicated form of hereditary spastic paraplegia with intellectual disability and skeletal abnormalities (SPG18) (60).

Conclusions and future perspectives

Until now, research on PLS genetics has been severely hindered by several factors. The first and foremost issue is the rarity of the disease itself, which study makes difficult to recruit sizeable cohorts for genetic screening. To compound this, the criteria proposed by Pringle et al. require the absence of familial history for motor neuron disorders (1), thus excluding from most PLS cohorts those patients with a higher likelihood of carrying pathogenic mutations. A recent effort to report genetic variants in PLS has been completed, aiming to better identify PLS patients, reducing diagnostic delay using more updated consensus diagnostic criteria (7). As a result, in the past the few genetic studies on PLS mostly adopted a traditional candidate gene approach, which is inherently limited by the existing *a priori* knowledge on disease pathomechanisms, and often yields results that do not stand the reproducibility test. A new effort has been made to initiate a large natural history of PLS using PLS-FRS, and DNA biosamples are the principal part of the study. In order to unravel the puzzle of PLS genetics, it will be thus crucial to study ever larger PLS cohort through international collaborative efforts, and to exploit the opportunities offered by innovative, Next Generation Sequence (NGS)-based analytical strategies that allow for a hypothesis-free, genome-wide scan for rare, disease-associated variants.

Declaration of interest

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