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Clinical and genetic aspects of hereditary spastic paraplegia in patients from Turkey

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ABSTRACT

Objectives. Hereditary spastic paraplegias (HSPs) are a heterogenous group of rare neurodegenerative disorders that present with lower limb spasticity. It is known as complicated HSP if spasticity is accompanied by additional features such as cognitive impairment, cerebellar syndrome, thin corpus callosum, or neuropathy. Most HSP families show autosomal dominant (AD) inheritance. On the other hand, autosomal recessive (AR) cases are also common because of the high frequency of consanguineous marriages in our country. This study aimed to investigate the clinical and genetic aetiology in a group of HSP patients.

Patients and methods. We studied 21 patients from 17 families. Six of them presented with recessive inheritance. All index patients were screened for *ATL1* and *SPAST* gene mutations to determine the prevalence of the most frequent types of HSP in our cohort. Whole exome sequencing was performed for an AD-HSP family, in combination with homozygosity mapping for five selected AR-HSP families.

Results. Two novel causative variants were identified in *PLP1* and *SPG11* genes, respectively. Distribution of HSP mutations in our AD patients was found to be similar to European populations.

Conclusion. Our genetic studies confirmed that clinical analysis can be misleading when defining HSP subtypes. Genetic testing is an important tool for diagnosis and genetic counselling. However, in the majority of AR HSP cases, a genetic diagnosis is not possible.

Key words: hereditary spastic paraplegia (HSP), atlastin (*ATL1*), spastin (*SPAST*), *PLP1*, rare diseases, Pelizaeus-Merzbacher Disease (PMD), *SPG11*

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Introduction

Hereditary spastic paraplegias (HSPs) are clinically and genetically heterogenous and constitute a large group of rare neurodegenerative disorders. The main symptom of the disease is a pyramidal tract dysfunction which affects primarily the lower extremities, accompanied by mildly decreased vibration sensation and urinary urgency. Neurological examination of patients with HSP reveals hyperreflexia in lower limbs, Babinski sign and spastic gait.

HSP is clinically classified as 'uncomplicated' (pure) or 'complicated' [1]. Uncomplicated HSP symptoms may emerge from early childhood through to late adulthood and do not shorten the lifespan. Clinical characteristics are as described above. The disease is referred to as 'complicated' HSP in the presence of accompanying features such as ataxia, seizures, mental retardation, cognitive impairment, dementia, amyotrophy, extrapyramidal disturbance, ichthyosis, deafness or peripheral neuropathy [1].

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Common to both uncomplicated and complicated HSPs is the degeneration of the corticospinal tract in the central nervous system (CNS). The degeneration is axonal and retrograde and affects the distal parts of the longest axons in both the corticospinal tract and the posterior columns. For this reason, this pathology is called 'dying back axonopathy' [2]. The genetic causes that lead to deterioration of function of the corticospinal tract axons are the subject of major interest in HSP research, and these studies have revealed at least 72 subtypes [3].

HSPs are also classified according to their mode of inheritance as autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL). Most uncomplicated HSPs are inherited in the AD pattern. Spastic paraplegia type 3A (SPG3A) and type 4 (SPG4) are the most common forms, comprising up to 45% of cases [4–6]. Complicated HSP is generally transmitted with AR inheritance, and the most common subtype is spastic paraplegia type 11 (SPG11) [3, 4, 7].

Clinical diagnosis of HSP requires the exclusion of other causes in patients with spastic gait [1]. Identifying the HSP subtype by clinical investigation can be highly challenging, especially in uncomplicated HSPs since the patients present with clinical similarity. Magnetic resonance imaging (MRI) of the brain and spinal cord are usually normal, and family history does not always reveal similarly affected relatives [1]. Genetic testing is useful in confirming the clinical diagnosis and for genetic subtype identification. However, due to the presence of unknown causative genes and technical problems, approximately half of all HSP cases cannot be genetically diagnosed [8].

We investigated the clinical and genetic features of HSP in our patient group. The aim of this study was to determine the prevalence of the most frequent subtypes of HSP, namely SPG3A and SPG4, in our cohort, and to investigate the genetic aetiology with whole exome sequencing (WES) in selected families.

Patients and methods

Twenty-one patients from 17 different families with progressive symptoms of spastic paraparesis were included in the study. All patients were negative for vitamin B12 deficiency, serum lactate, pyruvate elevation, demyelinating diseases, L-dopa responsive dystonia, and infectious diseases. Routine cerebrospinal fluid examination was normal in all patients and their MRIs showed no evidence of structural abnormalities of the brain or the spinal cord. Informed consent was obtained from all the patients and their recruited family members in accordance with the approval of the Ethics Committee of Istanbul Medical Faculty. Clinical data was collected from each patient according to a standardised scheme (see Tab. 1 and supplementary data).

Genomic DNA was isolated from peripheral blood using standard protocols. All index patients were screened for *ATL1* and *SPAST* gene mutations for a possible genetic diagnosis of SPG3A and SPG4, respectively. Exons and exon-intron boundaries of the genes were investigated for sequence variations by direct sequencing. For two patients, single strand conformation polymorphism (SSCP) was used to determine possible variants. Multiple ligation-dependent probe amplification (MLPA) was performed to investigate *SPAST* deletion in nine individuals (six isolated cases and three patients from AD-HSP families) that were negative for *SPAST* mutations.

Among the *ATL1* and *SPAST* negative families that had more than one affected individual, six families volunteered to participate in a further genetic study. DNA samples of the index patients (F1, F3.1, F5.1, F6.1, F9.1 and F14) from these families were analysed by WES. The analysis was outsourced with criteria of 50x coverage and 100bp paired-end reads. In WES data, variants in the known HSP genes were analysed initially and subsequently all variants in homozygous or heterozygous states were stringently filtered [9].

To find the candidate variants in four families with possible autosomal recessive inheritance, SNP genotyping and homozygosity mapping were performed. Illumina Infinium OmniExpress-24 array was used to analyse SNPs of two affected individuals chosen from each family. Homozygous regions of the patient F1 were determined from WES data by using the PLINK program since DNA samples from other affected family members were not available.

Candidate variants were analysed by Sanger sequencing in available siblings and parents. The novelty of an identified variant was evaluated using the Genome Aggregation Database (GnomAD). SIFT and Polyphen tools were used to predict the potential effects of novel non-synonymous variations on the protein structure or function.

Results

In this study, 17 families were investigated. Eight families were classified as uncomplicated and nine as complicated. The majority of the patients were male (13/21). The features of the complicated phenotype were: cerebellar syndrome (8), polyneuropathy (3), learning and intellectual disability (3), epilepsy (1), and hyperpigmentation (1). Average age at onset was 14.3 ± 10 years for uncomplicated HSP and 23.4 ± 11 for complicated HSP. Thin corpus callosum (CC) (6) was the most common anomaly in the MRI, with T2 white matter abnormalities (5), dorsal spinal atrophy (3), and cerebral (4) and cerebellar atrophy (1) respectively.

The *ATL1* and *SPAST* gene mutation screening revealed an *ATL1* (NM_015915) heterozygous c.773A > G; p.His258Arg variant in patient F2. This patient had an early onset uncomplicated HSP with AD inheritance pattern (Tab. 1). The MLPA analysis in F16 showed a heterozygous deletion of exon 17 of *SPAST* gene. This patient had a late onset uncomplicated HSP. Brain and spinal MRI investigations were normal in both. No

Table 1. Clinical and genetic findings of the patients

Patient ID	Sex	Cons§	Possible heredity	HSP type	Onset age	Initial symptom	MRI (brain and spinal)	Additional neurological features	Age at exam	Mental and motor development	EMG	Contractures, deformities and other features	Genetic results
F1	Male	+	AR/XL	complicated	48	walking difficulty	minimal dorsal spinal atrophy	dysarthria, ataxia, dysmetria	62	Normal	Sensory & motor axonal polyneuropathy	Negative for SCA1,2,3,6 nucleotide expansion	Undiagnosed (WES)
F2	Female	—	AD	uncomplicated	1,5	Delay in walking, walking difficulty (2)	Normal	—	47	Walking age later than 18 months	Normal	—	ATL1 (NM_015915), heterozygous c. 773A > G; p.His258Arg (rs119476048)
F3.1	Male	+	AR	uncomplicated	11	walking difficulty	Normal	—	17	Normal	Normal	—	Undiagnosed (WES)
F3.2	Female	+	AR	uncomplicated	10	walking difficulty	Normal	—	13	Normal	Normal	—	Undiagnosed (*ATL1*, *SPAST* negative)
F4	Male	—	Isolated case	uncomplicated	15	walking difficulty	Normal	—	41	Normal	Normal	—	Undiagnosed (*ATL1*, *SPAST*, *REEP1*, *NIPA1*negative)
F5.1	Male	+	AR	complicated	13	walking on tiptoes	thin CC, cortical atrophy, bilateral fronto-parietal T2 & FLAIR white matter hyperintensities (ears-of-the-lynx sign)	dysarthria, ataxia, dysdiadocokynesia, atrophy of thenar and hypothenar muscles	22	Learning disability, started to speak after age of 2	Sensory & motor nerve studies normal, needle EMG chronic first motor neuron signs	Ankles contracture, syncope, second degree cousin has CMT	SPG11 (NM_025137) c.6215_6219dupAGAT, p.Phe2074ArgfsTer15 NOVEL
F5.2	Male	+	AR	complicated	13	walking on tiptoes	thin CC, cortical atrophy, minimal bilateral fronto-parietal T2 & FLAIR white matter hyperintensities	dysarthria, ataxia, dysdiadocokynesia, atrophy of the thenar and hypothenar muscles	18	Normal	Sensory & motor nerve studies are normal, needle EMG chronic first motor neuron signs	Ankles contracture, obesity, second degree cousin has CMT	SPG11 (NM_025137) c.6215_6219dupAGAT, p.Phe2074ArgfsTer15 NOVEL
F6.1	Female	—	AD	uncomplicated	15	walking difficulty	multifocal areas of T2 white matter hyperintensities, normal spinal MRI	dysarthria, ataxia, dysdiadocokynesia (after age of 40)	48	Normal	Normal	Oligoclonal band was negative	PLP1 (NM_001128834) heterozygous c. 233_236delTCTT, p.Phe78Serfs*35 NOVEL

Table 1 cont. Clinical and genetic findings of the patients

Patient ID	Sex	Cons§	Possible heredity	HSP type	Onset age	Initial symptom	MRI (brain and spinal)	Additional neurological features	Age at exam	Mental and motor development	EMG	Contractures, deformities and other features	Genetic results
F6.2	Female	—	AD	uncomplicated	2	delay in walking, walking difficulty (15)	multifocal areas of T2 white matter hyperintensities, normal spinal MRI	dysarthria	24	Walking after age of 2	Normal	Oligoclonal band was negative	PLP1 (NM_001128834)heterozygous c. 233_236delTCTT, p.Phe78Serfs*35 NOVEL
F7	Male	—	AD	complicated	24	walking difficulty	Normal	—	58	Normal	Normal	Pes cavus, epilepsy	Undiagnosed (*ATL1*, *SPAST*, *REEP1*, *NIPA1*negative)
F8	Male	—	Isolated case	uncomplicated	33	walking difficulty	Normal	—	44	Normal	Sensory & motor axonal polyneuropathy	—	Undiagnosed (*ATL1*, *SPAST*, *REEP1*, *NIPA1*negative)
F9.1	Female	+	AR	complicated	13	walking difficulty	thin CC, cortical atrophy	dysarthria, ataxia, dysmetria, atrophy of thenar and hypothenar muscles	27	Learning disability	Sensory & motor nerve studies normal, needle EMG chronic first motor neuron signs	Ankles contracture, pes cavus, intellectual disability (IQ: 65), muscle cramps	Undiagnosed (WES)
F9.2	Female	+	AR	complicated	22	walking difficulty	thin CC	dysarthria, ataxia	33	Normal	Normal	Ankles contracture, pes cavus, severe muscle cramps	Undiagnosed (*ATL1*, *SPAST* negative)
F10	Male	+	Isolated case (AR?)	uncomplicated	12	walking difficulty	Normal	—	28	Normal	Normal	—	Undiagnosed (*ATL1*, *SPAST* negative)

Table 1 cont. Clinical and genetic findings of the patients

Patient ID	Sex	Cons§	Possible heredity	HSP type	Onset age	Initial symptom	MRI (brain and spinal)	Additional neurological features	Age at exam	Mental and motor development	EMG	Contractures, deformities and other features	Genetic results
F11	Male	+	Isolated case (AR?)	uncomplicated	1,5	delay in walking, walking on tiptoes (13)	minimal dorsal spinal atrophy	—	24	Walking age after 18 months	Normal	—	Undiagnosed (*ATL1*, *SPAST* negative)
F12	Male	+	Isolated case (AR?)	complicated	22	walking difficulty & dysarthri a	minimal cerebral and cerebellar atrophy	dysarthria, dysmetria	32	Normal	Normal	scoliosis and sensorineural hearing impairment	Undiagnosed (*ATL1*, *SPAST* negative)
F13	Male	+	AR/XL	complicated	27	walking difficulty	Normal	dysarthria	36	Normal	Sensory & motor axonal polyneuropathy	sensorineural hearing impairment	Undiagnosed (*ATL1*, *SPAST* negative)
F14	Female	+	AR	complicated	51	walking difficulty	thin CC, bilateral fronto-parietal T2 & FLAIR nonspecific white matter hyperintensities	—	57	Normal	Normal	—	Undiagnosed (WES)
F15	Male	—	AD/XL	complicated	12	walking difficulty	minimal dorsal spinal atrophy	—	22	Normal	Normal	Ankles contracture, pes cavus, hyperpigmentati on	Undiagnosed (*ATL1*, *SPAST* negative)
F16	Female	—	AD	uncomplicated	42	walking difficulty	Normal	—	52	Normal	Normal	—	*SPAST* heterozygous exon 17 deletion
F17	Male	+	Isolated case (AR?)	complicated	13	delay in walking, walking on tiptoes (13)	thin CC	dysarthria, dysmetria, minimal atrophy of thenar and hypothenar muscles	22	Learning disability, started speaking after age of 3	Sensory & motor nerve studies are normal, needle EMG chronic first motor neuron signs	—	Undiagnosed (ATL1, SPAST negative)

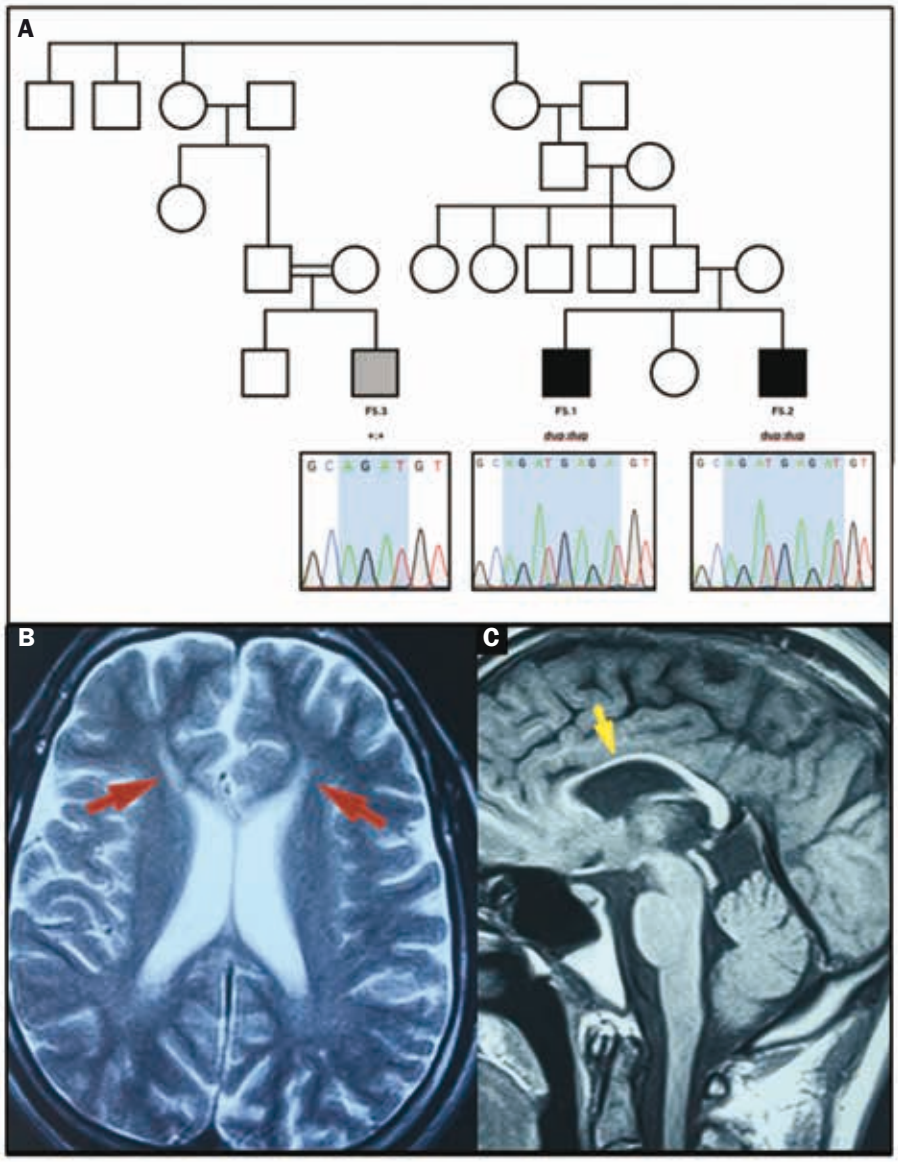

Figure 1. A — Pedigree of F5 family. The homozygous c.6215_6219dupAGAT variant in *SPG11* (NM_025137) was found in patients F5.1 and F5.2. Their second-degree cousin F5.3 does not carry the mutation; **B, C** — Brain MR images of patient F5.1 at age 21: sagittal T2 weighted images show bilateral fronto-parietal white matter hyperintensities. Red arrows indicate abnormal hyperintense signals at corner of frontal horn of lateral ventricles. These are known as 'ears-of-the-lynx' (B). These hyperintense signals lose their density with distance from ventricles. (Axial T1 weighted MRI showed thin CC. Thinning seen predominantly anterior and middle parts of the CC (yellow arrow) (C)

other variants in these genes were segregated and identified in our cohort.

Filtering of WES data in patients F1, F3.1, F5.1, F6.1, F9.1 and F14 for variants in the known HSP genes revealed two novel mutations. The homozygous c.6215_6219dupAGAT, p.Phe2074ArgfsTer15 variant in *SPG11* (NM_025137) was found in patient F5.1. Segregation analyses showed that his sibling, patient F5.2, was homozygous for the micro-duplication. Their second-degree cousin, F5.3, had Charcot Marie Tooth (CMT) disease and he was homozygous for the native allele. Siblings F5.1 and F5.2 had complicated phenotype with cerebellar signs and a learning disability. Additional phenotypic features were intellectual disability and obesity for siblings F5.1 and F5.2, respectively. Brain MRIs of both showed thin corpus callosum, cortical atrophy and bilateral fronto-parietal T2 and FLAIR hyperintensities. F5.1's findings were more prominent than his brother's and had an 'ears-of-the-lynx' sign at the forceps minor (Fig.1).

The second novel variant (c.233_236delTCTT, p.Phe78Serfs*35) was identified in a heterozygous condition in *PLP1* (NM_001128834) on chromosome X in patient F6.1. Segregation analyses showed that her affected

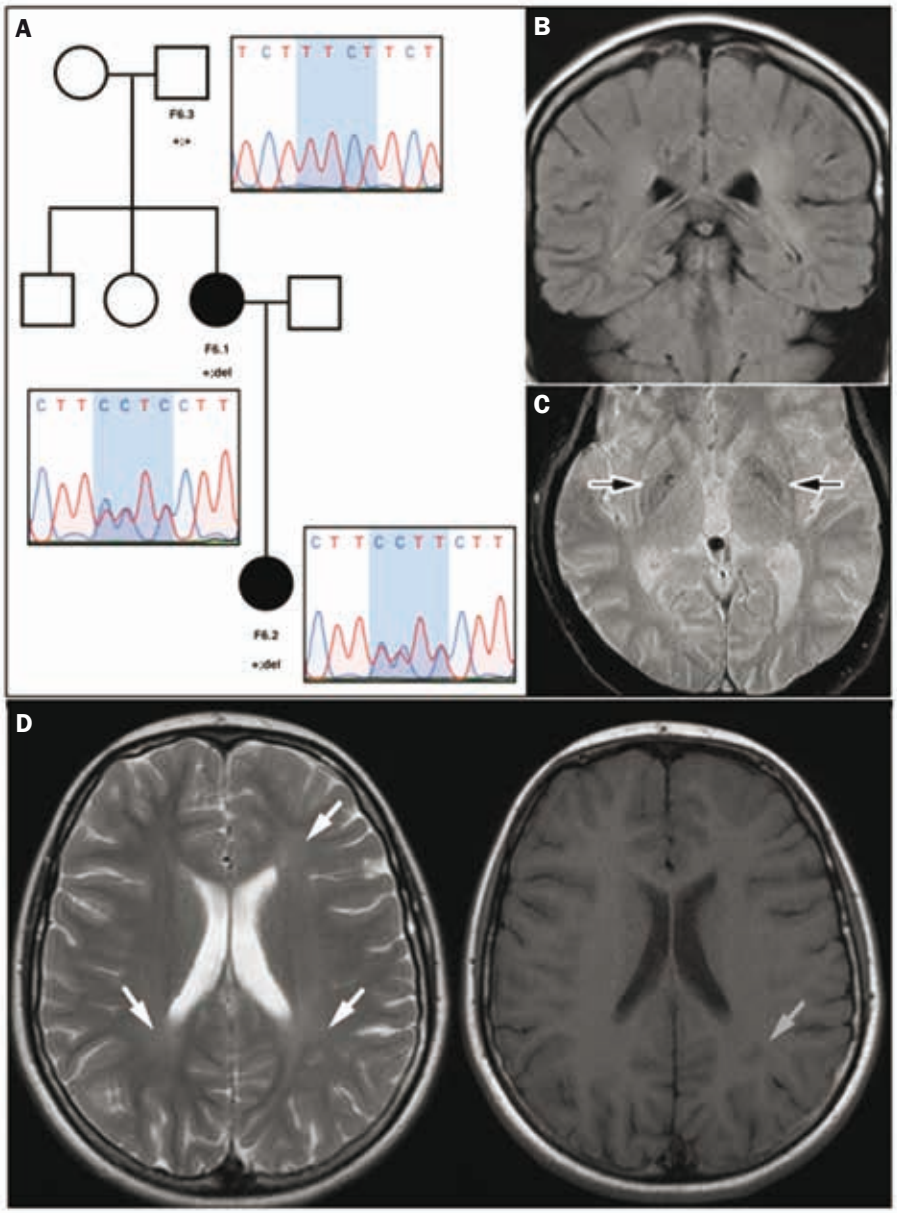

Figure 2. A — Pedigree of F6 family. The heterozygous c.233_236delTCTT, p.Phe78Serfs*35 variant in *PLP1* (NM_001128834) on chromosome X was found in patients F6.1 and F6.2. The father F6.3 does not carry the mutation; **B, C** — Brain MR images of patient F6.1. The FLAIR axial section shows confluent lesions in deep and periventricular white matter (B). SWI sagittal section shows heterogeneous, non-specific hypointensities in globus pallidus (black arrows) (C); **D** — Brain MR images of patient F6.2. T2 sagittal section shows confluent hyperintensities (white arrows) in deep and periventricular white matter and T1 sagittal section shows a hypointensity (grey arrow) very similar to a demyelinating plaque sequel

daughter (F6.2) carried the same heterozygous mutation and her healthy sister was homozygous for the wild type allele. Patients F6.1 and F6.2 had uncomplicated HSP. Their brain MRIs showed confluent periventricular areas of FLAIR and T2 white matter hyperintensities (Fig. 2). Candidate variants analysed in patients F.1, F3.1, F9.1 and F14 were not segregating with the disease in the family, rendering these families undiagnosed.

Discussion

Progressive spastic paraparesis is a common feature of both uncomplicated and complicated HSPs. Although HSP can simply be divided into two phenotypes, clinically there is great heterogeneity, depending on age at onset, progression rate, and other clinical and radiological characteristics [3]. To determine the exact diagnosis, molecular testing is mandatory

because clinical features are not sufficient to reliably differentiate HSP subtypes.

Inheritance is most often AD in the European population [10]. Our study describes the genetic spectrum of HSP in Turkey for the first time. The proportion of consanguineous marriage is up to 25% in our country. Our cohort has a high rate of AR-HSP compared to other reported series. Five families had AD inheritance pattern, six had AR, and six patients were isolated cases. Even in isolated cases there was a high consanguinity rate (4/6). WES was performed for five families with a history of consanguinity. The c.6215_6219dupAGAT, p.Phe2074ArgfsTer15 *SPG11* (NM_025137) novel variant was detected in patient F5.1 (Fig. 1A). The SPG11 is one of the most frequent HSP genotypes that is clinically described as complicated [7]. The MRI findings including the 'ears--of-the-lynx' sign in patient F5.1 are said to be typical for SPG11 (Fig. 1B). Involvement of the frontal lobe fibres may have contributed to the cognitive impairment in this patient [11]. HSP with *SPG11* mutations is allelic with juvenile amyotrophic lateral sclerosis type 5 (ALS5) and Charcot--Marie-Tooth type 2X (CMT2X). All these disorders show overlapping features with unpredictable genotype/phenotype correlations. These siblings along with spastic paraparesis also had other phenotypic features such as dysarthria, ataxia, dysdiadocokynesia, thin CC, and atrophy of the thenar and hypothenar muscles. Their second-degree cousin with CMT does not carry the mutation (Fig. 1A). Observation of two different neurological diseases within the same large family highlights the possibility of inheriting a rare disease in consanguineous marriages.

Prevalence data shows that most AR HSP cases do not have a mutation in known HSP genes/loci [4]. By combining the data of homozygosity mapping and WES, disease-causing gene candidates were determined for patients F1, F3.1, F9.1 and F14. Among the candidates determined, *PDGFRL* gene in F1, *SPINT3* gene in F3.1, *WDR90* gene in F9.1, and *ARNT, EMC1, WFS1* genes in F14 were highlighted as the strongest ones in terms of gene function and the frequency of the variants in the population databases (MAF < 0.05). Analyses of these candidates and other candidate variants by Sanger sequencing in the families revealed that these variants were not segregating with the disease in the family, rendering the families F1, F3, F9 and F14 undiagnosed. The combination of WES and homozygosity mapping is widely used and effective in genetic diagnosis of AR diseases. Even if these useful genetic tools are applied, some cases are still undiagnosed due to limitations of WES and undiscovered genetic causes.

Previously reported HSP series generally showed AD inheritance with uncomplicated phenotype [4–6, 8, 12]. In our cohort, among the five families with AD inheritance, three of them were uncomplicated. Mutations in *ATL1* (SPG3A) and *SPAST* (SPG4) genes were found to be causative in two of the families. These results showed that *ATL1* and *SPAST* genes are frequently observed in uncomplicated AD HSP cases in Turkey, as in other populations. By using WES, we found a *PLP1* (SPG2) mutation in the third family with uncomplicated phenotype and dominant inheritance (Fig. 2A).

The PLP1 is predominantly expressed in CNS myelin and its pathogenic mutations cause two different allelic disorders: Pelizaeus Merzbacher Disease (PMD) and spastic paraplegia type 2 (SPG2). PMD is a progressive dysmyelinating leukodystrophy which begins in infancy. Initial symptoms are hypotonia, nystagmus and head tremor. Choreoathetosis, spasticity, ataxia, microcephaly, optic atrophy and psychomotor deterioration are other features which may develop in the first 10 years of life. SPG2 presents only with spastic paraparesis. Both diseases cause cerebral and spinal white matter lesions. Bonneau et al. [13] in 1993 reported the first female patient who suffered from spastic paraplegia. Due to skewed X inactivation, heterozygous *PLP1* mutations rarely lead to SPG2 in females [14, 15]. Periventricular and subependymal white matter MRI changes have been described in SPG2 and asymptomatic carrier mothers for classical PMD. The signal alterations are defined as bilateral, diffuse and subtle in FLAIR and T2 weighted images [14]. The presence of white matter lesions and progressive spastic paraparesis in young women suggests demyelinating diseases. Patient F6.1 and her daughter F6.2 had slow progressive spastic paraparesis with confluent lesions in the deep and periventricular white matter (Fig. 2B and 2D). Investigations and treatment attempts for a probable demyelinating disease gave negative results. F6.1 developed cerebellar signs in her fifth decade. Additionally, MRI showed heterogeneous, non-specific hypo-intensities in globus pallidus in SWI (Fig. 2C). This finding is not compatible with a primary iron deposition disorder. On the other hand, these hypointensities at the basal ganglia and the thalamus can be present in *PLP1* associated disorders [16]. Despite all the clinical and radiological documentation of both the mother and daughter, the diagnosis could not be defined until the WES was performed.

The characteristics of an HSP patient group from Turkey with a high proportion of consanguinity are here discussed for the first time.

Our data shows that clinical analysis can be misleading in defining HSP subtypes. To shorten the diagnostic odyssey of HSP, the advent of next generation sequencing has proved effective. All HSP cases should be subject to further examination after the recognition of common mutations especially in sporadic and dominantly inherited ones. Patients with AR HSP who cannot be diagnosed despite the current and proven methods suggest that different mechanisms exist underlying HSP pathology.

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