Journal of Neurology (2021) 268:2065–2082
https://doi.org/10.1007/s00415-019-09633-1

REVIEW

Genotype–phenotype associations in hereditary spastic paraplegia: a systematic review and meta-analysis on 13,570 patients

Maryam Erfanian Omidvar[1] · Shahram Torkamandi[2] · Somaye Rezaei[3] · Behnam Alipoor[4] · Mir Davood Omrani[5] · Hossein Darvish[6] · Hamid Ghaedi[5]

Received: 14 October 2019 / Revised: 7 November 2019 / Accepted: 9 November 2019 / Published online: 19 November 2019

Abstract

Aims The hereditary spastic paraplegias (HSPs) are a heterogeneous group of inherited neurodegenerative disorders. Although, several genotype–phenotype studies have carried out on HSPs, the association between genotypes and clinical phenotypes remain incomplete since most studies are small in size or restricted to a few genes. Accordingly, this study provides the systematic meta-analysis of genotype–phenotype associations in HSP.

Methods and results We retrieved literature on genotype–phenotype associations in patients with HSP and mutated *SPAST*, *REEP1*, *ATL1*, *SPG11*, *SPG15*, *SPG7*, *SPG35*, *SPG54*, *SPG5*. In total, 147 studies with 13,570 HSP patients were included in our meta-analysis. The frequency of mutations in *SPAST* (25%) was higher than *REEP1* (3%), as well as *ATL1* (5%) in AD-HSP patients. As for AR-HSP patients, the rates of mutations in *SPG11* (18%), *SPG15* (7%) and *SPG7* (13%) were higher than *SPG5* (5%), as well as *SPG35* (8%) and *SPG54* (7%). The mean age of AD-HSP onset for *ATL1* mutation-positive patients was earlier than patients with *SPAST*, *REEP1* mutations. Also, the tendency toward younger age at AR-HSP onset for *SPG35* was higher than other mutated genes. It is noteworthy that the mean age at HSP onset ranged from infancy to adulthood. As for the gender distribution, the male proportion in *SPG7*-HSP (90%) and *REEP1*-HSP (78%) was markedly high. The frequency of symptoms was varied among patients with different mutated genes. The rates of LL weakness, superficial sensory abnormalities, neuropathy, and deep sensory impairment were noticeably high in REEP1 mutations carriers. Also, in AR-HSP patients with *SPG11* mutations, the presentation of symptoms including pes cavus, Neuropathy, and UL spasticity was higher.

Conclusion Our comprehensive genotype–phenotype assessment of available data displays that the mean age at disease onset and particular sub-phenotypes are associated with specific mutated genes which might be beneficial for a diagnostic procedure and differentiation of the specific mutated genes phenotype among diverse forms of HSP.

Keywords HSP · Genotype–phenotype associations · Meta-analysis

Introduction

The hereditary spastic paraplegias (HSPs) include a diverse clinically and genetically heterogeneous group of inherited neurodegenerative disorders [1]. Affected individuals predominantly present bilateral progressive spasticity and weakness of the lower limbs. Mainly, HSP-related symptoms are associated with degeneration of the longest corticospinal nerves [2]. In the clinical perspective, HSPs have been classified into uncomplicated (or pure) and complicated (or complex) forms. The pure forms refer to a condition that most of the affected individuals display similar clinical characteristics including progressive lower extremity spastic weakness, urinary bladder symptoms and mild diminution of distal

Maryam Erfanian Omidvar and Shahram Torkamandi contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09633-1) contains supplementary material, which is available to authorized users.

✉ Hamid Ghaedi
h.qaedi@sbmu.ac.ir

Extended author information available on the last page of the article

vibratory sensation. The complex form is characterized by additional features such as ataxia, seizures, intellectual disability, parkinsonism, cognitive impairment, extrapyramidal disturbance, and peripheral neuropathy, among others [1, 3].

In the field of neurogenetics, HSPs are conceivably the disorders with the most striking genetic heterogeneity, with all patterns of Mendelian inheritance reported. The autosomal dominant HSP (AD-HSP) is the predominant form of the disorder, responsible for up to 80% of all cases with pure HSP in developed societies. This is while autosomal recessive HSPs (AR-HSPs) are prevalent in populations with a high rate of inbreeding and frequently is associated with complex forms. However, there are reports of HSP cases with X-linked or mitochondrial transmission, but they are rare [1, 2, 4].

Thus far, more than 80 genes for HSPs have been identified and yet the genetic landscape of HSP is far from complete [5]. Mutations in *SPAST* (formerly known as *SPG4*) are the most common genetic findings in patients present with AD-HSP. In the autosomal recessive HSPs, thinning of the corpus callosum is the frequent abnormality of the disorder that is mostly due to pathogenic mutations in *SPG11* [6, 7]. There is a relatively large list of other genes implicated in dominant and recessive HSP. Interestingly, genes like *SPAST* and *SPG11* have seen with the transmission in both dominant and recessive models [8–10].

In general, HSP has a subtle onset and, therefore, the exact age of onset (AO) for symptoms is not always accurate. There is a significant difference between AOs among the distinct genetic subtypes of HSP. It is noteworthy that the disease can occur at any age, but it is more common in childhood or early adulthood [11].

There are different concomitant neurologic and non-neurologic symptoms such as intellectual disability, dysarthria, and ataxia in patients with AR-HSPs. A considerable number of reports support the existence of an association between the mutated genes and clinical features. It is most common in patients with mutated *ATL1* to present distal atrophy or neuropathy. As for patients with mutated *SPG7*, the manifestation of ataxia is more prevalent. Despite the fact that several studies described the relationship between the phenotypes of HSP patients and their mutations by genotype–phenotype correlation analysis, the findings of a single study are mainly descriptive and also cannot be generalized due to the small cohort size [12–15]. Also, most records have used the sequences of a small number of genes to identify disease-causing mutations in index patients and their relatives, leading to a heterogeneous perspective of clinical genetic results in terms of the affected genes, the studied patient cohorts, and outcome variables.

Accordingly, in this study, we performed a more comprehensive systematic review on the mutation frequency, AO and the genotype–phenotype correlation in distinct HSP genetic subtypes via meta-analyzing the currently available literature on the genotype–phenotype association to sustain better-personalized treatment of HSP patients.

Methods

Search strategy and selection criteria

We performed a search on PubMed, Embase, Google Scholar, Scopus and Science Direct databases, for papers published in English up to March 2019, using a combination of key terms "Hereditary Spastic Paraplegia", "HSP", "AD-HSP", "AR-HSP","SPAST","REEP1", "ATL1", "KIF5A", "SPG4", "SPG31", "SPG3A", "SPG10", "SPG11", "SPG15", "ZFYVE26", "SPG7", "SPG35", "FA2H", "SPG54", "DDHD2", "SPG5A", "CYP7B1", "mutation", "genetic", "variant" and "genotype". The lexicons of related risk factors were also searched for having a comprehensive study. Studies that evaluated genotype–phenotype correlation in HSP patients were selected. Furthermore, the abstract and title of the individual papers were perused thoroughly, and then studies of interest were selected for assessment of the full article. Case report studies, meta-analysis, reviews, abstract or conference papers, studies on cell line and animal models were excluded.

Data gathering and statistical analysis

Two independent reviewers assessed and selected the studies according to the predetermined inclusion criteria, and the consensus was achieved by a third reviewer. The following data were extracted from the selected studies: author name, year, sample size, patients age, gender, mutated genes, and clinical findings like upper limb (UL) spasticity, lower limb (LL) spasticity, LL weakness, pes cavus, bladder abnormalities, UL hyperreflexia, LL hyperreflexia, extensor plantar, intellectual disability (ID), dysarthria or speech disorder), peripheral neuropathy, epilepsy, ataxia, thin corpus callosum (TCC), white matter abnormalities (WMA), cataracts or visual problems, and superficial sensory abnormalities.

The meta-analysis was conducted as stated by the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [16]. The "meta" package (version 4.9-5) in R (version-3.5.3, The R Foundation for Statistics Computing, March 11, 2019) was employed to fit meta-analysis models for the proportions and means. We used Q test to test for subgroup differences. Heterogeneity between trials was quantified using the Cochrane's Q statistic and the I^2 test and considered significant at $I^2 > 50\%$ or P value < 0.1. In the case of significant heterogeneity, the random-effects model was used for the meta-analysis. Otherwise, a fixed-effect model was fitted. Chi-squared test and Fisher's exact

test were used to evaluate the association of clinical features with genotypes. Moreover, the Benjamini–Hochberg procedure (BH) was run to control the false discovery rate. A P value < 0.05 was considered statistically significant.

Results

Characteristics of included studies

Studies that met our inclusion criteria are listed in Table 1. More details about the included studies for AD-HSP and AR-HSP are summarized in Supplementary Table 1 and Table 2, respectively.

Mutation frequency of HSPs

To estimate pooled frequency of mutations in HSP patients, we performed proportion meta-analysis (*metaprop*). We included *SPAST*, *REEP1* and *ATL1* gene for AD-HSP and S*PG11*, *SPG15*, *SPG7*, *SPG35*, *SPG54*, *SPG5* for AR-HSP. Table 2 provides details on gene mutation frequencies in HSP patients.

Mutation frequencies in AD-HSP patients

We found a total of 57 studies screened 5084 HSP patients, for mutation frequency of *SPAST*. A pooled frequency of 25.00% (95% CI 21.00–30.00) for *SPAST* mutations in HSP cases was found (Fig. 1). However, we found a non-significant difference regarding *SPAST* mutation frequencies among different populations ($Q = 3.47$, $P = 1.00$); the frequency of mutations in the Asian population (32.62%) was higher than that of Caucasians (23.07%) and Americans (24.83%) (Table 3).

For *REEP1*, a total of 12 studies that investigated 1972 HSP patients revealed a mutation frequency of 3.00% (95% CI 2.00–5.00) (Fig. 2). A frequency of 5.00% (95% CI 3.00–9.00) related to *ATL1* mutations was identified considering 26 studies, including 3107 HSP patients (Fig. 3). Moreover, the mutation frequency of *ATL1* in the Caucasian population (8%) was higher than that of Asians and Americans (4% each) (Table 3).

Mutation frequencies in AR-HSP patients

For *SPG11*, a total of 27 studies with 2126 HSP cases were assessed, resulting in a frequency of 18.00% (95% CI 9.00–33.00%) (Fig. 4). Population sub-group analysis revealed that the mutation frequency of *SPG11* in the Asian population was higher (87.98%) than that of Caucasians (10.55%), and Americans (24.23%) (Table 3). As for *SPG15*, a frequency of 7.00% (95% CI 3.00–15.00%) in five studies including 296 HSP cases was reported (Fig. 5a). Our analysis revealed a frequency of 13.00% (95% CI 5.00–30.00%) related to *SPG7* mutations, in seven studies including 303 HSP cases (Fig. 5b). In sub-group analysis, we found a higher frequency of mutated *SPG7* in Americans in comparison to Caucasians (18.97% vs. 13.29%) (Table 3). A total of four studies investigated 198 HSP patients for mutations in *SPG35* and a pooled frequency of 8.00% (95% CI 1.00–35.00%) was observed (Fig. 5c). There were five studies tested 289 HSP patients for mutations in *SPG54* and we found a frequency of 7.00% (95% CI 0.00–50.00%) (Fig. 5d). A total of five studies screened 195 HSP patients for mutations in *SPG5* with an overall frequency of 5.00% (95% CI 3.00–9.00%) (Fig. 5e).

Mean AO in HSP patients

The meta-analysis result of mean AO of both AD-HSP and AR-HSP is presented in Table 4.

Our result suggested that patients with *ATL1* mutations have the earliest mean AO as 4.53 (95% CI 3.09–5.98) in comparison to other AD-HSP genes. As for *SPAST* and *REEP1*, the mean of AO was 24.79 (95% CI 21.00–28.58) and 17.00 (95% CI 11.18–22.82), respectively (Fig. 6) (Table 4). The assessment of mean AO of AD-HSP genes in different ethnicity indicated a significantly earlier onset of disease for *ATL1*-HSP in the Asian population as well as Caucasians ($P = 0.018$). It is also a significant tendency toward younger age at HSP onset for *SPAST* with a mean age of 21.88 (95% CI 17.71–26.06) in the Caucasians ($P = 0.023$) (Table 5).

With regard to the AO of AR-HSP, *SPG7*-HSP tends to manifest in older years than HSP cases due to mutations in *SPG11*, *SPG15*, *SPG35* and *SPG5* group (Table 4) (Fig. 6). The mean age at the onset of *SPG7*-HSP patients was 37.17 (95% CI 33.31–41.02), for the *SPG11*-HSPs was 13.10 (95% CI 11.30–14.90), for the *SPG15*-HSP group was 14.67 (95% CI 11.44–17.91) and in the *SPG35*-HSP was 13.89 (95% CI 0.00–28.92) years, as well. It was 20.07 (95% CI 10.38–29.76) in *SPG5* mutation-positive patients group (Fig. 6). The mean age at HSP onset in the *SPG11* group is similar among patients with different ethnicities (Table 5).

Gender distribution in HSP patients

Frequently, males were more reported to have HSP due to mutations in *SPG5*, *SPG11*, *SPG7*, *ATL1*, *REEP1*, and *SPAST*, while there was an equal gender distribution among patients with mutated *SPG35*. We found that male to female ratio for *SPAST*–HSP patients was 1.27 (171 male out of 305 patients). This ratio for *SPG7*-HSP patients was 9.00 (18 male out of 20 patients). Also, 67% of *SPG5*-HSP, 54% of

Table 1 The included studies for each gene

Gene	Feature	Studies	References
SPAST	Mutation frequency	57	[8–10, 16–69]
	Mutation frequency in sub-populations	55	[8–10, 16–24, 26–63, 65–69]
	Mean age of onset	40	[9, 18, 20, 23, 25, 27, 28, 30–37, 39–52, 54–59, 62–65, 69]
	Mean age of onset in sub-populations	38	[9, 18, 20, 23, 27, 28, 30–37, 39–52, 54–59, 62, 63, 65, 69]
	UL spasticity	14	[18, 23, 27, 28, 31, 34, 35, 44, 51, 54, 55, 57, 62, 63]
	LL weakness	18	[18, 25, 27, 28, 31, 34, 35, 37, 44, 50, 51, 54, 56–58, 62–64]
	UL hyperreflexia	25	[18, 20, 23–25, 27, 28, 31, 32, 34, 35, 39–41, 44, 50, 51, 54–57, 59, 62–64]
	LL hyperreflexia	26	[10, 18, 20, 23, 25, 28, 30, 31, 34, 35, 38–41, 44, 47, 50, 51, 54–56, 58, 59, 62–64],
	Extensor plantar	28	[10, 18, 20, 23, 25, 27, 28, 30–32, 34, 35, 38, 39, 41, 44, 47, 50, 51, 54–59, 62–64]
	Deep sensory impairment	25	[9, 10, 18, 23–25, 27, 28, 30–32, 34, 35, 41, 44, 47, 50, 51, 54–57, 59, 63, 64]
	ID	25	[9, 10, 20, 23, 25, 27, 28, 30–35, 41, 44, 47, 48, 52–57, 59, 64]
	Dysarthria	25	[9, 10, 20, 23, 25, 27, 28, 30–35, 39, 44–47, 49–51, 54–57, 59]
	Superficial sensory abnormalities	22	[9, 10, 23, 25, 27, 28, 30–32, 34, 35, 37, 44, 47, 50, 51, 54–57, 59, 62]
	Spine curvature disorders	21	[9, 10, 23, 25, 27, 28, 30–32, 34, 35, 44, 47, 50, 51, 54–57, 59, 64]
	Neuropathy	17	[9, 10, 23, 27, 28, 31–35, 44, 49, 51, 53–55, 57]
REEP1	Mutation frequency	12	[10, 19, 34, 37, 43, 49, 58, 70–74]
	Mean age of onset	6	[19, 34, 49, 71, 73, 74]
	UL spasticity	4	[10, 71–73]
	LL weakness	6	[10, 19, 58, 71–73]
	UL hyperreflexia	5	[10, 70–73]
	LL hyperreflexia	6	[10, 19, 58, 71–73]
	Extensor plantar	7	[10, 19, 58, 70–73]
	Deep sensory impairment	5	[10, 19, 70–72]
	ID	4	[10, 70, 71, 73]
	Dysarthria	4	[10, 49, 70, 71]
	Superficial sensory abnormalities	4	[10, 70, 71, 73]
	Spine curvature disorders	4	[10, 70, 71, 73]
	Neuropathy	6	[10, 19, 58, 71–73]
ATL1	Mutation frequency	26	[8, 9, 20, 22, 34, 37, 38, 43, 44, 47, 49, 54, 65, 67, 68, 70–72, 74–81]
	Mutation frequency in sub-populations	25	[8, 9, 20, 22, 34, 37, 38, 43, 47, 49, 54, 65, 67, 68, 70–72, 74–81]
	Mean age of onset	16	[8, 20, 22, 37, 38, 43, 44, 49, 54, 65, 71, 72, 74, 75, 77, 80]
	Mean age of onset in sub-populations	16	[8, 20, 22, 37, 38, 43, 44, 49, 54, 65, 71, 72, 74, 75, 77, 80]
	UL spasticity	5	[44, 54, 71, 72, 81]
	LL weakness	6	[20, 44, 54, 71, 72, 81]
	UL hyperreflexia	6	[44, 54, 70–72, 81]
	LL hyperreflexia	5	[44, 54, 71, 72, 81]
	Extensor plantar	6	[44, 54, 70–72, 81]
	Deep sensory impairment	8	[9, 22, 47, 54, 70–72, 81]
	ID	5	[9, 54, 70, 71, 81]
	Dysarthria	6	[9, 49, 54, 70, 71, 81]
	Superficial sensory abnormalities	8	[9, 20, 44, 47, 54, 70, 71, 81]
	Spine curvature disorders	5	[9, 54, 70, 71, 81]
	Neuropathy	7	[9, 49, 54, 70, 71, 74, 81]

Table 1 (continued)

Gene	Feature	Studies	References
SPG11	Mutation frequency	27	[8–10, 25, 31, 32, 34, 43, 70, 75, 82–98]
	Mutation frequency in sub-populations	26	[8–10, 25, 31, 32, 34, 43, 70, 75, 82–89, 91–98]
	Mean age of onset	22	[9, 10, 32, 34, 43, 70, 75, 82, 83, 85–92, 94–98]
	Mean age of onset in sub-populations	21	[9, 10, 32, 34, 43, 70, 75, 82, 83, 85–89, 91, 92, 94–98]
	UL spasticity	4	[10, 25, 85, 92]
	LL weakness	6	[10, 84, 87, 92, 95, 97]
	UL hyperreflexia	21	[25, 31, 32, 34, 43, 70, 75, 82–88, 90–94, 96, 97]
	ID	16	[10, 70, 75, 82–85, 88, 90–92, 94–98]
	Dysarthria	15	[25, 70, 75, 82, 84, 86–88, 90–92, 94–97]
	Neuropathy	13	[25, 70, 82, 83, 86–88, 91, 94–98]
	Pes cavus	6	[25, 82, 90, 92, 94, 95]
	Ataxia	13	[70, 75, 82, 84–88, 90, 92, 95, 96, 98]
	TCC	19	[25, 70, 82–98]
	Epilepsy	7	[25, 70, 85, 93–95, 98]
	WMA	19	[25, 70, 75, 82–97]
	Cataract (or visual impairment)	7	[82, 86, 87, 90, 93, 94, 96]
SPG15	Mutation frequency	5	[10, 32, 91, 93, 99]
	Mean age of onset	2	[32, 99]
	LL weakness	2	[10, 99]
	UL hyperreflexia	4	[32, 91, 93, 99]
	ID	3	[10, 91, 99]
	TCC	4	[32, 91, 93, 99]
	Epilepsy	2	[93, 99]
	WMA	4	[32, 91, 93, 99]
	Cataract [or visual impairment]	2	[93, 99]
	Neuropathy	2	[91, 99]
	Ataxia	1	[99]
SPG7	Mutation frequency	7	[9, 10, 31, 70, 82, 91, 100]
	Mutation frequency in sub-populations	7	[9, 10, 31, 70, 82, 91, 100]
	Mean age of onset	6	[9, 10, 31, 82, 91, 100],
	UL hyperreflexia	5	[31, 70, 82, 91, 100]
	ID	4	[10, 70, 82, 91]
	TCC	4	[10, 70, 82, 91]
	Dysarthria	5	[10, 70, 82, 91, 100]
	WMA	5	[31, 70, 82, 91, 100]
	Neuropathy	3	[70, 82, 91]
	Ataxia	4	[10, 70, 82, 100]
	Cataract (or visual impairment)	2	[82, 100]
SPG35	Mutation frequency	4	[32, 75, 101, 102]
	Mean age of onset	3	[32, 101, 102]
	ID	3	[75, 101, 102]
	Ataxia	3	[75, 101, 102]

Table 1 (continued)

Gene	Feature	Studies	References
SPG54	Mutation frequency	5	[75, 103–106]
	UL hyperreflexia	4	[75, 103, 104, 106]
	UL Spasticity	2	[103, 106]
	ID	5	[75, 103–106]
	TCC	2	[103–106]
	Dysarthria	3	[75, 103, 106]
	WMA	4	[75, 103, 104, 106]
	Cataract (or visual impairment)	3	[103, 104, 106]
	Pes cavous	2	[103, 106]
SPG5	Mutation frequency	4	[10, 70, 82, 93]
	Mean age of onset	2	[10, 70]

Table 2 Overall mutation frequencies of reported genes in HSP patients

Gene	Meta-analysis		Test for heterogeneity		
	%Frequency [95% CI]	*k*	*Q*	Q_p	I^2 (%)
AD-HSP					
SPAST	25.00 [21.00–30.00]	57	349.92	< 0.00	87.00
REEP1	3.00 [2.00–5.00]	12	24.66	0.01	55.00
ALT1	5.00 [3.00–9.00]	26	191.63	< 0.00	89.00
AR-HSP					
SPG11	18.00 [9.00–33.00]	27	326.47	< 0.00	94.00
SPG15	7.00 [3.00–15.00]	5	17.49	0.00	72.00
SPG7	13.00 [5.00–30.00]	7	30.37	< 0.00	84.00
SPG35	8.00 [1.00–35.00]	4	13.89	0.00	78.00
SPG54	7.00 [0.00–50.00]	5	33.54	< 0.00	89.00
SPG5	5.00 [2.00–12.00]	4	8.46	0.03	50.00

SPG11-HSP, 65% of *ATL1*-HSP, and 78% of *REEP1*-HSP patients were male (Fig. 7).

The male/female ratio was significantly higher in *SPG7*-HSP patients compared to those with mutation in *SPG5* ($P = 0.0001$), *SPG11* ($P < 0.0001$), and *SPG35* ($P < 0.0001$). As for AD-HSP patients, numerically the males were significantly higher in *REEP1* mutation carriers in comparison with *SPAST*-HSP patients ($P = 0.0015$).

Genotype–phenotype correlation in HSP patients

However, the lower limbs weakness and spasticity are considered to be the predominant clinical characteristics; there are significant differences showing special characteristics with regard to the underlying gene. Figure 8a, b represents the relative frequency of finding the clinical features in AR-HSP and AD-HSP, respectively.

Findings in neurological examination

We were able to only include *SPG11* and *SPG15* to investigate the association of AR-HSP-related genes with LL weakness. The results evidenced that all the patients ($n = 8$) with *SPG15* mutations presented LL weakness which was significantly higher than those with *SPG11*-HSP ($P < 0.0001$) (Fig. 8a). In the case of AD-HSP, we found 25 out of 29 patients (86%) with *REEP1*-related HSP were discerned with LL weakness. This frequency is significantly higher than that observed in HSP cases due to *ATL1* mutations (50%, 8 out of 16 patients) and *SPAST* mutations (47%, 113 out of 241 patients) (Fig. 8b).

The frequency of UL spasticity was 69% (11 out of 16 patients) in *SPG11*-HSP patients, while 3/5 of patients with mutations in *SPG54* and 3/7 of *SPG15*-HSP cases were reported to have UL spasticity. In the case of AD-HSP patients, UL spasticity was reported in 13% of *SPAST*-HSP (23 out of 178 patients) and 11% of *REEP1*-HSP patients (2 out of 19 patients). The UL spasticity was not observed in patients with *ATL1* mutations.

In general, UL hyperreflexia is a more common finding in AR-HSP than AD-HSP. All included HSP patients with mutated *SPG15*, *SPG7*, and *SPG54* to manifest UL hyperreflexia; however, 90% of *SPG11*-HSP showed such lesions (Fig. 8a) (Supplementary Table 3). In AD-HSP, almost 37% of *SPAST*-HSP (102 out of 274 patients) and 33% of *REEP1*-HSP (6 out of 18 patients) also showed UL hyperreflexia, which was higher than in patients with *ATL1* mutations (1 out of 15 patients).

For hyperreflexia in the lower limbs, we found data for AD-HSP-related genes. Data evidenced that all the *ATL1*-HSP patients have diagnosed with LL hyperreflexia (14 out of 14 patients). Moreover, LL hyperreflexia is a frequent finding in *SPAST*-HSP patients, with a rate of 96% (220 out

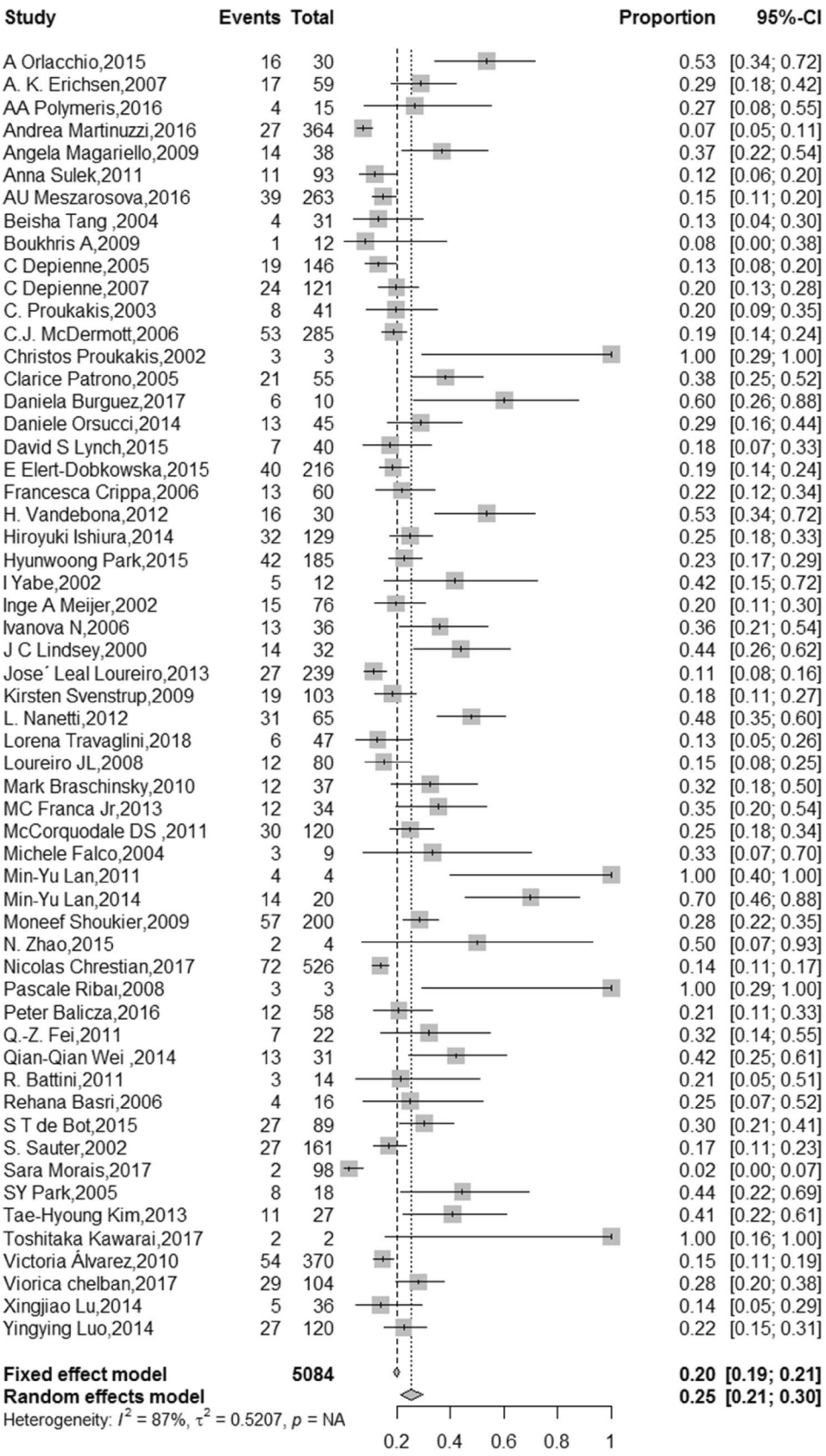

Fig. 1 Forest plot of *SPAST* mutation frequencies in HSP patients. A total of 25% of AD-HSP patients carry *SPAST* mutations. *CI* confidence interval

Table 3 Mutation frequency of reported genes in sub-populations

Gene	Pop	Meta-analysis		Test for heterogeneity		Test for sub-group differences	
		%Frequency [95% CI]	*k*	τ^2	I^2 (%)	*Q*	*P*
SPAST	Caucasian	23.07 [18.73–28.06]	36	0.50	87.50	3.47	1.00
	Asian	32.62 [23.93–42.70]	14	0.42	76.80		
	American	24.83 [15.59–37.15]	5	0.28	81.90		
ATL1	Caucasian	8.00 [4.00–14.00]	17	1.83	89.00	5.51	1.00
	Asian	4.00 [1.00–10.00]	6	1.09	67.00		
	American	4.00 [3.00–6.00]	2	0	0.00		
SPG11	Caucasian	10.55 [4.97–21.01]	18	2.66	92.40	5.37	1.00
	Asian	87.98 [5.89–99.88]	5	15.20	96.80		
	American	24.23 [13.46–39.66]	3	0.09	26.10		
SPG7	Caucasian	13.29 [2.74–45.50]	5	3.05	89.60	0.21	0.990
	American	18.97 [10.83–31.09]	2	0.00	0.00		

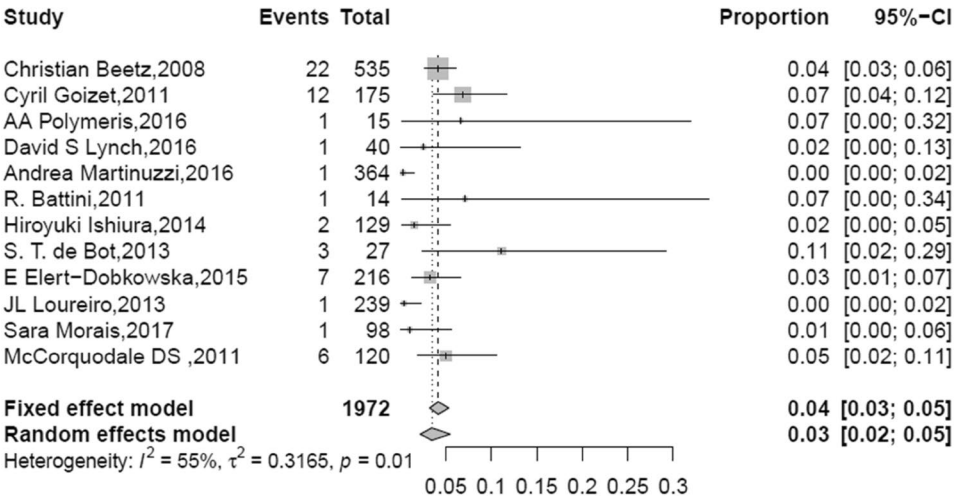

Fig. 2 Forest plot of *REEP1* mutation frequencies in HSP patients. A total of 3% of HSP patients carry *REEP1* mutations. *CI* confidence interval

of 228 patients) and also in *REEP1*-HSP patients was 86% (24 out of 28 mutation-positive patients (Fig. 8b).

For a number of neurological findings like superficial sensory abnormalities, deep sensory impairments and extensor plantar we found eligible data only for AD-HSPs. A greater percentage of patients with *REEP1* mutations showed disorders such as superficial sensory abnormalities (50%), deep sensory impairments (41%) in comparison to *SPAST*- and *ALT1*-related cases. All the AD-HSP patients with mutated *ATL1* were identified with extensor plantar. Moreover, the diagnosis of extensor plantar was significantly higher in *REEP1*-HSP patients than those with mutated *SPAST* ($P < 0.0001$) (Fig. 8b) (Supplementary Table 4).

Intellectual disability

As can be seen from Fig. 8a, intellectual disability was more often observed in *SPG54*-HSP than in the other AR-HSPs. The relative frequency of intellectual disability frequency in HSP patients in order of highest to lowest was as follows: *SPG54* (89%), *SPG11* (86%), *SPG15* (78%), *SPG35* (71%) and *SPG7* (8%) (Fig. 8a).

As for AD-HSP, *SPAST*-HSP patients were most often diagnosed with intellectual disability. However, there was no report of intellectual disability in patients with *ATL1* mutations (Fig. 8b).

Ataxia

Data evidenced that 39% of *SPG11*-HSP patients manifested with ataxia (37 out of 96 patients). Also, ataxia was reported in 71% of *SPG35*-HSP (5 out of 7 patients), in 62% of *SPG7*-HSP patients (5 out of 8 patients), and 25% of *SPG15*-HSP (2 out of 8 patients) (Fig. 8a).

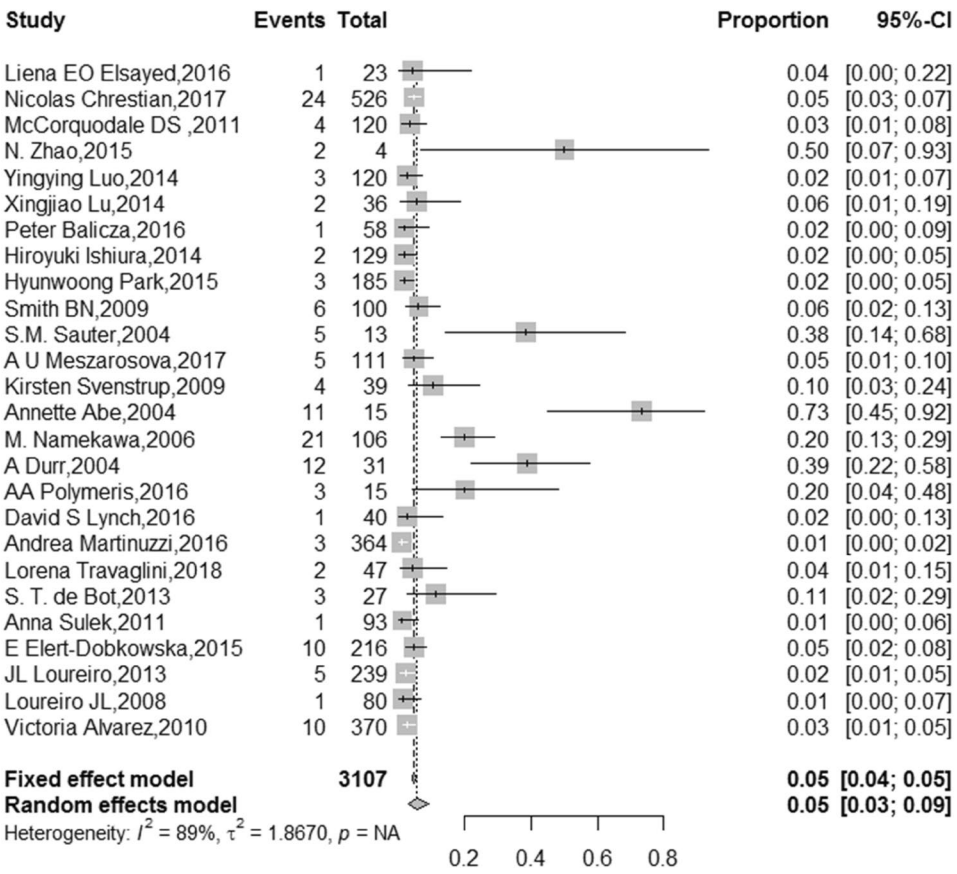

Fig. 3 Forest plot of *ATL1* mutation frequencies in HSP patients. Five percent of HSP patients carry *ATL1* mutations. *CI* confidence interval

Cataract

In the case of cataract, data showed that ~ 67% (4/6) with *SPG54* mutations and 39% (19/60) of patients with *SPG11* mutations were diagnosed with cataract. Also, cataract was reported in two out of nine (~ 22%) *SPG11*-HSP patients. There was an evident association between *SPG7* mutations and cataract, as five out of six *SPG7*-HSP patients were identified with cataract (Fig. 8a).

White matter abnormalities (WMA)

We found all the included cases for *HSP-SPG54* (7/7), 78% of *SPG15-HSP* cases (7/9), 73% of *SPG11*-HSP patients (85/116) and 20% of SPG7-HSP patients (3/15) manifested WMA (Fig. 8a).

Thin corpus callosum (TCC)

In the case of *SPG11*-HSP, 101 out of 114 patients (89%) reported having TCC. All HSP cases due to mutations in *SPG15* (8 out of 8) and *SPG54* (8 out of 8) reported showing TCC. None of the *SPG7*-HSP patients identified with TTC (Fig. 8a).

Pes cavus

Pes cavus was observed in 33% (15/46) of HSP cases due to mutations in *SPG11*, in 20% (1/5) of patients with mutations in *SPG54*, and 12% (1/8) of cases with mutations in *SPG15*. It seems that patients with mutated *SPG11* were at significantly higher risk of developing pes cavus (Fig. 8a).

Dysarthria

Dysarthria was reported in both AD and AR-HSPs. For AD-HSP patients, only a number of those with mutated *SPAST* were diagnosed with dysarthria. Data evidenced that 4% of *SPAST*-HSP (11 out of 270 patients) has dysarthria (Fig. 8b).

In AR-HSPs, 62% (61/99) of *SPG11*-HSP patients, 83% (5/6) of *SPG54*-HSPs and 56% of *SPG7*-HSP cases (9/16) were found to have dysarthria (Fig. 8a).

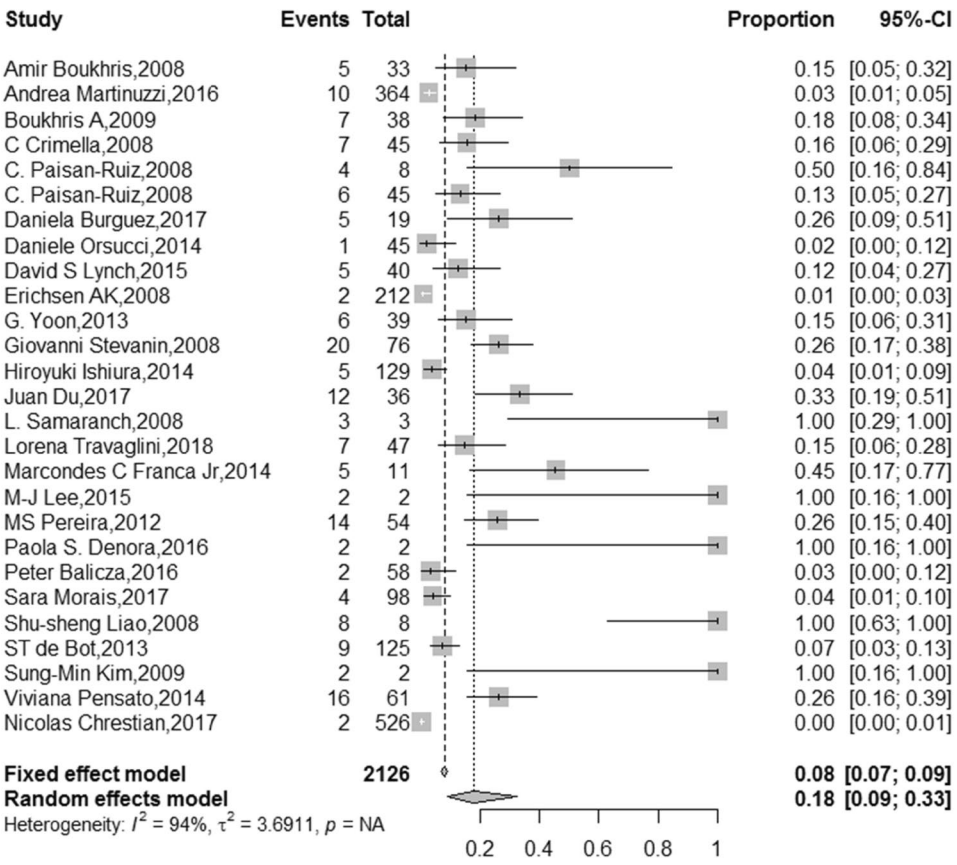

Fig. 4 Forest plot of *SPG11* mutation frequencies in HSP patients. A total of 18% of HSP patients carry *SPG11* mutations. *CI* confidence interval

Neuropathy

From 90, 46 patients with *SPG11*-HSP showed neuropathy. This is less frequent in *SPG15*-HSP (38%, 3 out of 8 patients), and in patients with mutations in *SPG7* (15%, 2 out of 13 patients) (Fig. 8a). Neuropathy was more often observed in the *SPG11* group than in two other groups.

In addition, in AD-HSP groups neuropathy was more often observed in *REEP1*-HSP patients (17%, 4 out of 24 patients) than those with mutated *ATL1* (11%, 2 out of 18) and *SPAST* (2%, 6 out of 260 patients) (Fig. 8b).

The total number of mutation-positive patients with HSP who were diagnosed with other reported abnormalities was also derived from the studies; however, there was no significant association between mutated genes and the sub-phenotypes. A summary of the results of the association of sub-phenotypes with mutated genes is presented in Supplementary Tables 3–6.

Discussion

HSP denotes a degenerative, genetically heterogeneous group of neurological disorders that primarily affect the upper motor neurons [1]. Thus far, multiple investigations have demonstrated the frequency of distinct mutations in individual cases, families, and cohorts of various sizes, and analyzed phenotype–genotype associations [108–110]. The growing application of next-generation sequencing is not only leading to the improvement of diagnosis processes but also leading to the unremitting identification of new causal genes for HSP [2]. To establish robust associations between genotypes and clinically relevant phenotypes and also increase the statistical power, having conclusive data on larger cohorts is indispensable. Accordingly, to strengthen diagnosis, we pooled altogether 147 studies encompassing as many as 13,570 HSP patients according to the stringent quality criteria. The potentiality of evidence for specific genotype–phenotype species and the existence of a predictable relevance between the essential clinical outcomes with distinct genotypes were ascertained by the current meta-analysis. Hitherto, a total of 12 genes for AD-HSP and 41 genes for AR-HSP have been discerned [6]. We encompassed the following genes (*SPAST*, *REEP1*, *ATL1*, *SPG11*, *SPG15*, *SPG7*, *SPG35*, *SPG54*, and *SPG5*) in the study for which an adequate number of individuals for evaluation was feasible.

We are aware that there are some limitations regarding the current study. In some cases, we could not evaluate the relationship of the reported gene mutations and specific risk factors because of the unavailability of relatable

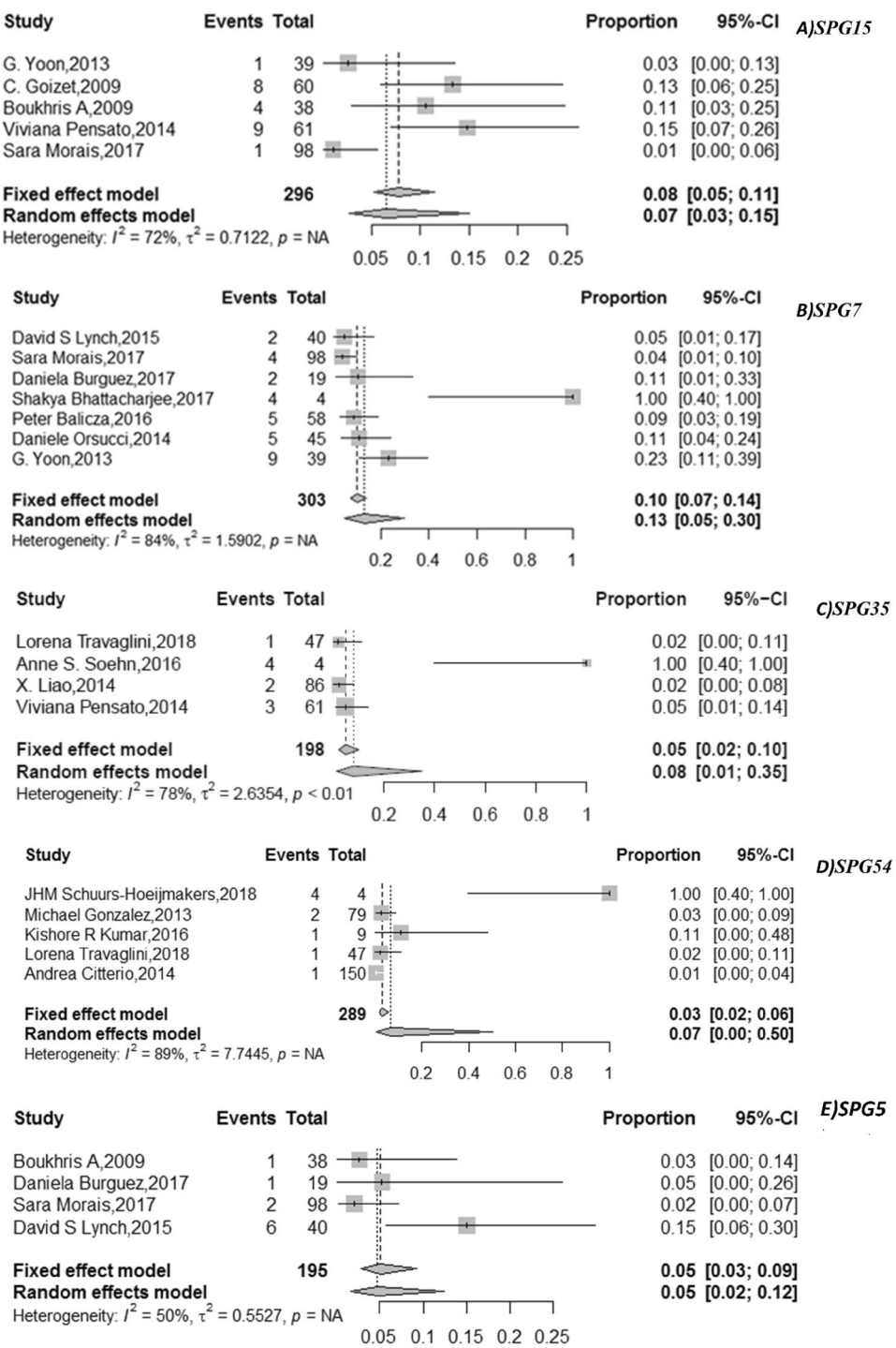

Fig. 5 **a** Forest plot of *SPG15* mutation frequencies in HSP patients. The frequency of SPG15 mutations among HSP patients was 7%. **b** Forest plot of *SPG7* mutation frequencies in HSP patients. The frequency of *SPG7* mutations among HSP patients was 13%. **c** Forest plot of *SPG35* mutation frequencies in HSP patients. The frequency of mutations among HSP patients was 8%. **d** Forest plot of *SPG54* mutation frequency in HSP patients. The frequency was as 7%. **e** Forest plot of *SPG5* mutation frequencies in HSP patients. A total of five percent of HSP patients found to carry *SPG5* mutations. *CI* confidence interval

data. Therefore, further studies are necessary to evaluate the predictive power of genotyping. Moreover, differences in genotyping methods, ethnical background of patients and study design could potentially impose bias into the obtained results. Nevertheless, the advantage of this study is its large sample size which enables statistical power to determine genotype–phenotype associations.

The weight of mutations in AD-HSP patients was on *SPAST* with a frequency of 25%, which is noticeably higher than *REEP1* (3%) and *ATL1* (5%). These findings are compatible with previous reports using a narrative methodology to review evidence of mutation frequency in HSPs [2].

However, it is not statically significant; the Asians showed a higher frequency of mutations in the *SPAST* gene (32.62%)

Table 4 Mean age at disease onset in HSP patients

Gene	Meta-analysis		Test for heterogeneity		
	Mean AO [95% CI]	*k*	*Q*	Q_p	I^2 (%)
AD-HSP					
SPAST	24.79 [21.00–28.58]	40	1584.00	< 0.00	97.50
REEP1	17.00 [11.18–22.82]	6	12.90	0.0251	61.00
ALT1	4.53 [3.09–5.98]	16	224.23	< 0.0001	93.30
AR-HSP					
SPG11	13.10 [11.30–14.90]	22	113.88	< 0.0001	81.60
SPG15	14.67 [11.44–17.91]	2	3.54	0.0598	71.80
SPG7	37.17 [33.31–41.02]	6	6.84	0.2331	26.90
SPG35	13.89 [0.00–28.92]	3	15.20	0.0005	86.80
SPG5	20.07 [10.38–29.76]	2	0.74	0.3907	0.0

in comparison to the Caucasians and Americans. Also, we found a higher frequency for mutations in the *ATL1* gene in the Caucasian HSP patients (8%) in comparison to the Asian and American populations (4%). In descriptive reviews, it has been reported that mutations in *SPAST* account for nearly 40% of AD-HSP cases [6].

As for AR-HSP patients, the contribution of *SPG11* mutations (18%) is higher than that of *SPG15* (11%), *SPG7* (13%), *SPG35* (8%), *SPG54* (7%), and *SPG5* (5%). Almost the obtained results are in line with previous findings that showed *SPG11* as the most common mutated gene in AR-HSP [99]. Interestingly, we found a high rate of *SPG11* mutation in Asian HSP patients (87.98%). This further emphasizes differences in the genetic architecture of different ethnic groups. There are reports tried to provide explanations for the high rate of *SPG11* mutations in populations. It has been determined that repeated Alu elements are one of the factors related to the *SPG11* locus instability which might lead to substantial gene rearrangements of the genomic region [99].

Our result also suggested that the age of onsets varied among patients regardless of the mutated genes. It has been determined that the age of onset can be ranged from 0 to 73 [111]. The results of this meta-analysis suggested that HSP-AD patients with *ATL1* mutations were younger than 10 years at the onset of the disease which are similar to the findings of the study carried by Namekawa et al. [81]. On the other hand, AD-HSP patients with mutated *SPAST* were older than 20 years old when they presented the disease. However, it has been reported that the average onset of AD-HSP in *SPAST* patients is mostly when they are in their 30s [6]. Among AR-HSP patients, *SPG7* mutated ones presented

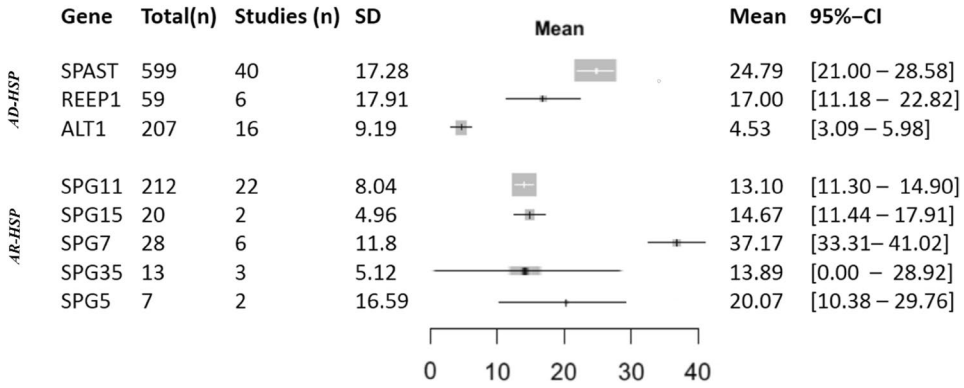

Fig. 6 Summaries of forest plots of mean age at HSP onset in HSP patients with mutations in different genes

Table 5 Mean age at disease onset of reported genes in subpopulations

Gene	Pop	Meta-analysis		Test for heterogeneity			Test for subgroup differences	
		%Frequency [95% CI]	*k*	*Q*	τ^2	I^2 (%)	*Q*	*P*
SPAST	Caucasian	21.88 [17.71–26.06]	23	993.89	86.95	97.8	7.51	0.023
	Asian	28.85 [25.50–32.20]	11	13.86	7.96	27.8		
	American	30.97 [21.86–40.07]	4	14.38	61.94	79.1		
ATL1	Caucasian	3.87 [2.43–5.31]	11	140.35	4.55	92.90	7.98	0.018
	Asian	2.19 [1.12–3.27]	2	0.87	0	0.00		
	American	13.74 [3.80–23.68]	2	3.00	38.18	66.70		
SPG11	Caucasian	13.09 [10.23–15.95]	14	105.26	23.15	87.6	0.03	0.982
	American	12.79 [9.57–16.01]	3	3.19	3.06	37.3		
	Asian	12.76 [10.73–14.80]	4	5.22	1.75	42.6		

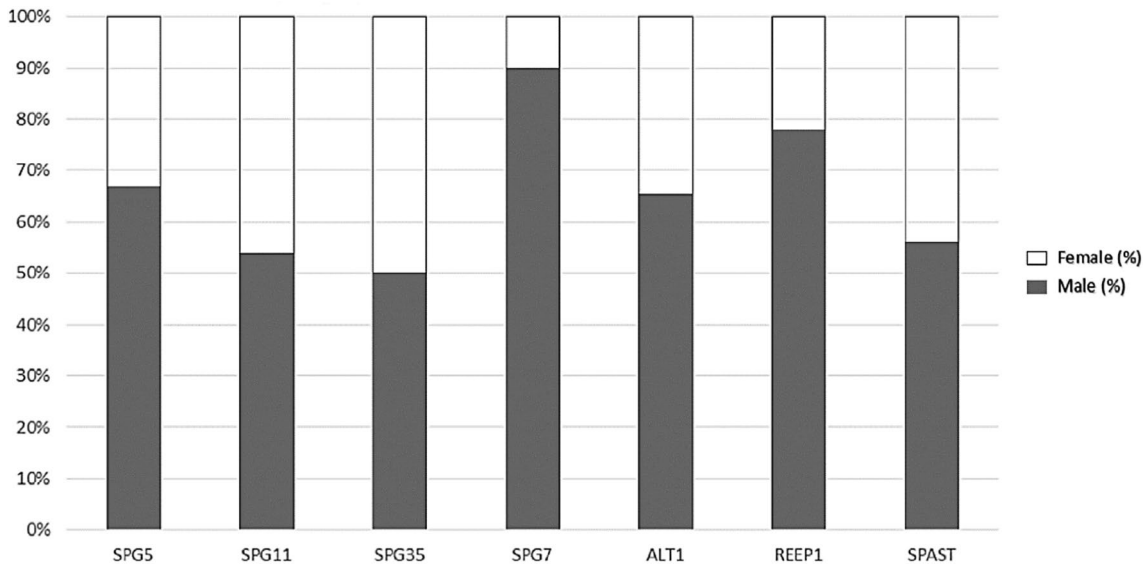

Fig. 7 Gender proportion in HSP patients with mutations in different genes. Numerically males are significantly higher in AR-HSP patients with *SPG7* mutations (90%) and in AD-HSP patients with *REEP1* mutations (78%) than females. The gender distribution among patients with mutated *SPG35* was even

the disease in the fourth decade of their life, which are older at diagnosis than AR-HSP patients with *SPG11*, *SPG15*, *SPG35*, and *SPG5* mutations. Also, our results displayed a significant tendency toward younger age at HSP onset for Caucasian patients with mutated *SPAST* and Asian patients with mutated *ATL1*.

Since HSPs are diseases with diverse range for age at symptom onset, symptoms progression rate and level of disability even in patients from families with the same mutations [6], genotype–phenotype relationships are not straightforward. Several factors contribute to a high level of phenotype variability in HSPs.

In contrast to the general conception that HSP affects males and females to the same degree, our findings represented the predominance of male patients in some specific mutations, notably *SPG7* in AR-HSP group and *REEP1* in AD-HSP group, suggesting the possibility of sex-dependent penetrance or intensity of the disease [112]. This could be attributed to unknown modifying factors. In some cases (*SPG4*-related HSP), age for symptom onset and penetrance is dependent on the patient gender [6].

Regarding the outcome and disease course, there is considerable variability between different subtypes of HSPs. AD-HSP patients with *REEP1* mutations more often present LL weakness, superficial sensory abnormalities, neuropathy, and deep sensory impairment. It has been reported that the manifestation of rare complicating features in *REEP1*-HSP patients is principally related peripheral nerve involvement [13]. Hence, as it has been determined, most *REEP1* patients represent pure spastic paraplegia [113]. Additionally, AD-HSP patients with *SPAST* mutations presented more often with related symptoms including UL spasticity, UL hyperreflexia, ID, and dysarthria than patients with *ATL1* mutations.

HSP-*SPAST* patients experience progressive degeneration of axons which lead to the weakness of lower limbs [114].

AR-HSP patients with *SPG11* mutation had symptoms including pes cavus, neuropathy, and UL spasticity more often than other patients. Furthermore, the rate of *SPG7* patients with cataract is higher than others. Klebe et al. demonstrated the optic abnormalities observed in all SPG7-positive patients [115]. Moreover, patients with mutated *SPG54* present WMA more often, which could be due to the fact that *SPG54* mutations were accompanied by accumulation of lipids [107]. Cognitive abnormalities, dysarthria, and TCC are most often manifested in *SPG54* patients. All in all, it can be inferred from these findings that each specific mutations may have different phenotypes among HSP patients.

Here, we generated the extensive dataset available on genotype–phenotype associations in HSP. Our data exhibit the frequency of each symptom associated with the specific gene mutations which might have prognostic and therapeutic values. In the case of *REEP1* mutations, a higher likelihood for unfavorable outcome including LL weakness, superficial sensory abnormalities, deep sensory impairment, and neuropathy was observed. In addition, AR-HSP patients with *SPG11* mutations would expect symptoms such as pes cavus, neuropathy, and UL spasticity more often. However, we could not evaluate the relationship of some of the reported gene mutations and specific risk factors because of the unavailability of

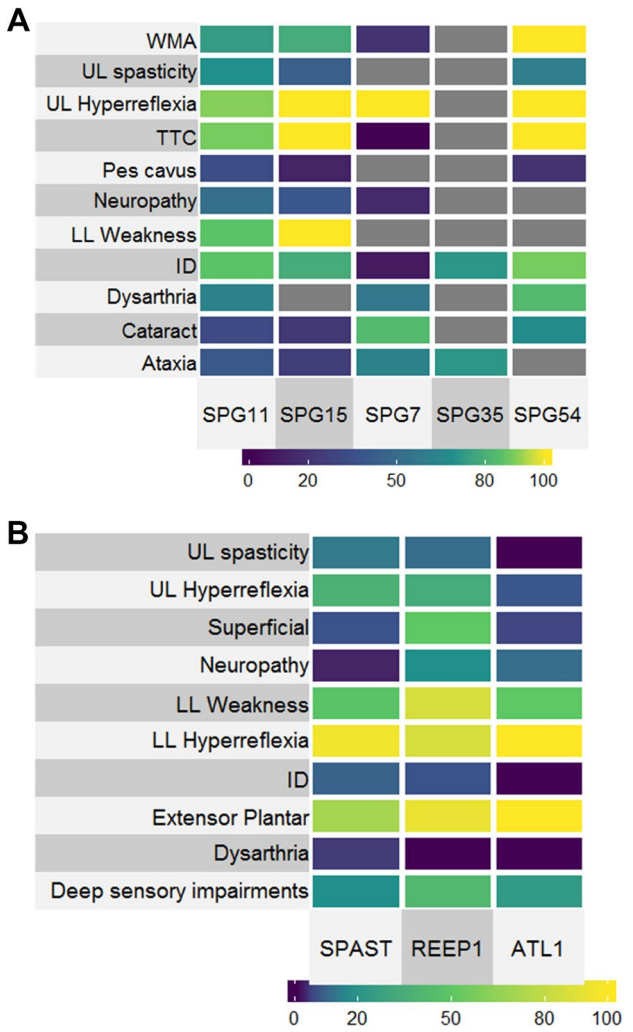

Fig. 8 **a** Relative frequency of findings of the clinical features in AR-HSP patients. **b** Relative frequency of findings of the clinical features in AD-HSP patients. The color gray indicates not available data

relatable data. Therefore, further studies are necessary to evaluate the predictive power of genotyping. Moreover, various genotyping methods or ethnical background of patients and also the evaluation of studies with different study design are limitations of this study. Also, the unavailability of clinical information of some patients, the genetic and clinical heterogeneity of the disease, and the limited number of studies regarding some countries impede the demonstration of more explicit genotype–phenotype relationships.

Acknowledgements The authors thank the Shahid Beheshti University of Medical Sciences for continuous support.

Funding The presented article is financially supported by "Research Department of the School of Medicine Shahid Beheshti University of Medical Sciences".

Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

References

1. Noreau A, Dion PA, Rouleau GA (2014) Molecular aspects of hereditary spastic paraplegia. Exp Cell Res 325(1):18–26
2. Boutry M, Morais S, Stevanin G (2019) Update on the genetics of spastic paraplegias. Curr Neurol Neurosci Rep 19(4):18
3. Tesson C, Koht J, Stevanin G (2015) Delving into the complexity of hereditary spastic paraplegias: how unexpected phenotypes and inheritance modes are revolutionizing their nosology. Hum Genet 134(6):511–538
4. Schlang KJ, Arning L, Epplen JT, Stemmler S (2008) Autosomal dominant hereditary spastic paraplegia: novel mutations in the REEP1 gene (SPG31). BMC Med Genet 9(1):71
5. D'Amore A, Tessa A, Casali C, Dotti MT, Filla A, Silvestri G et al (2018) Next generation molecular diagnosis of Hereditary Spastic Paraplegias: an Italian cross-sectional study. Front Neurol. 9:981
6. Giudice TL, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A (2014) Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. Exp Neurol 261:518–539
7. Paisan-Ruiz C, Dogu O, Yilmaz A, Houlden H, Singleton A (2008) SPG11 mutations are common in familial cases of complicated hereditary spastic paraplegia. Neurology 70(16):1384–1389
8. Chrestian N, Dupre N, Gan-Or Z, Szuto A, Chen S, Venkitachalam A et al (2017) Clinical and genetic study of hereditary spastic paraplegia in Canada. Neurol Genet 3(1):e122
9. Balicza P, Grosz Z, Gonzalez MA, Bencsik R, Pentelenyi K, Gal A et al (2016) Genetic background of the hereditary spastic paraplegia phenotypes in Hungary—an analysis of 58 probands. J Neurol Sci 364:116–121
10. Morais S, Raymond L, Mairey M, Coutinho P, Brandao E, Ribeiro P et al (2017) Massive sequencing of 70 genes reveals a myriad of missing genes or mechanisms to be uncovered in hereditary spastic paraplegias. EJHG 25(11):1217–1228
11. Adam M, Ardinger H, Pagon R, Wallace S, Bean L, Stephens K, et al. Hereditary spastic paraplegia overview—GeneReviews®
12. Faber J, Fonseca LM (2014) How sample size influences research outcomes. Dent Press J Orthodont 19(4):27–29
13. Beetz C, Schüle R, Deconinck T, Tran-Viet K-N, Zhu H, Kremer BP et al (2008) REEP1 mutation spectrum and genotype/phenotype correlation in hereditary spastic paraplegia type 31. Brain 131(4):1078–1086
14. Zhao G-h, Liu X-m (2017) Clinical features and genotype-phenotype correlation analysis in patients with ATL1 mutations: a literature reanalysis. Transl Neurodegen 6(1):9
15. Fink JK (2013) Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. Acta Neuropathol 126(3):307–328
16. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264–269
17. Orlacchio A, Patrono C, Borreca A, Babalini C, Bernardi G, Kawarai T (2008) Spastic paraplegia in Romania: high prevalence of SPG4 mutations. J Neurol Neurosurg Psychiatry 79(5):606–607

18. Erichsen A, Inderhaug E, Mattingsdal M, Eiklid K, Tallaksen C (2007) Seven novel mutations and four exon deletions in a collection of Norwegian patients with SPG4 hereditary spastic paraplegia. Eur J Neurol 14(7):809–814
19. Polymeris AA, Tessa A, Anagnostopoulou K, Rubegni A, Galatolo D, Dinopoulos A et al (2016) A series of Greek children with pure hereditary spastic paraplegia: clinical features and genetic findings. J Neurol 263(8):1604–1611
20. Martinuzzi A, Montanaro D, Vavla M, Paparella G, Bonanni P, Musumeci O et al (2016) Clinical and paraclinical indicators of motor system impairment in hereditary spastic paraplegia: a pilot study. PLoS One 11(4):e0153283
21. Magariello A, Muglia M, Patitucci A, Ungaro C, Mazzei R, Gabriele AL et al (2010) Mutation analysis of the SPG4 gene in Italian patients with pure and complicated forms of spastic paraplegia. J Neurol Sci 288(1–2):96–100
22. Sulek A, Elert E, Rajkiewicz M, Zdzienicka E, Stepniak I, Krysa W et al (2013) Screening for the hereditary spastic paraplaegias SPG4 and SPG3A with the multiplex ligation-dependent probe amplification technique in a large population of affected individuals. Neurol Sci 34(2):239–242
23. Mészárosová AU, Putzová M, Čermáková M, Vávrová D, Doležalová K, Smetanová I et al (2016) SPAST mutation spectrum and familial occurrence among Czech patients with pure hereditary spastic paraplegia. J Hum Genet 61(10):845
24. Tang B, Zhao G, Xia K, Pan Q, Luo W, Shen L et al (2004) Three novel mutations of the spastin gene in Chinese patients with hereditary spastic paraplegia. Arch Neurol 61(1):49–55
25. Boukhris A, Stevanin G, Feki I, Denora P, Elleuch N, Miladi M et al (2009) Tunisian hereditary spastic paraplegias: clinical variability supported by genetic heterogeneity. Clin Genet 75(6):527–536
26. Depienne C, Tallaksen C, Lephay J-Y, Bricka B, Poea-Guyon S, Fontaine B et al (2006) Spastin mutations are frequent in sporadic spastic paraparesis and their spectrum is different from that observed in familial cases. J Med Genet 43(3):259–265
27. Proukakis C, Auer-Grumbach M, Wagner K, Wilkinson P, Reid E, Patton M et al (2003) Screening of patients with hereditary spastic paraplegia reveals seven novel mutations in the SPG4 (Spastin) gene. Hum Mutat 21(2):170
28. McDermott C, Burness C, Kirby J, Cox L, Rao D, Hewamadduma C et al (2006) Clinical features of hereditary spastic paraplegia due to spastin mutation. Neurology. 67(1):45–51
29. Proukakis C, Hart PE, Cornish A, Warner TT, Crosby AH (2002) Three novel spastin (SPG4) mutations in families with autosomal dominant hereditary spastic paraplegia. J Neurol Sci 201(1–2):65–69
30. Patrono C, Scarano V, Cricchi F, Melone MA, Chiriaco M, Napolitano A et al (2005) Autosomal dominant hereditary spastic paraplegia: DHPLC-based mutation analysis of SPG4 reveals eleven novel mutations. Hum Mutat 25(5):506
31. Burguez D, Polese-Bonatto M, Scudeiro LAJ, Björkhem I, Schöls L, Jardim LB et al (2017) Clinical and molecular characterization of hereditary spastic paraplegias: a next-generation sequencing panel approach. J Neurol Sci 383:18–25
32. Orsucci D, Petrucci L, Ienco EC, Chico L, Simi P, Fogli A et al (2014) Hereditary spastic paraparesis in adults. A clinical and genetic perspective from Tuscany. Clin Neurol Neurosurg 120:14–19
33. Lynch DS, Koutsis G, Tucci A, Panas M, Baklou M, Breza M et al (2016) Hereditary spastic paraplegia in Greece: characterisation of a previously unexplored population using next-generation sequencing. Eur J Hum Genet 24(6):857
34. Elert-Dobkowska E, Stepniak I, Krysa W, Rajkiewicz M, Rakowicz M, Sobanska A et al (2015) Molecular spectrum of the SPAST, ATL1 and REEP1 gene mutations associated with the most common hereditary spastic paraplegias in a group of Polish patients. J Neurol Sci 359(1–2):35–39
35. Crippa F, Panzeri C, Martinuzzi A, Arnoldi A, Redaelli F, Tonelli A et al (2006) Eight novel mutations in SPG4 in a large sample of patients with hereditary spastic paraplegia. Arch Neurol 63(5):750–755
36. Vandebona H, Kerr N, Liang C, Sue C (2012) SPAST mutations in A ustralian patients with hereditary spastic paraplegia. Internal Med J 42(12):1342–1347
37. Ishiura H, Takahashi Y, Hayashi T, Saito K, Furuya H, Watanabe M et al (2014) Molecular epidemiology and clinical spectrum of hereditary spastic paraplegia in the Japanese population based on comprehensive mutational analyses. J Hum Genet 59(3):163
38. Park H, Kang S-H, Park S, Kim SY, Seo SH, Lee SJ et al (2015) Mutational spectrum of the SPAST and ATL1 genes in Korean patients with hereditary spastic paraplegia. J Neurol Sci 357(1–2):167–172
39. Yabe I, Sasaki H, Tashiro K, Matsuura T, Takegami T, Satoh T (2002) Spastin gene mutation in Japanese with hereditary spastic paraplegia. J Med Genet 39(8):e46-e
40. Meijer IA, Hand CK, Cossette P, Figlewicz DA, Rouleau GA (2002) Spectrum of SPG4 mutations in a large collection of North American families with hereditary spastic paraplegia. Arch Neurol 59(2):281–286
41. Ivanova N, Löfgren A, Tournev I, Rousev R, Andreeva A, Jordanova A et al (2006) Spastin gene mutations in Bulgarian patients with hereditary spastic paraplegia. Clin Genet 70(6):490–495
42. Lindsey J, Lusher M, McDermott C, White K, Reid E, Rubinsztein D et al (2000) Mutation analysis of the spastin gene (SPG4) in patients with hereditary spastic paraparesis. J Med Genet 37(10):759–765
43. Loureiro JL, Brandão E, Ruano L, Brandão AF, Lopes AM, Thieleke-Matos C et al (2013) Autosomal dominant spastic paraplegias: a review of 89 families resulting from a portuguese survey. JAMA Neurol 70(4):481–487
44. Svenstrup K, Bross P, Koefoed P, Hjermind LE, Eiberg H, Born AP et al (2009) Sequence variants in SPAST, SPG3A and HSPD1 in hereditary spastic paraplegia. J Neurol Sci 284(1–2):90–95
45. Nanetti L, Baratta S, Panzeri M, Tomasello C, Lovati C, Azzollini J et al (2012) Novel and recurrent spastin mutations in a large series of SPG4 Italian families. Neurosci Lett 528(1):42–45
46. Travaglini L, Aiello C, Stregapede F, D'Amico A, Alesi V, Ciolfi A et al (2018) The impact of next-generation sequencing on the diagnosis of pediatric-onset hereditary spastic paraplegias: new genotype-phenotype correlations for rare HSP-related genes. Neurogenetics 19:111–121
47. Loureiro J, Miller-Fleming L, Thieleke-Matos C, Magalhães P, Cruz V, Coutinho P et al (2009) Novel SPG3A and SPG4 mutations in dominant spastic paraplegia families. Acta Neurol Scand 119(2):113–118
48. Braschinsky M, Tamm R, Beetz C, Sachez-Ferrero E, Raukas E, Lüüs S-M et al (2010) Unique spectrum of SPAST variants in Estonian HSP patients: presence of benign missense changes but lack of exonic rearrangements. BMC Neurol 10(1):17
49. Franca MC Jr, Dogini DB, D'Abreu A, Teive HA, Munhoz RP, Raskin S et al (2014) SPG4-related hereditary spastic paraplegia: frequency and mutation spectrum in Brazil. Clin Genet 86(2):194–196
50. McCorquodale DS 3rd, Ozomaro U, Huang J, Montenegro G, Kushman A, Citrigno L et al (2011) Mutation screening of spastin, atlastin, and REEP1 in hereditary spastic paraplegia. Clin Genet 79(6):523–530
51. Falco M, Scuderi C, Musumeci S, Sturnio M, Neri M, Bigoni S et al (2004) Two novel mutations in the spastin gene (SPG4) found by DHPLC mutation analysis. NMD 14(11):750–753

52. Lan MY, Fu SC, Chang YY, Wu-Chou YH, Lai SC, Chen RS et al (2012) Clinical and genetic analysis of four Taiwanese families with autosomal dominant hereditary spastic paraplegia. J Formosan Med Assoc Taiwan yi zhi. 111(7):380–385
53. Lan MY, Chang YY, Yeh TH, Lai SC, Liou CW, Kuo HC et al (2014) High frequency of SPG4 in Taiwanese families with autosomal dominant hereditary spastic paraplegia. BMC Neurol 14:216
54. Shoukier M, Neesen J, Sauter SM, Argyriou L, Doerwald N, Pantakani DV et al (2009) Expansion of mutation spectrum, determination of mutation cluster regions and predictive structural classification of SPAST mutations in hereditary spastic paraplegia. EJHG 17(2):187–194
55. Zhao N, Sui Y, Li XF, Liu W, Lu YP, Feng WH et al (2015) Mutation analysis of four Chinese families with pure hereditary spastic paraplegia: pseudo- X-linked dominant inheritance and male lethality due to a novel ATL1 mutation. GMR 14(4):14690–14697
56. Ribai P, Depienne C, Fedirko E, Jothy AC, Viveweger C, Hahn-Barma V et al (2008) Mental deficiency in three families with SPG4 spastic paraplegia. EJHG 16(1):97–104
57. Fei QZ, Tang WG, Rong TY, Tang HD, Liu JR, Guo ZL et al (2011) Two novel mutations in the Spastin gene of Chinese patients with hereditary spastic paraplegia. Eur J Neurol 18(9):1194–1196
58. Reddy MA, Chen Z, Park JT, Wang M, Lanting L, Zhang Q, et al. Regulation of inflammatory phenotype in macrophages by a diabetes-induced long non-coding RNA. Diabetes. 2014:DB_140298
59. Battini R, Fogli A, Borghetti D, Michelucci A, Perazza S, Baldinotti F et al (2011) Clinical and genetic findings in a series of Italian children with pure hereditary spastic paraplegia. Eur J Neurol 18(1):150–157
60. Basri R, Yabe I, Soma H, Takei A, Nishimura H, Machino Y et al (2006) Four mutations of the spastin gene in Japanese families with spastic paraplegia. J Hum Genet 51(8):711–715
61. de Bot ST, van den Elzen RT, Mensenkamp AR, Schelhaas HJ, Willemsen MA, Knoers NV et al (2010) Hereditary spastic paraplegia due to SPAST mutations in 151 Dutch patients: new clinical aspects and 27 novel mutations. J Neurol Neurosurg Psychiatry 81(10):1073–1078
62. Sauter S, Miterski B, Klimpe S, Bonsch D, Schols L, Visbeck A et al (2002) Mutation analysis of the spastin gene (SPG4) in patients in Germany with autosomal dominant hereditary spastic paraplegia. Hum Mutat 20(2):127–132
63. Park SY, Ki CS, Kim HJ, Kim JW, Sung DH, Kim BJ et al (2005) Mutation analysis of SPG4 and SPG3A genes and its implication in molecular diagnosis of Korean patients with hereditary spastic paraplegia. Arch Neurol 62(7):1118–1121
64. Kim TH, Lee JH, Park YE, Shin JH, Nam TS, Kim HS et al (2014) Mutation analysis of SPAST, ATL1, and REEP1 in Korean patients with hereditary spastic paraplegia. J Clin Neurol (Seoul, Korea) 10(3):257–261
65. Kawarai T, Montecchiani C, Miyamoto R, Gaudiello F, Caltagirone C, Izumi Y et al (2017) Spastic paraplegia type 4: a novel SPAST splice site donor mutation and expansion of the phenotype variability. J Neurol Sci 380:92–97
66. Alvarez V, Sanchez-Ferrero E, Beetz C, Diaz M, Alonso B, Corao AI et al (2010) Mutational spectrum of the SPG4 (SPAST) and SPG3A (ATL1) genes in Spanish patients with hereditary spastic paraplegia. BMC Neurol 10:89
67. Chelban V, Tucci A, Lynch DS, Polke JM, Santos L, Jonvik H et al (2017) Truncating mutations in SPAST patients are associated with a high rate of psychiatric comorbidities in hereditary spastic paraplegia. J Neurol Neurosurg Psychiatry 88(8):681–687
68. Lu X, Cen Z, Xie F, Ouyang Z, Zhang B, Zhao G et al (2014) Genetic analysis of SPG4 and SPG3A genes in a cohort of Chinese patients with hereditary spastic paraplegia. J Neurol Sci 347(1–2):368–371
69. Luo Y, Chen C, Zhan Z, Wang Y, Du J, Hu Z et al (2014) Mutation and clinical characteristics of autosomal-dominant hereditary spastic paraplegias in China. Neuro-degen Dis 14(4):176–183
70. Depienne C, Fedirko E, Forlani S, Cazeneuve C, Ribai P, Feki I et al (2007) Exon deletions of SPG4 are a frequent cause of hereditary spastic paraplegia. J Med Genet 44(4):281–284
71. Lynch DS, Koutsis G, Tucci A, Panas M, Baklou M, Breza M et al (2016) Hereditary spastic paraplegia in Greece: characterisation of a previously unexplored population using next-generation sequencing. EJHG 24(6):857–863
72. de Bot ST, Veldink JH, Vermeer S, Mensenkamp AR, Brugman F, Scheffer H et al (2013) ATL1 and REEP1 mutations in hereditary and sporadic upper motor neuron syndromes. J Neurol 260(3):869–875
73. Beetz C, Schule R, Deconinck T, Tran-Viet KN, Zhu H, Kremer BP et al (2008) REEP1 mutation spectrum and genotype/phenotype correlation in hereditary spastic paraplegia type 31. Brain 131(Pt 4):1078–1086
74. Goizet C, Depienne C, Benard G, Boukhris A, Mundwiller E, Sole G et al (2011) REEP1 mutations in SPG31: frequency, mutational spectrum, and potential association with mitochondrial morpho-functional dysfunction. Hum Mutat 32(10):1118–1127
75. Elsayed LE, Mohammed IN, Hamed AA, Elseed MA, Johnson A, Mairey M et al (2016) Hereditary spastic paraplegias: identification of a novel SPG57 variant affecting TFG oligomerization and description of HSP subtypes in Sudan. EJHG 25(1):100–110
76. Travaglini L, Aiello C, Stregapede F, D'Amico A, Alesi V, Ciolfi A et al (2018) The impact of next-generation sequencing on the diagnosis of pediatric-onset hereditary spastic paraplegias: new genotype-phenotype correlations for rare HSP-related genes. Neurogenetics. 19(2):111–121
77. Smith BN, Bevan S, Vance C, Renwick P, Wilkinson P, Proukakis C et al (2009) Four novel SPG3A/atlastin mutations identified in autosomal dominant hereditary spastic paraplegia kindreds with intra-familial variability in age of onset and complex phenotype. Clin Genet 75(5):485–489
78. Durr A, Camuzat A, Colin E, Tallaksen C, Hannequin D, Coutinho P et al (2004) Atlastin1 mutations are frequent in young-onset autosomal dominant spastic paraplegia. Arch Neurol 61(12):1867–1872
79. Meszarosova AU, Grecmalova D, Brazdilova M, Dvorackova N, Kalina Z, Cermakova M et al (2017) Disease-causing variants in the ATL1 gene are a rare cause of hereditary spastic paraplegia among Czech patients. Ann Hum Genet 81(6):249–257
80. Abel A, Fonknechten N, Hofer A, Durr A, Cruaud C, Voit T et al (2004) Early onset autosomal dominant spastic paraplegia caused by novel mutations in SPG3A. Neurogenetics 5(4):239–243
81. Namekawa M, Ribai P, Nelson I, Forlani S, Fellmann F, Goizet C et al (2006) SPG3A is the most frequent cause of hereditary spastic paraplegia with onset before age 10 years. Neurology 66(1):112–114
82. Sauter SM, Engel W, Neumann LM, Kunze J, Neesen J (2004) Novel mutations in the Atlastin gene (SPG3A) in families with autosomal dominant hereditary spastic paraplegia and evidence for late onset forms of HSP linked to the SPG3A locus. Hum Mutat 23(1):98
83. Pensato V, Castellotti B, Gellera C, Pareyson D, Ciano C, Nanetti L et al (2014) Overlapping phenotypes in complex spastic paraplegias SPG11, SPG15, SPG35 and SPG48. Brain 137(Pt 7):1907–1920

84. Franca MC Jr, Yasuda CL, Pereira FR, D'Abreu A, Lopes-Ramos CM, Rosa MV et al (2012) White and grey matter abnormalities in patients with SPG11 mutations. J Neurol Neurosurg Psychiatry 83(8):828–833
85. Kim SM, Lee JS, Kim S, Kim HJ, Kim MH, Lee KM et al (2009) Novel compound heterozygous mutations of the SPG11 gene in Korean families with hereditary spastic paraplegia with thin corpus callosum. J Neurol 256(10):1714–1718
86. Lee MJ, Cheng TW, Hua MS, Pan MK, Wang J, Stephenson DA et al (2008) Mutations of the SPG11 gene in patients with autosomal recessive spastic paraparesis and thin corpus callosum. J Neurol Neurosurg Psychiatry 79(5):607–609
87. Liao SS, Shen L, Du J, Zhao GH, Wang XY, Yang Y et al (2008) Novel mutations of the SPG11 gene in hereditary spastic paraplegia with thin corpus callosum. J Neurol Sci 275(1–2):92–99
88. Paisan-Ruiz C, Dogu O, Yilmaz A, Houlden H, Singleton A (2008) SPG11 mutations are common in familial cases of complicated hereditary spastic paraplegia. Neurology 70(16 Pt 2):1384–1389
89. Paisan-Ruiz C, Nath P, Wood NW, Singleton A, Houlden H (2008) Clinical heterogeneity and genotype-phenotype correlations in hereditary spastic paraplegia because of Spatacsin mutations (SPG11). Eur J Neurol 15(10):1065–1070
90. Samaranch L, Riverol M, Masdeu JC, Lorenzo E, Vidal-Taboada JM, Irigoyen J et al (2008) SPG11 compound mutations in spastic paraparesis with thin corpus callosum. Neurology 71(5):332–336
91. Stevanin G, Azzedine H, Denora P, Boukhris A, Tazir M, Lossos A et al (2008) Mutations in SPG11 are frequent in autosomal recessive spastic paraplegia with thin corpus callosum, cognitive decline and lower motor neuron degeneration. Brain 131(Pt 3):772–784
92. Yoon G, Baskin B, Tarnopolsky M, Boycott KM, Geraghty MT, Sell E et al (2013) Autosomal recessive hereditary spastic paraplegia-clinical and genetic characteristics of a well-defined cohort. Neurogenetics 14(3–4):181–188
93. Boukhris A, Stevanin G, Feki I, Denis E, Elleuch N, Miladi MI et al (2008) Hereditary spastic paraplegia with mental impairment and thin corpus callosum in Tunisia: SPG11, SPG15, and further genetic heterogeneity. Arch Neurol 65(3):393–402
94. Crimella C, Arnoldi A, Crippa F, Mostacciuolo ML, Boaretto F, Sironi M et al (2009) Point mutations and a large intragenic deletion in SPG11 in complicated spastic paraplegia without thin corpus callosum. J Med Genet 46(5):345–351
95. Denora PS, Smets K, Zolfanelli F, Ceuterick-de Groote C, Casali C, Deconinck T et al (2016) Motor neuron degeneration in spastic paraplegia 11 mimics amyotrophic lateral sclerosis lesions. Brain 139(Pt 6):1723–1734
96. de Bot ST, Burggraaff RC, Herkert JC, Schelhaas HJ, Post B, Diekstra A et al (2013) Rapidly deteriorating course in Dutch hereditary spastic paraplegia type 11 patients. EJHG 21(11):1312–1315
97. Du J, Hu YC, Tang BS, Jiang H, Shen L (2018) Identification of novel SPG11 mutations in a cohort of Chinese families with hereditary spastic paraplegia. Int J Neurosci 128(2):146–150
98. Erichsen AK, Stevanin G, Denora P, Brice A, Tallaksen CM (2008) SPG11–the most common type of recessive spastic paraplegia in Norway? Acta Neurol Scand Suppl 188:46–50
99. Conceicao Pereira M, Loureiro JL, Pinto-Basto J, Brandao E, Margarida Lopes A, Neves G et al (2012) Alu elements mediate large SPG11 gene rearrangements: further spatacsin mutations. Genet Med 14(1):143–151
100. Goizet C, Boukhris A, Maltete D, Guyant-Marechal L, Truchetto J, Mundwiller E et al (2009) SPG15 is the second most common cause of hereditary spastic paraplegia with thin corpus callosum. Neurology 73(14):1111–1119
101. Bhattacharjee S, Beauchamp N, Murray BE, Lynch T (2017) Case series of autosomal recessive hereditary spastic paraparesis with novel mutation in SPG 7 gene. Neurosciences (Riyadh, Saudi Arabia) 22(4):303–307
102. Soehn AS, Rattay TW, Beck-Wodl S, Schaferhoff K, Monk D, Dobler-Neumann M et al (2016) Uniparental disomy of chromosome 16 unmasks recessive mutations of FA2H/SPG35 in 4 families. Neurology 87(2):186–191
103. Liao X, Luo Y, Zhan Z, Du J, Hu Z, Wang J et al (2015) SPG35 contributes to the second common subtype of AR-HSP in China: frequency analysis and functional characterization of FA2H gene mutations. Clin Genet 87(1):85–89
104. Citterio A, Arnoldi A, Panzeri E, D'Angelo MG, Filosto M, Dilena R et al (2014) Mutations in CYP2U1, DDHD2 and GBA2 genes are rare causes of complicated forms of hereditary spastic paraparesis. J Neurol 261(2):373–381
105. Kumar KR, Wali GM, Kamate M, Wali G, Minoche AE, Puttick C et al (2016) Defining the genetic basis of early onset hereditary spastic paraplegia using whole genome sequencing. Neurogenetics 17(4):265–270
106. Gonzalez M, Nampoothiri S, Kornblum C, Oteyza AC, Walter J, Konidari I et al (2013) Mutations in phospholipase DDHD2 cause autosomal recessive hereditary spastic paraplegia (SPG54). EJHG 21(11):1214–1218
107. Schuurs-Hoeijmakers JH, Geraghty MT, Kamsteeg EJ, Ben-Salem S, de Bot ST, Nijhof B et al (2012) Mutations in DDHD2, encoding an intracellular phospholipase A(1), cause a recessive form of complex hereditary spastic paraplegia. Am J Hum Genet 91(6):1073–1081
108. Helbig KL, Hedrich UB, Shinde DN, Krey I, Teichmann AC, Hentschel J, et al. A recurrent mutation in KCNA2 as a novel cause of hereditary spastic paraplegia and ataxia. Ann Neurol. 2016;80(4):638–642
109. Kumar KR, Blair NF, Sue CM (2015) An update on the hereditary spastic paraplegias: new genes and new disease models. Mov Disord Clin Pract 2(3):213–223
110. Faber I, Branco LMT, Júnior F, Cavalvante M (2016) Cognitive dysfunction in hereditary spastic paraplegias and other motor neuron disorders. Dement Neuropsychol 10(4):276–279
111. Schüle R, Wiethoff S, Martus P, Karle KN, Otto S, Klebe S et al (2016) Hereditary spastic paraplegia: clinicogenetic lessons from 608 patients. Ann Neurol 79(4):646–658
112. Fjermestad KW, Kanavin ØJ, Næss EE, Hoxmark LB, Hummelvoll G (2016) Health survey of adults with hereditary spastic paraparesis compared to population study controls. Orphanet J Rare Dis 11(1):98
113. Züchner S, Wang G, Tran-Viet K-N, Nance MA, Gaskell PC, Vance JM et al (2006) Mutations in the novel mitochondrial protein REEP1 cause hereditary spastic paraplegia type 31. Am J Hum Genet 79(2):365–369
114. Solowska JM, Rao AN, Baas PW (2017) Truncating mutations of SPAST associated with hereditary spastic paraplegia indicate greater accumulation and toxicity of the M1 isoform of spastin. Mol Biol Cell 28(13):1728–1737
115. Klebe S, Depienne C, Gerber S, Challe G, Anheim M, Charles P et al (2012) Spastic paraplegia gene 7 in patients with spasticity and/or optic neuropathy. Brain 135(10):2980–2993

Affiliations

Maryam Erfanian Omidvar[1] · Shahram Torkamandi[2] · Somaye Rezaei[3] · Behnam Alipoor[4] · Mir Davood Omrani[5] · Hossein Darvish[6] · Hamid Ghaedi[5]

1 Department of Medical Laboratory Technology, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2 Department of Medical Genetics and Immunology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran

3 Department of Neurology, Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran

4 Department of Laboratory Sciences, Faculty of Parmedicine, Yasuj University of Medical Sciences, Yasuj, Iran

5 Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Velenjak St., Shahid Chamran Highway, Tehran, IR, Iran

6 Department of Medical Genetics, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran