ORIGINAL ARTICLE

Movement disorders in hereditary spastic paraplegia (HSP): a systematic review and individual participant data meta-analysis

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Abstract

Background Hereditary spastic paraplegia (HSP) is a rare genetic disorder associated with mutations in > 80 loci designated *SPG* (SPastic parapleGia). The phenotypic spectrum of HSP can extend to include other neurologic features, including movement disorders. Our aim was to investigate genotype–phenotype associations in HSP with a focus on movement disorders.

Methods We performed a systematic review and individual participant data (IPD)-level meta-analysis by retrieving publications from Medline/EMBASE/Web of Science on HSP with a SPG genotype. Studies were included only if individual-level information was accessible and at least one patient with a movement disorder was reported for that genotype. Out of 21,957 hits, 192 manuscripts with a total of 1413 HSP cases were eligible. Data were compared between two HSP groups: manifested with (HSP-MD, $n = 767$) or without (HSP-nMD, $n = 646$) a movement disorder.

Results The HSP-MD group had an older age of onset (20.5 ± 16.0 vs. 17.1 ± 14.2 yr, $p < 0.001$) and less frequent autosomal dominant inheritance (7.6% vs. 30.1%, $p < 0.001$) compared to HSP-nMD. SPG7 (31.2%) and SPG11 (23.8%) were the most frequent genotypes in the HSP-MD group. HSP-MD with SPG7 had higher frequency of later onset during adulthood (82.9% vs. 8.5%), ataxia (OR = 12.6), extraocular movement disturbances (OR = 3.4) and seizure (OR = 3.7) compared to HSP-MD with SPG11. Conversely, SPG11 mutations were more frequently associated with consanguinity (OR = 4.1), parkinsonism (OR = 7.8), dystonia (OR = 5.4), peripheral neuropathy (OR = 26.9), and cognitive dysfunction (OR = 34.5).

Conclusion This systematic IPD-level meta-analysis provides the largest data on genotype–phenotype associations in HSP-MD. Several clinically relevant phenotypic differences were found between various genotypes, which can possibly facilitate diagnosis in resource-limited settings.

Keywords Hereditary spastic paraplegia (HSP) · Movement disorders · Genotype · Phenotype · *SPG* (SPastic parapleGia)

Introduction

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Hereditary spastic paraplegia (HSP) is a large and diverse group of genetic disorders primarily associated with corticospinal tract dysfunction. HSP is highly heterogeneous—both clinically and genetically—and contributes to challenging landscapes in clinical practice. It has been traditionally classified as pure/uncomplicated, when pyramidal tract signs are prominent and sometimes accompanied by sensory or urinary symptoms, or complex/complicated, when additional features such as seizures and cognitive impairment are present [1]. Distinct modes of inheritance have been described (autosomal dominant, autosomal recessive, X-linked, and rarely, mitochondrial), and over 80 distinct genetic loci have been linked to HSP [2, 3]. Mutations in the *SPAST* (*SPG4*) gene are the most frequent

cause of autosomal dominant HSP, while *SPG11* mutations are responsible for most autosomal recessive forms [2].

Movement disorders, such as ataxia, parkinsonism, and dystonia, can be accompanying neurological features in HSP. In fact, genes responsible for hereditary ataxias overlap with HSP genes, and ataxia-spasticity may be considered along a continuous disease spectrum [4, 5]. For instance, ataxia is a major clinical presentation in patients with *SPG7* mutations [6, 7]. Parkinsonism—sometimes L-dopa responsive—and dystonia have been described in *SPG11* [2, 8–11] and *SPG15* [12, 13], while cervical dystonia, spasmodic dysphonia, and limb dystonia have been reported in *SPG7* [14–16]. Myoclonus is a rare feature of HSP [17]. While these previous studies have started to delineate associations between specific SPG loci and movement disorders, a large but focused effort is needed to draw stronger, more accurate, and potentially predictive correlations.

Our aim is to systematically review and perform an individual participant data-level meta-analysis on HSP with known *SPG* genotype, exploring the prevalence and type of movement disorders and other clinically relevant phenotypic differences in patients with distinct genotypes. In view of the wide HSP phenotypic heterogeneity, we suspect the presence and type of movement disorder may aid in the diagnosis of this complex disorder.

Methods

Data sources and searching strategy

We performed a systematic review of available literature, according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (the PRISMA-IPD) guideline [18], on HSP with a known SPG genotype published from 1990 to June 2018 (flow diagram in Fig. 1). A research librarian conducted literature searches of three major scientific databases (Medline, EMBASE, and Web of Science (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI) using relevant database-specific subject headings and keywords (Supplementary Material). The initial search was performed in September 2015 and an update search was run June 2018. All articles published prior to 1990 were excluded. Duplicate articles were removed. Abstract screening of the remaining articles was performed by three separate investigators (S. M. F., P. A. S., N. P.). Lists of included articles were then compared, and a final decision as to include or exclude a particular article was made by the three investigators (S. M. F., P. A. S., N. P.). In case of discrepancy between the investigators, a fourth investigator (L. V. K.) decided.

Abstract screening

Abstracts were included if reference was made to a clinical description of at least one HSP patient with a numerically defined loci with an SPG designation according to McKusick's Online Mendelian Inheritance in Man (OMIM®) [19]. Mitochondrial HSP is extremely rare, and we did not encounter any SPG designation associated with mutations in the mitochondrial genome. Articles were excluded if they were published prior to 1990. Review articles and non-human studies were also excluded. For all included abstracts and all potentially relevant articles without an abstract, we attempted to access full-text articles through the University of Toronto library. Articles were excluded if not found or if published in a language other than English and an English translation was unavailable.

Full-text screening

Among the full-text articles, case reports, case series, cross-sectional studies, and retrospective chart review articles were all eligible for inclusion. Eligible articles were read and included only if individual-level information was accessible for every patient and at least one patient with a movement disorder was reported. Movement disorders were defined as ataxia, dystonia, parkinsonism, rest tremor, action tremor (e.g., intention tremor, terminal tremor), myoclonus, chorea, or dyskinesia related or unrelated to dopaminergic therapy. Eligible articles also required the genetic confirmation of a suspected pathogenic variant of a *SPG* gene. In vitro studies and in silico studies were also excluded. Patients without pyramidal signs were excluded unless they had a movement disorder (e.g., ataxia). Patients with a known pathogenic *SPG* mutation but with a well-characterized non-HSP presentation (i.e., Pelizaeus Merzbacher disease, Gordon Holmes syndrome, and Boucher-Neuhauser syndrome) were also excluded. To avoid duplicating a case that was reported in more than one publication, articles referencing previously published cases were excluded and, during data extraction, we audited the datasheet by the names of the first authors and patients' characteristics to identify and delete duplicates.

Data extraction

Five investigators (S. M. F., P. A. S., N. P., S. B., G. S.) extracted manuscript characteristics (e.g., first authors name) and IPD for all reported cases from eligible articles that met the inclusion criteria. HSP cases within families were treated as individual cases and considered separately when meeting inclusion criteria and compiling data. Therefore, we included any other family member for whom the

PRISMA IPD Flow Diagram

Identification

First iteration: **17963** articles
Second iteration: **3994** articles

Number of additional studies identified through other sources including contact with researchers: (n = **0**)

Screening

First iteration: **9083** articles
Second iteration: **2574** articles

Eligibility

First iteration: **9083** articles
Second iteration: **2575** articles

Excluded:
First iteration: **8362** articles
Second iteration: **2255** articles

Obtaining data

IPD sought for:
First iteration: **721** articles
Second iteration: **320** articles

Excluded after seeking IPD:
First iteration: **591** articles (217 article not found, 8 aggregate data, 366 exclusion criteria or duplicate data)
Second iteration: **248** articles (69 article not found, 179 exclusion criteria or duplicate data

Available data

Number of studies for which IPD were provided:
First iteration: **130** articles
Second iteration: **72** articles
Number of participants for whom data were provided
Number participants for whom no data were provided (give reasons)

Number of studies for which IPD were not provided:
First iteration: **0** articles
Second iteration: **0** articles

Number of studies for which aggregate data were available (n = **0**)

We did not include studies with aggregate data, only studies with available IPD were included.

Analysed data

IPD (report for each main outcome)

Number of studies included in analysis: **202**

Number of participants included in analysis: **1423**

Fig. 1 The PRISMA-IPD flow diagram

genotype (SPG designation) and individualized phenotypic information (clinical features) were reported. For articles with supplementary data, additional clinical and genetic data were extracted from the supplementary materials published with the articles. The IPD variables consisted of *SPG* gene, sex, age at symptom(s) onset, age at reported assessment, family history of HSP, initial presentation, motor features (i.e., pyramidal signs, motor weakness, gait or posture abnormalities, ataxia, dystonia, action tremor, rest tremor, parkinsonism, levodopa-responsiveness, motor fluctuations, dyskinesia, chorea, myoclonus), and non-motor features (i.e., cognitive impairment, speech disorder, peripheral neuropathy, urinary symptoms, seizure, extraocular movement abnormalities, retina/optic nerve abnormalities, dysphagia, deafness, sleep disorder, depression, skin lesions). We did not aim to include aggregate group-level data, and we did not contact authors of these manuscripts for IPD information.

Data synthesis and analysis

Extracted IPD was pooled for statistical analysis. We divided the study population into two groups: (1) HSP patients with movement disorder (HSP-MD) and (2) HSP patients without movement disorders (HSP-nMD). Demographic, genotype (i.e., *SPG* mutation), and clinical data were then compared between the two groups. We used frequency percentages and mean (standard deviation (SD)) for description of categorical/nominal and numeric variables, respectively. Descriptive statistics were reported only for *SPG* subtypes with at least five reported cases. Differences in demographics, genotypes, and clinical characteristics between HSP-MD and HSP-nMD

groups were statistically compared using chi-square or independent-samples *t* test where appropriate. For the HSP-MD group, Kendall's correlation was used to explore pair-wise associations between various clinical presentations, and a corresponding correlation coefficient was calculated and reported as a percentage in the correlation matrix. We used the chi-square test to compare clinical features between the two most common *SPG* subtypes within the HSP-MD group (*SPG7* versus *SPG11*). For each significant difference, corresponding odds ratio (OR) and its 95% confidence interval (CI) were calculated. Logistic regression models were applied to adjust these between-group differences (*SPG7* versus *SPG11*) for disease duration as a covariate in each model, and to calculate adjusted ORs for each clinical feature. All analyses were performed using *R* (R, version 3.3.3; the R Core Development team, 2010) and *IBM SPSS* Statistics software (version 23.0). For all analyses, two-sided *p*-values < 0.05 were considered statistically significant.

Results

IPD was extracted for 1423 patients with genetically confirmed HSP: 767 with movement disorders (HSP-MD) and 646 without movement disorders (HSP-nMND). The demographic features for all included patients are summarized in Table 1. HSP-MD and HSP-nMD patients were similar with respect to sex and family history of HSP. HSP-MD patients were more likely to have a later age of onset and thus an older age of assessment. Disease duration, defined as age at the time of clinical assessment

Table 1 Demographic and baseline characteristics of recruited individuals with hereditary spastic paraplegia (HSP) manifested with (HSP-MD, *n* = 767) or without (HSP-nMD, *n* = 646) a movement disorder

Genotype	Sex Male (%)	Age of Onset (yr) Mean ± SD	Age at Visit (yr) Mean ± SD	Family history (%)	Inheritance (%)	Initial presentation* (%)
HSP-MD (*n* = 767)	53.4%	20.5 ± 16.0 (range: < 1 mo–65 yr)	38.0 ± 17.9 (range: 1 mo–90 yr)	78.9%	AR (58.4%) AD (7.6%) AR/AD (31.4%) X-linked (2.6%)	Gait disturbance (50.0%) Ataxia (8.7%) Spasticity (8.1%)
HSP-nMD (*n* = 646)	48.9%	17.1 ± 14.2 (range: < 1 mo – 70 yr)	33.3 ± 16.6 (range: < 1 mo – 82 yr)	79.6%	AR (57.1%) AD (30.1%) AR/AD (10.8%) X-linked (2.0%)	Gait disturbance (34.3%) Spasticity (28.1%) Learning/Cognitive problems (11.9%)
Total (*N* = 1413)	51.0%	18.7 ± 15.2 (range: < 1 mo–70 yr)	35.5 ± 17.4 (range: < 1 mo–90 yr)	79.3%	AR (57.7%) AD (19.8%) AR/AD (20.2%) X-linked (2.3%)	Gait disturbance (42.2%) Spasticity (18.1%) Learning/cognitive problems (9.9%)
*p-value*****	0.150	**< 0.001**	**< 0.001**	0.828	**< 0.001**	**< 0.001**

HSP-MD, hereditary spastic paraplegia (HSP) with movement disorder (MD); *HSP-nMD*, hereditary spastic paraplegia (HSP) without movement disorder (nMD); *AR*, autosomal recessive; *AD*, autosomal dominant; *yr*, year; *mo*, month

*Three most common initial presentations

**Statistical comparison between HSP-MD and HSP-nMD groups using chi-square with continuity correction or independent-samples *t* test
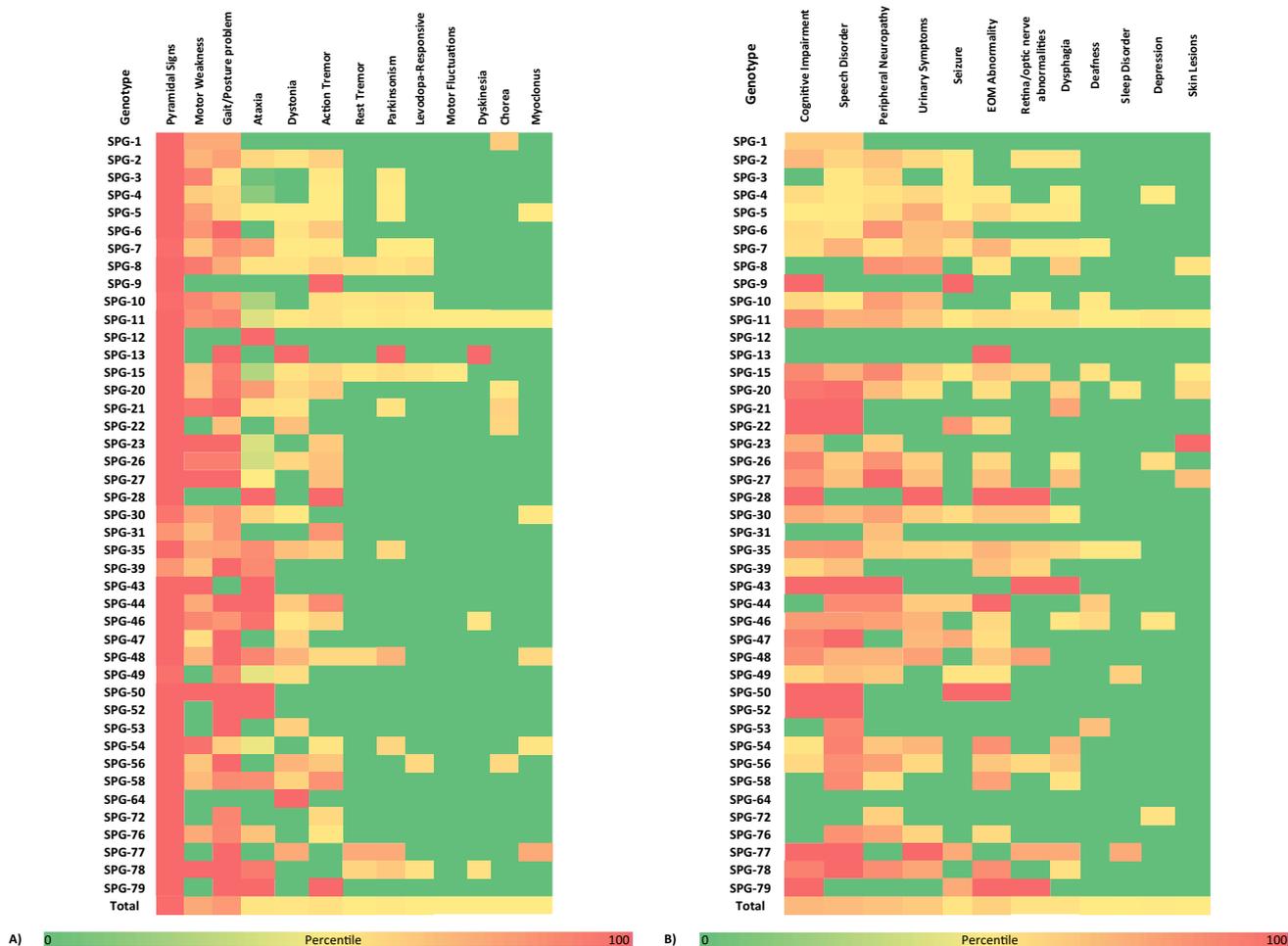
Fig. 2 Heatmap of the prevalence of movement (**A**) and non-motor (**B**) disorders among different genotypes (SPGs) of hereditary spastic paraplegia (HSP) (cognitive impairment included dementia, mental retardation, learning disabilities; peripheral neuropathy included pes cavus, hammer toes, or NCS studies consistent with peripheral neuropathy; speech disorder included dysarthria, dysphasia) (EOM, extraocular movement)

minus age at symptoms onset, was slightly longer in HSP-MD group (18.3 (SD = 12.8) years vs. 16.1 (SD = 12.7) years, $p = 0.004$). Autosomal dominant inheritance was less common in the HSP-MD group. Gait abnormalities and spasticity were common initial presentations, although the former was more frequent among HSP-MD, and the latter was more frequent among HSP-nMD. Ataxia and cognitive impairment were also common initial presentations among HSP-MD and HSP-nMD, respectively.

A total of 43 different *SPG* genes were affected across the entire HSP group. In our dataset, *SPG11* ($n = 391$, 27.7%), *SPG7* ($n = 256$, 18.1%), *SPG4* ($n = 171$, 12.1%), and *SPG5* ($n = 95$, 6.7%) were the most frequently affected genes. Figure 2 provides a summary of the frequency of motor and non-motor features for each *SPG* subtype. While pyramidal signs were almost universally present, gait/posture problems were frequently reported in most genotypes except for *SPG9*, *SPG12*, *SPG28*, *SPG43*, and *SPG64*. Ataxia was highly

prevalent in *SPG7*, *SPG12*, *SPG28*, *SPG43*, *SPG44*, *SPG46*, *SPG50*, *SPG52*, and *SPG79*, among others. Dystonia was reported very often in *SPG13* and *SPG64*. Regarding non-motor features, cognitive impairment and speech disorder were most commonly reported. Peripheral neuropathy and urinary symptoms were also frequently reported in various genotypes. Abnormalities in extraocular movements were commonly reported in *SPG13*, *SPG28*, *SPG44*, *SPG50*, and *SPG79*, while retinal and/or optic nerve abnormalities were frequent in *SPG28*, *SPG43*, and *SPG79*. Table 2 summarizes the commonest genotypes within each individual movement disorder. Ataxia was the most common movement disorder reported in 82.1% of recruited HSP population. SPG7 (36.8%), SPG11 (20.4%), and SPG5 (6.3%) were the commonest genotypes among those manifesting with ataxia. SPG11 was the most prevalent genotype in individuals presenting with action tremor (32.4%), dystonia (27.3%), parkinsonism (35.6%), rest tremor (52.9%), dyskinesia (66.7%),

and myoclonus (40%). Majority of HSP cases manifested with chorea had SPG21 genotype (60%).

Demographics and baseline characteristics of the HSP-MD cohort with various *SPG* genotypes are summarized in Supplementary Table 1. *SPG7* (31.2%) and *SPG11* (23.8%) were the most frequent genotypes in the HSP-MD group. Besides comprising the second most common genotype in the HSP-MD group, *SPG11* was the most frequent genotype identified in the HSP-nMD cohort (32.3%). Among other large genotype groups, *SPG4* (19.9% vs. 2.8%) and *SPG3* (4.7% vs. 0.5%) were more commonly associated with an HSP-nMD phenotype (Supplementary Fig. 1). As shown in Supplementary Fig. 2, among SPGs with at least 5 reported cases, *SPG78* presented only with an HSP-MD phenotype. Other genotypes that were more likely to present with MD were *SPG46* (95.2%), *SPG48* (85.7%), *SPG35* (84.8%), *SPG20* (84.2%), *SPG39* (83.3%), and *SPG58* (81.3%). Conversely, most cases with *SPG3* (92.3%), *SPG4* (89.5%), *SPG72* (85.7%), and *SPG47* (80.0%) presented with an HSP-nMD phenotype.

In the HSP-MD cohort, patients with *SPG49* (0.3 ± 0.4 years) and *SPG20* (3.0 ± 5.5 years) genotypes had the youngest age of onset, while those with *SPG7* (34.4 ± 12.7 years) and *SPG8* (33.5 ± 14.2 years) were the oldest at the time of initial manifestation (Supplementary Table 1 and Supplementary Fig. 3). In this cohort, *SPG2*, *SPG20*, *SPG46*, and *SPG54* (11.8% for each) were the commonest genotypes among those manifesting during infancy, while *SPG11* (43.6%) and *SPG7* (66.1%) were the most common genotypes in individuals with onset during childhood/adolescence and adulthood, respectively (Fig. 3A). As illustrated in Fig. 3A, frequency of *SPG7* in HSP-MD phenotype remarkably increases by the age of onset; with no *SPG7* case manifested during infancy, reaching a frequency rate as high as 72.5% of cases with late-adulthood onset (age > 40 years). Regarding sex distribution of different genotypes in the HSP-MD group, *SPG11* was more common in females (31.8% vs. 20.9%), while *SPG7* was more frequently reported in males (26.0% vs. 17.9%) ($p = 0.007$, Fig. 3B).

Notable variations in the initial presenting features according to different genotypes in the HSP-MD group were seen, as illustrated in Fig. 4. For instance, all patients with *SPG10* and *SPG21* presented with spasticity (100%) and gait disturbance (100%); all *SPG26* cases manifested initially with ataxia (100%). As expected, gait difficulty was commonly seen as the initial presenting symptom in several genotypes, especially in *SPG2*, *SPG4*, *SPG7*, *SPG11*, *SPG15*, *SPG30*, *SPG76*, and *SPG78* (> 50% prevalence). In most individuals with *SPG20*, developmental delay (55.6%) was the initial manifestation. The only genotypes in which tremor was reported as the initial manifestation were *SPG11*, *SPG46*, and *SPG58*. Figure 3C identifies the most frequent genotypes based on each initial presenting feature. In HSP-MD cases, SPG11 was the commonest genotype among those who initially manifested with tremor (76.9%) and learning/cognitive problems (76%). On the other hand, *SPG7* was the most common genotype reported in HSP-MD cases manifesting initially with stiff leg (87.5%), ataxia (56.0%), and gait disturbance (45.9%). Presentation at

Table 2 Commonest SPGs genotypes in recruited individuals with hereditary spastic paraplegia (HSP) presenting with various movement disorders	Movement disorders	Frequency (%)	Commonest SPGs genotypes (%)
	Ataxia	82.1%	SPG7 (36.8%) SPG11 (20.4%) SPG5 (6.3%)
	Gait/postural problems	71.3%	SPG7 (32.4%) SPG11 (27.0%) SPG35 (3.5%)
	Action tremor	18.4%	SPG11 (32.4%) SPG58 (9.9%) SPG7/SPG15/SPG26/SPG35 (7.2%)
	Dystonia	9.1%	SPG11 (27.3%) SPG35 (20.0%) SPG7/SPG26 (7.3%)
	Parkinsonism	7.5%	SPG11 (35.6%) SPG15 (11.1%) SPG35 (11.1%)
	Rest tremor	2.8%	SPG11 (52.9%) SPG8/SPG10/SPG15/SPG78 (11.8%)
	Dyskinesia	1.0%	SPG11 (66.7%)
	Myoclonus	0.8%	SPG11 (40%)
	Chorea	0.8%	SPG21 (60%)

Only SPGs with at least 2 cases are reported

Fig. 3 Frequency of different genotypes (SPGs) in patients with hereditary spastic paraplegia (HSP) manifested with a movement disorder (HSP-MD) and **A** various age of onsets, **B** different sexes, and **C** various initial presentation (*All SPGs have at least n = 5 reported cases*)
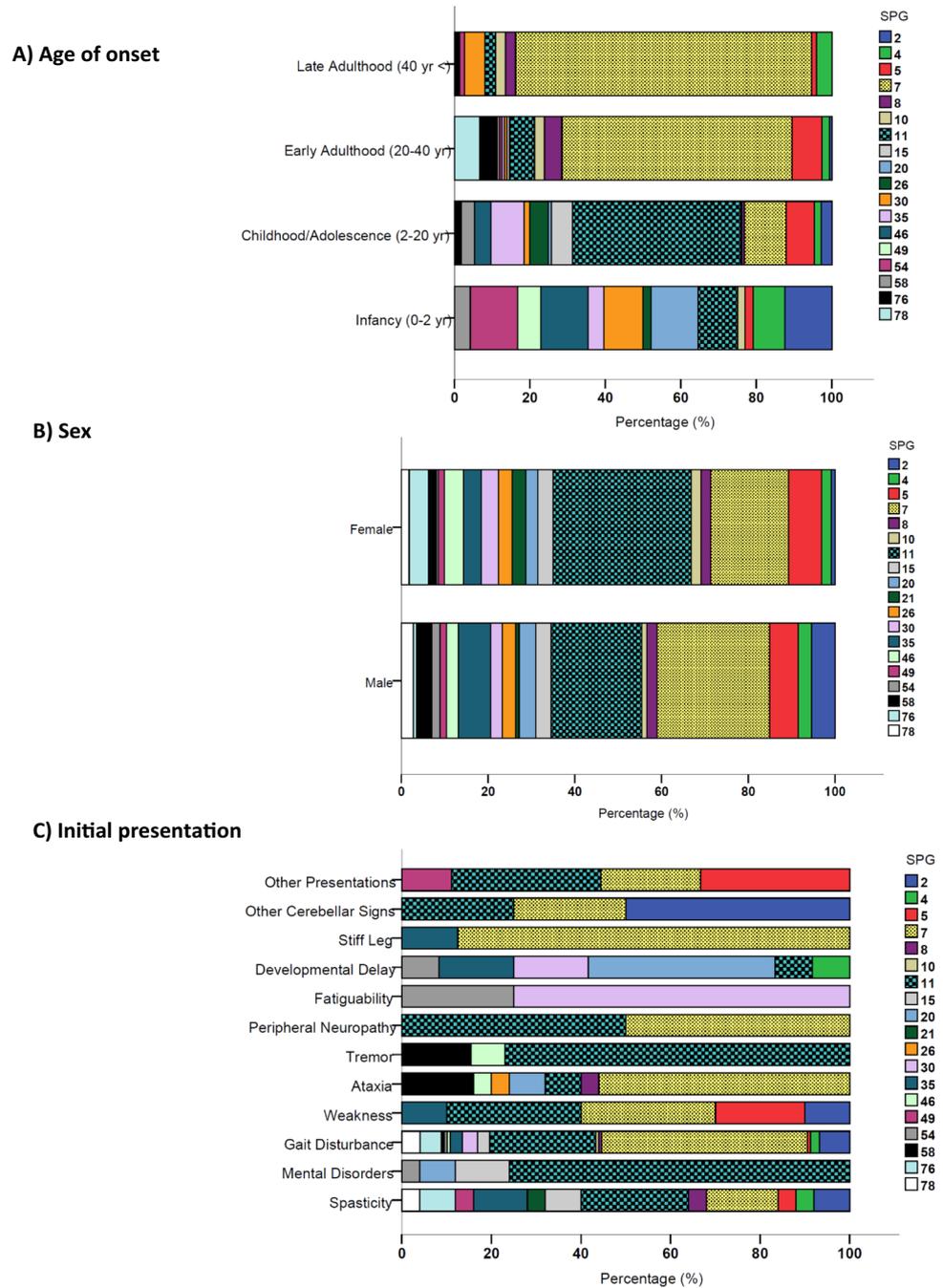
onset with cerebellar signs other than ataxia was more likely linked with *SPG2* (50.0%) (Fig. 3C).

In addition to the age of onset, significant phenotypical differences were found between the two most common genotypes identified in the HSP-MD cohort, *SPG7* and *SPG11* (Fig. 5). Disease duration at the time of clinical assessment was longer in patients with *SPG7* (19.3 (SD = 13.9) years vs. 15.9 (SD = 9.0) years, $p = 0.014$). HSP-MD patients with *SPG7* had significantly higher likelihood of presenting with ataxia (96.8% vs. 70.6%, OR = 12.6 (5.2–30.7), adjusted OR = 11.7

(4.4–31.0), $p < 0.001$); extraocular movement disturbances (52.7% vs. 24.5%, OR = 3.4 (2.1–5.5), adjusted OR = 3.1 (1.9–5.1), $p < 0.001$); and seizure (11.7% vs. 3.5%, OR = 3.7 (1.3–9.9), adjusted OR = 4.2 (1.5–11.5), $p = 0.005$) compared to those with *SPG11*, whereas *SPG11* mutants showed significantly more frequent history of consanguinity in the family (65.1% vs. 31.3%, OR = 4.1 (1.3–12.9), $p = 0.012$), parkinsonism (11.2% vs. 1.6%, OR = 7.8 (2.2–27.2), adjusted OR = 5.7 (1.6–20.3), $p = 0.007$); dystonia (10.5% vs. 2.1%, OR = 5.4 (1.7–16.6), adjusted OR = 4.5 (1.4–14.3), $p = 0.010$); pes

Fig. 4 Frequency of various initial symptoms in patients with hereditary spastic paraplegia and a movement disorder (HSP-MD) with different genotypes (SPGs) (*All SPGs have at least n = 5 reported cases*)
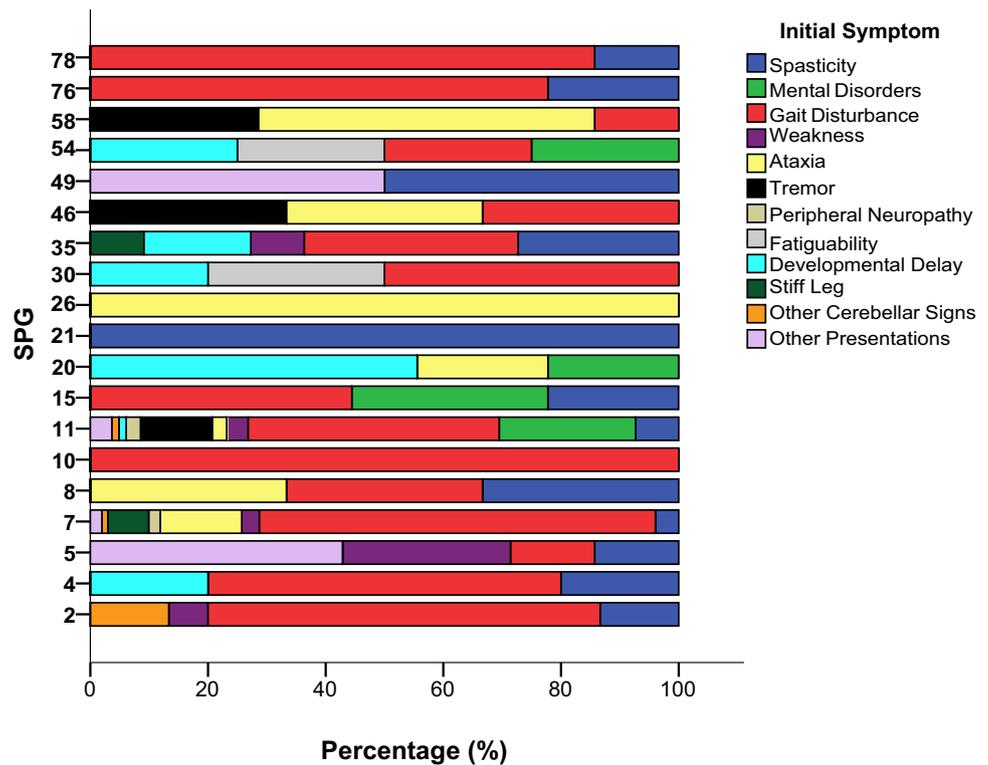
cavus/peripheral neuropathy (60.1% vs. 5.3%, OR = 26.9 (13.1–55.2), adjusted OR = 30.8 (14.0–67.7), $p < 0.001$); dysphagia (16.1% vs. 5.9%, OR = 3.1 (1.4–6.6), adjusted OR = 3.4 (1.5–7.8), $p = 0.004$); cognitive impairment (80.4% vs. 10.6%, OR = 34.5 (18.5–64.2), adjusted OR = 36.9 (18.6–73.3), $p < 0.001$); depression (7.0% vs. 0, $p < 0.001$); and retinopathy/optic nerve atrophy (10.5% vs. 4.8%, OR = 2.3 (1.0–5.5), adjusted OR = 2.5 (1.0–6.2), $p = 0.050$) compared to *SPG7*. All differences remained statistically significant after multivariate adjustment for disease duration (adjusted ORs).

A correlation matrix of the inter-associations between various clinical features in patients with HSP-MD is shown in Fig. 6. In our exploratory analysis, cognitive impairment accompanies with higher prevalence of pes cavus/peripheral neuropathy ($r = 0.47$, $p < 0.001$). Among other significant correlations were direct association between dysphagia and chorea ($r = 0.22$, $p < 0.001$), myoclonus and depression ($r = 0.23$, $p < 0.001$), and extraocular movement abnormalities with urinary symptoms ($r = 0.19$, $p < 0.001$) and speech disorders ($r = 0.28$, $p < 0.001$). Ataxia inversely correlated with action tremor ($r = -0.48$, $p < 0.001$), parkinsonism ($r = -0.31$, $p < 0.001$), dystonia ($r = -0.30$, $p < 0.001$), resting tremor ($r = -0.23$, $p < 0.001$), pes cavus/peripheral neuropathy ($r = -0.20$, $p < 0.001$), and cognitive impairment ($r = -0.19$, $p < 0.001$).

Discussion

HSP is a heterogeneous group of genetic disorders with a vast genotypic and phenotypic variability. Although there have been few studies on genotype–phenotype correlations in HSP [20, 21], details on the presence and type of MD in HSP are lacking. Furthermore, there is a dearth of knowledge on less frequent genotypes as these rarer variants are sparsely published as case reports and have been excluded from the only previously published conventional meta-analysis [20]. Implementing an IPD-level meta-analysis enabled us, for the first time, to compare demographics and clinical features between the widest variety of HSP genotypes manifesting with or without a movement disorder, to analyze genotype–phenotype associations in detail, and to provide important diagnostic clues even for the rarer variants by pooling data from case reports and case series.

In line with previous studies, we showed that HSP has a wide age at onset, ranging from a few months to 73 years [21]. Significant differences were seen according to genetic subtype, but variability may occur even within the same genotype. For instance, members of the same family with *SPG4* can present with SPG symptoms at very distinct decades in life [22]. In our study, the HSP-MD group had later age at onset and less frequent autosomal dominant inheritance than the HSP-nMD group. This could be in part related to the
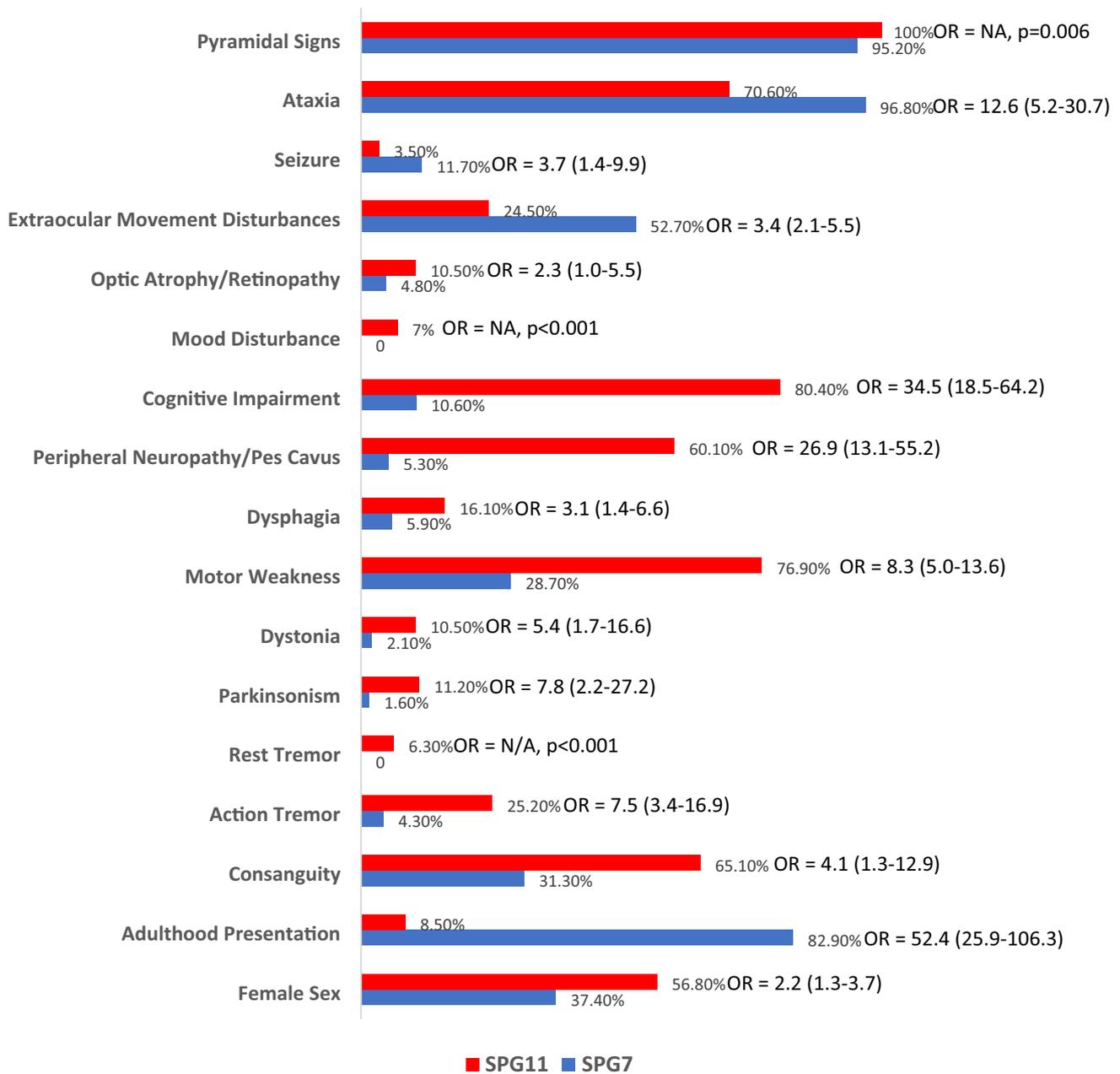
Fig. 5 Significant differences in the prevalence of demographics and clinical features in patients with hereditary spastic paraplegia (HSP) manifested with a movement disorder (HSP-MD) with genotype SPG7 versus SPG11 (all corresponding odds' ratios are calculated for the SPG with the higher prevalence rate) (OR, odds ratio; NA, not able to calculate OR due to 0 as denominator)

higher frequency of *SPG3* in the HSP-nMD group. A recent meta-analysis suggested that *ATL1* mutations (*SPG3*) are associated with earlier age at onset compared to other autosomal dominant forms such as SPAST (*SPG4*) and REEP1 (*SPG31*) [20]. The same finding has been shown in a previous study [23].

As may be expected, gait disturbance was the most frequent initial presentation. It is known that spasticity associated with HSP may only be evident on walking [22, 24].

Ataxia was the initial presentation in 8.7% of the HSP-MD group, and all *SPG26* cases manifested initially with ataxia (100%). Although ataxia is variably present during the course of *SPG26*, it has not been previously recognized as a major presenting feature in other studies analyzing the entire *SPG26* population (with or without MD). Ataxia was common at onset in *SPG7*, *SPG8*, *SPG20*, *SPG46*, and *SPG58*. The *SPG* genotype classically associated with ataxia in the literature is *SPG7* [5]. We found that early cognitive
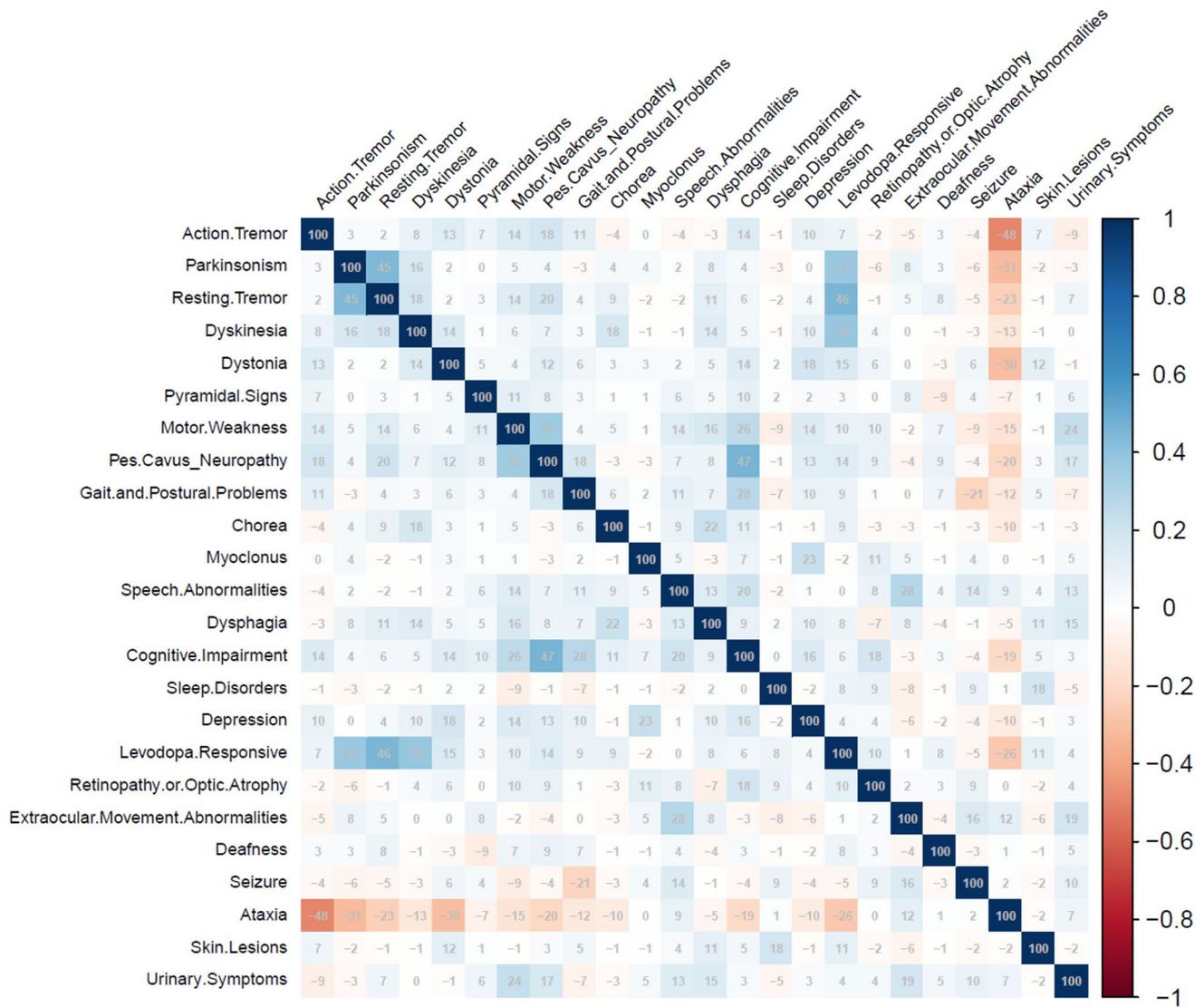
Fig. 6 Correlation matrix of the associations between various presentations in patients with hereditary spastic paraplegia (HSP) manifested with a movement disorder (HSP-MD) (Corresponding Kendall's correlation coefficient is presented as a percentage in each cell)

impairment and learning disabilities could be initial manifestations in HSP-nMD patients. *SPG4*, *SPG20*, *SPG30*, *SPG35*, and *SPG54* are the genotypes that can manifest initially with cognitive developmental delay. In our pooled IPD meta-analysis, early cognitive impairment was the most common initial presentation in *SPG20*, while in previous literature, SPG54 is known to more commonly present with cognitive abnormalities [20].

Our analysis also demonstrated several other genotypic differences between the two major phenotypic groups, with and without MD. *SPG11* was the most frequent genotype in the entire HSP group and in the HSP-nMD subgroup and the second most common in the HSP-MD group. The two most frequent genotypes in the HSP-MD group, *SPG7* and *SPG11*, were identified in nearly half of the cases with

adulthood onset and childhood/adolescence onset, respectively, suggesting that age at onset is an important clue. Apart from age of onset, our analysis revealed numerous phenotypic features that help differentiating *SPG7* and *SPG11*. Individuals with SPG7 are more likely to develop ataxia, extraocular movement disturbances and seizure, whereas those with SPG11 more commonly experience parkinsonism, dystonia, peripheral neuropathy, dysphagia, retinopathy/optic nerve atrophy, cognitive, and mood impairment. Although some of our findings were previously shown in original cohorts (e.g., higher frequency of dysphagia and cognitive deficit in *SPG11* [21]), others are not necessarily in keeping with previous literature; for instance, frequency of parkinsonism in *SPG7* (21% in one study[25] versus < 2% in our report). A possible reason for this discrepancy is that

the majority of previous studies reported their findings based on small case series with limited statistical power.

Our IPD-level meta-analysis also suggests numerous others important diagnostic clues in HSP-MD based on genotype–phenotype correlations depicted in the heatmaps as well as post hoc descriptive analysis based on initial presentation and age at onset. For example, all patients with *SPG10* and *SPG21* presented initially with spasticity and gait disturbance; developmental delay (55.6%) was the initial manifestation in most individuals with SPG20; the only genotypes in which tremor was reported as the initial presenting symptom were *SPG11*, *SPG46*, and *SPG58*, yet *SPG11* was the commonest genotype among those who initially manifested with tremor (76.9%) and mental disorders (76.0%). Furthermore, the most common genotype that manifested initially with stiff leg (87.5%), ataxia (56.0%), and gait disturbance (45.9%) was SPG7; and onset presentation with cerebellar signs other than ataxia was more likely linked with *SPG2* genotype (50.0%). Correlation matrix showed novel interesting phenotypic patterns. For instance, cognitive impairment and learning disabilities frequently accompany pes cavus/peripheral neuropathy, dysphagia correlates with chorea, myoclonus is common in patients with mood disturbances, and extraocular movement abnormalities co-occur with speech disorders.

To our knowledge, our study is the first meta-analysis of IPD in the context of HSP, while a conventional meta-analysis has been recently published [20]. IPD-level meta-analysis is a useful method for disease entities such as HSP where the majority of the published literature consists of small sample-size case series or case reports. Its main advantage is to boost statistical power by pooling individual-level data from all reported genotypes and therefore avoiding exclusion of rarer SPGs from genotype–phenotype analysis, which are otherwise usually eliminated from conventional meta-analysis given low statistical power in their original studies. As such, our study is the most inclusive and comprehensive genotype–phenotype analysis of the SPG subtypes. Other strengths of an IPD-level meta-analysis is the ability to account for missing information at the individual level, enabling various original statistical methods for comparison and correlation analyses, and obtaining results for specific subgroups of participants [26]. Many of these genotypic-phenotypic associations in our study were not previously reported given lack of available data in an original small-size case series. Furthermore, our analysis is the first to focus on two major phenotypes of HSP, with and without a movement disorder.

We acknowledge several limitations. First and most importantly, since our main objective was to focus on HSP patients with a movement disorder as at least one major phenotypic trait, our search strategy was designed to be systematically inclusive only of individuals with HSP-MD

and not the entire HSP population. Nevertheless, data from the subset of HSP-nMD patients collectively reported in the articles included in our study were gathered, and this subset of patients was used as a comparison group, assuming these cases are representative of the entire HSP-nMD population. This search strategy has potentially resulted in an under-representation of *SPG4*, which is one of the commonest genotypes of HSP in patients with no prominent movement disorder [27]. Second, handling missing data is quite challenging in an IPD-level meta-analysis due to considerable inconsistencies in reporting symptoms and signs between original reports and the lack of a standardized checklist for data gathering. In our analysis, we considered any missing data on a specific symptom as "not reported or unknown" rather than absence of the symptom. Also, we did not provide specific mutation-level genotype–phenotype correlations. Lastly, due to the huge amount of work to extract individual-level data for every single case from each article, we were not able to update our database after the second iteration of literature searching in June 2018; therefore, original studies published after that date were not included.

In conclusion, our systematic IPD-level meta-analysis provides several clinically relevant phenotypic clues regarding demographic and neurologic features for various HSP genotypes. Many of these genotype–phenotype associations are novel and reported for the first time. Recognition of these genotype–phenotype correlates facilitate diagnosis in resource-limited settings where genetic diagnosis is not available or when genotyping is inconclusive. While symptoms are not evenly distributed among different HSPs, a direct multi-gene testing panel is required. Future studies are required to explore whether specific HSP clusters exist, based on these genotype–phenotype correlations, that correspond to known or unknown SPG loci with common pathogenesis.

Author contribution Seyed-Mohammad Fereshtehnejad: research project: conception, literature review, data collection; statistical analysis: design, execution, review and critique; manuscript preparation: writing of the first draft, review and critique

Philip A. Saleh: research project: conception, literature review, data collection; manuscript preparation: writing of the first draft, review and critique

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Suvorit Bhowmick: research project: literature review, data collection; manuscript preparation: review and critique

Gerard Saranza: research project: literature review, data collection; manuscript preparation: review and critique

Lorraine V. Kalia: research project: organization, conception; statistical analysis: review and critique; manuscript preparation: review and critique

Declarations

Ethical approval None.

Conflict of interest In the past year, S. M. F. has received honoraria from the European Science Foundation. L. V. K. has received research support from Canadian Health Institutes of Research (CIHR), Michael J. Fox Foundation for Parkinson's Research, Natural Sciences and Engineering Research Council of Canada (NSERC), Ontario Brain Institute, Parkinson Canada, and Toronto General and Western Hospital Foundation; held contracts with ApoPharma and UCB; and received honoraria from National Institutes of Health (NIH) and Takeda. Other authors (P. A. S., L. M. O., N. P., S. B., and G. S.) reported no financial disclosure.

References

1. Harding AE (1983) Classification of the hereditary ataxias and paraplegias. Lancet 1(8334):1151–1155. https://doi.org/10.1016/s0140-6736(83)92879-9

2. Kara E, Tucci A, Manzoni C, Lynch DS, Elpidorou M, Bettencourt C, Chelban V, Manole A, Hamed SA, Haridy NA, Federoff M, Preza E, Hughes D, Pittman A, Jaunmuktane Z, Brandner S, Xiromerisiou G, Wiethoff S, Schottlaender L, Proukakis C, Morris H, Warner T, Bhatia KP, Korlipara LV, Singleton AB, Hardy J, Wood NW, Lewis PA, Houlden H (2016) Genetic and phenotypic characterization of complex hereditary spastic paraplegia. Brain 139(Pt 7):1904–1918. https://doi.org/10.1093/brain/aww111

3. de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, Bortholin T, Oliveira ASB (2017) Hereditary spastic paraplegia: clinical and genetic hallmarks. Cerebellum 16(2):525–551. https://doi.org/10.1007/s12311-016-0803-z

4. Kim A, Kumar KR, Davis RL, Mallawaarachchi AC, Gayevskiy V, Minoche AE, Walls Z, Kim HJ, Jang M, Cowley MJ, Choi JH, Shin C, Sue CM, Jeon B (2019) Increased diagnostic yield of spastic paraplegia with or without cerebellar ataxia through whole-genome sequencing. Cerebellum 18(4):781–790. https://doi.org/10.1007/s12311-019-01038-0

5. Synofzik M, Schule R (2017) Overcoming the divide between ataxias and spastic paraplegias: Shared phenotypes, genes, and pathways. Mov Disord 32(3):332–345. https://doi.org/10.1002/mds.26944

6. Hewamadduma CA, Hoggard N, O'Malley R, Robinson MK, Beauchamp NJ, Segamogaite R, Martindale J, Rodgers T, Rao G, Sarrigiannis P, Shanmugarajah P, Zis P, Sharrack B, McDermott CJ, Shaw PJ, Hadjivassiliou M (2018) Novel genotype-phenotype and MRI correlations in a large cohort of patients with SPG7 mutations. Neurol Genet 4(6):e279. https://doi.org/10.1212/NXG.0000000000000279

7. Salgado P, Latorre A, Del Gamba C, Menozzi E, Balint B, Bhatia KP (2019) SPG7: the great imitator of MSA-C within the ILOCAs. Mov Disord Clin Pract 6(2):174–175. https://doi.org/10.1002/mdc3.12711

8. Anheim M, Lagier-Tourenne C, Stevanin G, Fleury M, Durr A, Namer IJ, Denora P, Brice A, Mandel JL, Koenig M, Tranchant C (2009) SPG11 spastic paraplegia. A new cause of juvenile parkinsonism. J Neurol 256(1):104–108. https://doi.org/10.1007/s00415-009-0083-3

9. Guidubaldi A, Piano C, Santorelli FM, Silvestri G, Petracca M, Tessa A, Bentivoglio AR (2011) Novel mutations in SPG11 cause hereditary spastic paraplegia associated with early-onset levodopa-responsive Parkinsonism. Mov Disord 26(3):553–556. https://doi.org/10.1002/mds.23552

10. Ramirez-Zamora A, Gee L, Youn Y, Shin DS, Pilitsis JG (2017) Pallidal deep brain stimulation for the treatment of levodopa-responsive juvenile dystonia and parkinsonism secondary to SPG11 mutation. JAMA Neurol 74(1):127–128. https://doi.org/10.1001/jamaneurol.2016.4297

11. Wijemanne S, Shulman JM, Jimenez-Shahed J, Curry D, Jankovic J (2015) SPG11 mutations associated with a complex phenotype resembling dopa-responsive dystonia. Mov Disord Clin Pract 2(2):149–154. https://doi.org/10.1002/mdc3.12144

12. Schicks J, Synofzik M, Petursson H, Huttenlocher J, Reimold M, Schols L, Bauer P (2011) Atypical juvenile parkinsonism in a consanguineous SPG15 family. Mov Disord 26(3):564–566. https://doi.org/10.1002/mds.23472

13. Mallaret M, Lagha-Boukbiza O, Biskup S, Namer IJ, Rudolf G, Anheim M, Tranchant C (2014) SPG15: a cause of juvenile atypical levodopa responsive parkinsonism. J Neurol 261(2):435–437. https://doi.org/10.1007/s00415-013-7216-4

14. Schaefer SM, Szekely AM, Moeller JJ, Tinaz S (2018) Hereditary spastic paraplegia presenting as limb dystonia with a rare SPG7 mutation. Neurol Clin Pract 8(6):e49–e50. https://doi.org/10.1212/CPJ.0000000000000552

15. van Gassen KL, van der Heijden CD, de Bot ST, den Dunnen WF, van den Berg LH, Verschuuren-Bemelmans CC, Kremer HP, Veldink JH, Kamsteeg EJ, Scheffer H, van de Warrenburg BP (2012) Genotype-phenotype correlations in spastic paraplegia type 7: a study in a large Dutch cohort. Brain 135(Pt 10):2994–3004. https://doi.org/10.1093/brain/aws224

16. Hall D, Stong N, Lippa N, Pitman MJ, Pullman SL, Levy OA (2018) Spasmodic dysphonia in hereditary spastic paraplegia type 7. Mov Disord Clin Pract 5(2):221–222. https://doi.org/10.1002/mdc3.12580

17. Hirst J, Madeo M, Smets K, Edgar JR, Schols L, Li J, Yarrow A, Deconinck T, Baets J, Van Aken E, De Bleecker J, Datiles MB 3rd, Roda RH, Liepert J, Zuchner S, Mariotti C, De Jonghe P, Blackstone C, Kruer MC (2016) Complicated spastic paraplegia in patients with AP5Z1 mutations (SPG48). Neurol Genet 2(5):e98. https://doi.org/10.1212/NXG.0000000000000098

18. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF, Group P-ID (2015) Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 313(16):1657–1665. https://doi.org/10.1001/jama.2015.3656

19. Amberger J, Bocchini CA, Scott AF, Hamosh A (2009) McKusick's Online Mendelian Inheritance in Man (OMIM). Nucleic Acids Res 37 (Database issue):D793–796. https://doi.org/10.1093/nar/gkn665

20. Erfanian Omidvar M, Torkamandi S, Rezaei S, Alipoor B, Omrani MD, Darvish H, Ghaedi H (2021) Genotype-phenotype associations in hereditary spastic paraplegia: a systematic review and meta-analysis on 13,570 patients. J Neurol 268(6):2065–2082. https://doi.org/10.1007/s00415-019-09633-1

21. Schule R, Wiethoff S, Martus P, Karle KN, Otto S, Klebe S, Klimpe S, Gallenmuller C, Kurzwelly D, Henkel D, Rimmele F, Stolze H, Kohl Z, Kassubek J, Klockgether T, Vielhaber S, Kamm C, Klopstock T, Bauer P, Zuchner S, Liepelt-Scarfone I, Schols L (2016) Hereditary spastic paraplegia: clinicogenetic lessons from 608 patients. Ann Neurol 79(4):646–658. https://doi.org/10.1002/ana.24611

22. Lallemant-Dudek P, Durr A (2021) Clinical and genetic update of hereditary spastic paraparesis. Rev Neurol (Paris) 177(5):550–556. https://doi.org/10.1016/j.neurol.2020.07.001

23. Namekawa M, Ribai P, Nelson I, Forlani S, Fellmann F, Goizet C, Depienne C, Stevanin G, Ruberg M, Durr A, Brice A (2006) SPG3A is the most frequent cause of hereditary spastic paraplegia with onset before age 10 years. Neurology 66(1):112–114. https://doi.org/10.1212/01.wnl.0000191390.20564.8e

24. Shribman S, Reid E, Crosby AH, Houlden H, Warner TT (2019) Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. Lancet Neurol 18(12):1136–1146. https://doi.org/10.1016/S1474-4422(19)30235-2

25. De la Casa-Fages B, Fernandez-Eulate G, Gamez J, Barahona-Hernando R, Moris G, Garcia-Barcina M, Infante J, Zulaica M, Fernandez-Pelayo U, Munoz-Oreja M, Urtasun M, Olaskoaga A, Zelaya V, Jerico I, Saez-Villaverde R, Catalina I, Sola E, Martinez-Saez E, Pujol A, Ruiz M, Schluter A, Spinazzola A, Munoz-Blanco JL, Grandas F, Holt I, Alvarez V, Lopez de Munain A (2019) Parkinsonism and spastic paraplegia type 7: expanding the spectrum of mitochondrial parkinsonism. Mov Disord 34(10):1547–1561. https://doi.org/10.1002/mds.27812

26. Riley RD, Lambert PC, Abo-Zaid G (2010) Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 340:c221. https://doi.org/10.1136/bmj.c221

27. Rossi S, Rubegni A, Riso V, Barghigiani M, Bassi MT, Battini R, Bertini E, Cereda C, Cioffi E, Criscuolo C, Dal Fabbro B, Dato C, D'Angelo MG, Di Muzio A, Diamanti L, Dotti MT, Filla A, Gioiosa V, Liguori R, Martinuzzi A, Massa R, Mignarri A, Moroni R, Musumeci O, Nicita F, Orologio I, Orsi L, Pegoraro E, Petrucci A, Plumari M, Ricca I, Rizzo G, Romano S, Rumore R, Sampaolo S, Scarlato M, Seri M, Stefan C, Straccia G, Tessa A, Travaglini L, Trovato R, Ulgheri L, Vazza G, Orlacchio A, Silvestri G, Santorelli FM, Melone MAB, Casali C (2022) Clinical-genetic features influencing disability in spastic paraplegia type 4: a cross-sectional study by the Italian DAISY Network. Neurol Genet 8(2):e664. https://doi.org/10.1212/NXG.0000000000000664

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