Genetic Findings in Over 500 Individuals Tested with a Spastic Paraplegia Gene Panel

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Introduction

Hereditary spastic paraplegia (HSP) is characterized by lower extremity weakness and spasticity. HSP is genetically heterogenous, with over 80 types identified to date.[1,2] Age of onset is variable with some forms presenting in childhood or adolescence.[3] Autosomal dominant HSP (AD-HSP) is thought to account for 75% to 80% of the cases, and variants in *SPAST* account for up to 40% of AD-HSP.[1,2,4] Despite increasing knowledge of the genetic causes of HSP, for many individuals with a clinical diagnosis of HSP, the genetic etiology remains undetermined. Few studies have evaluated the yield of broad genetic testing in a large heterogenous cohort. We evaluated the yield of genetic testing in a cohort of individuals with suspected HSP who underwent sequencing and copy number variant (CNV) analysis.

Methods

We performed a retrospective review of de-identified data from consecutive individuals who underwent testing via a Spastic Paraplegia panel. Individuals were included if they were suspected of having HSP based on the clinical history provided. The panel included sequencing and CNV analysis by a targeted next-generation sequencing (NGS) assay. Target regions included coding exons (±20 bp from the intron/exon boundary) of up to 75 nuclear genes associated with spastic paraplegia, as well as up to 42 non-coding variants in these genes catalogued as disease-associated by HGMD and/or ClinVar. Gene content varied due to the addition of genes to the panel over time. Variant interpretation was performed in accordance with modified ACMG/AMP guidelines. An informative result in a gene was defined as the identification of a pathogenic (P) or likely pathogenic (LP) variant(s) consistent with the reported phenotype and disease inheritance. Chi-square analyses determined statistical significance (α=0.05).

Results

A total of 533 individuals underwent testing; 70.5% (376/533) were adults (≥18 years of age) at the time of testing, and over half (56.8%, 303/533) were male. In all, 28.3% of individuals (151/533) received an informative test result. Most informative results (80.1%, 121/151) were in adults. Pathogenic and likely pathogenic variants were reported in 25 different genes.

Adults were significantly more likely to receive an informative result (32.2%, 121/376 vs 19.1%, 30/157, $P<0.05$, $\chi^2=9.13$) (Figure 1). LP/P variants in *SPG7* and *KIF5A* were seen only in adults. LP/P variants in *CTNNB1, PAH,* and *C19orf12* were seen only in pediatric patients (Figure 2).

Autosomal dominant inheritance was observed in 67.5% (102/151) of individuals with informative results, and 68.6% (70/102) of those variants were in *SPAST*. Autosomal recessive inheritance accounted for 29.1% (44/151) and X-linked recessive inheritance accounted for 3.3% (5/151) of informative results. Of the autosomal recessive genes, *SPG7* (n=18) and *SPG11* (n=11) were most frequent. Two genes (*ABCD1* and *PLP1*) accounted for all the X-linked cases. Variants in X-linked genes were reported in a total of 3 females and 2 males.

Overall, 11.3% (17/151) of informative results involved a CNV, ranging in size from a single exon to entire gene deletions. In the pediatric population, 10% (3/30) of informative results involved a CNV. Seventy percent of all CNVs (12/17) were in *SPAST,* and CNVs accounted for 17% (12/70) of the variants in *SPAST*. Seven (58.3%, 7/12) of these were less than 1 kb in size. Non-coding variants contributed to <1% of informative results.

Twenty-eight percent of individuals tested with a spastic paraplegia gene panel received an informative result. Adults (≥ age 18) were significantly more likely to receive an informative result.

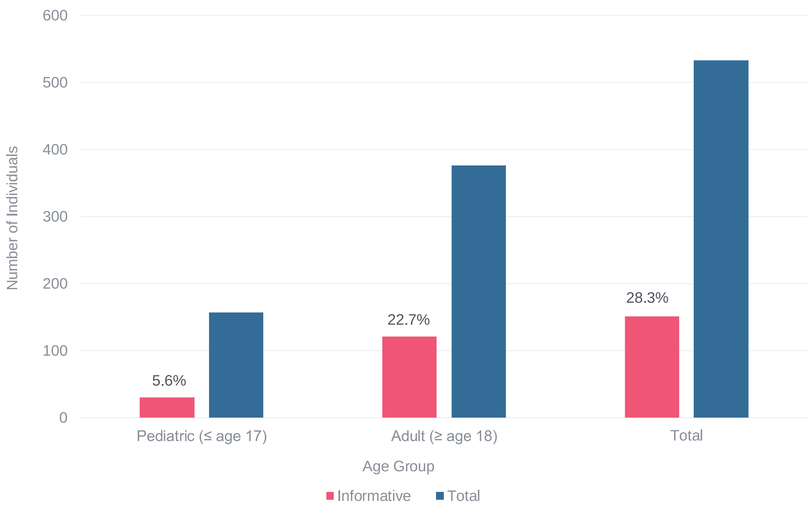

Figure 1. Total informative findings in the pediatric and adult population. Percentage displayed above the bars represents the percent of the total cohort (n=553).

Figure 2. Distribution of informative results by gene in the pediatric and adult population.
*Note: a total 70 informative results were in *SPAST.*

Conclusions

- **An informative result was received by 28% of individuals who underwent testing for HSP using a broad gene panel.**
- **Adults were significantly more likely than children to receive an informative result.**
- **The most frequent informative results were in *SPAST, SPG7,* and *SPG11*. The frequency of *SPAST* variants among those found to have AD-HSP was higher than previously reported.[2]**
- **CNVs contributed to the overall informative results, particularly in the *SPAST* gene. Fifty-eight percent of the CNVs in *SPAST* were less than 1 kb in size, highlighting the importance of small CNV detection.**
- **Non-coding variants contributed to <1% of informative results.**

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Conflict of interest statement: All authors are employed by Blueprint Genetics.