Hereditary ataxias: Looking beyond the repeats

Kimberly Gall[1], Julie Hathaway[1], Allison Sluyters[1], Lotta Koskinen[2], Eija Seppälä[2], Kirsi Alakurtti[2], Monica Segura Castell[2], Åsa Hagström[2], Rocio Sanchez Alcudia[2], Heli Kuisma[2], Inka Saarinen[2], Mikko Muona[2], Tuuli Pietilä[2], Matias Rantanen[2], Massimiliano Gentile[2], Pertteli Salmenperä[2], Jussi Paananen[2], Samuel Myllykangas[2], Juha Koskenvuo[2].

1. Blueprint Genetics Inc. Marlborough MA, USA
2. Blueprint Genetics, Espoo, Finland

Introduction

The most common hereditary ataxias (HAs) are the spinocerebellar ataxias (SCAs) with nucleotide repeat expansions as the primary molecular mechanism. Repeat expansion testing, which cannot be readily evaluated with current short-read next-generation sequencing (NGS) technologies, is typically performed first. If uninformative, an NGS-based multigene panel or exome sequencing may be pursued. While the yield from NGS-based testing has been reported, cohorts were small, and few studies included mitochondrial DNA (mtDNA) analysis. To inform the clinical utility of NGS panel testing, including mtDNA analysis, we describe the genetic findings of this testing approach for a cohort of patients with suspected HA.

Methods

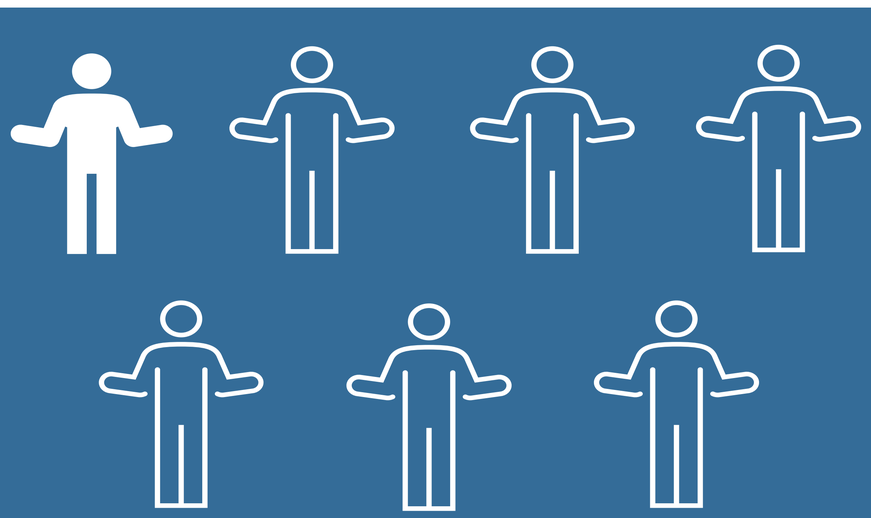
We retrospectively reviewed NGS multigene panel genetic test results of consecutive patients with suspected HA. It was not possible to confirm whether patients had repeat expansion testing. The panel included only NGS-based sequencing and copy number variant (CNV) analysis of up to 220 nuclear and mtDNA genes associated with ataxia. Pediatric patients were <18 years old at the time of testing. An informative case was defined as the identification of pathogenic (P) or likely pathogenic (LP) variant(s) (classified using a modified ACMG/AMP variant classification scheme). Chi-square analysis was utilized to determine statistical significance where appropriate, and a *P*-value <0.05 was considered significant.

Results

A total of 866 index patients underwent testing, including 696 (78.5%) adults. Almost half (48.0%, n=425) were female; the mean age at the time of testing was 46.0 years. A total of 59.1% (n=524) patients had a panel that included mtDNA. A total of 15.0% of patients (n=133) received an informative test result (Table). Overall, 15 patients with informative results (11.3%) had at least one LP/P CNV. Of these patients with LP/P CNVs, 10 (66.7%) had intragenic CNVs and 3 of the 10 intragenic CNVs (30.0%) were <1,000bp in size. Of patients with an informative genetic test result, 5 patients (3.8%) had P/LP variants in genes associated with gene-specific management recommendations or potential clinical trial eligibility (clinicaltrials.gov).

Of the 696 adults, 96 (13.8%) had an informative result. P/LP variants seen most often involved *SPG7* (n=15), *CACNA1A* (n=13), *STUB1* (autosomal dominant) and *SYNE1* (n=9 each) (Figure 1). AD was the most common inheritance pattern (52.1%), followed by autosomal recessive (AR; 42.7%) and, finally, mitochondrial (5.2%).

Of the 170 pediatric patients, 37 (21.8%) had an informative result. The P/LP variants seen most often involved *ATM* (n=10), *CACNA1A* (n=4), as well as *KCNC3* and *SPTBN2* (n=3 each) (Figure 1). AR was the predominant mode of inheritance (62.2%) in pediatric patients (Figure 2b). The proportion of informative cases was significantly higher in pediatric, compared to adult patients (21.8% vs 13.8% *P*<0.05).



One in 7 patients undergoing NGS panel testing for hereditary ataxia* received an informative result.

*prior repeat expansion testing presumed to be uninformative

One in 25 patients had a LP/P variant in a gene associated with an interventional clinical trial or gene-specific therapy*[1,2]

**POLG, SLC2A1*

Patient age at the time of testing	# of patients (% of cohort)	% with informative result (n)
Total	**866 (100%)**	**15.4% (133)**
Adult ≥18 years	696 (78.5%)	13.8% (96)
Pediatric <18 years	170 (21.5%)	21.8% (37)

Table. Patient demographics and relative proportion of informative results
Informative test results were significantly higher in pediatric patients (*P*<0.05**)**

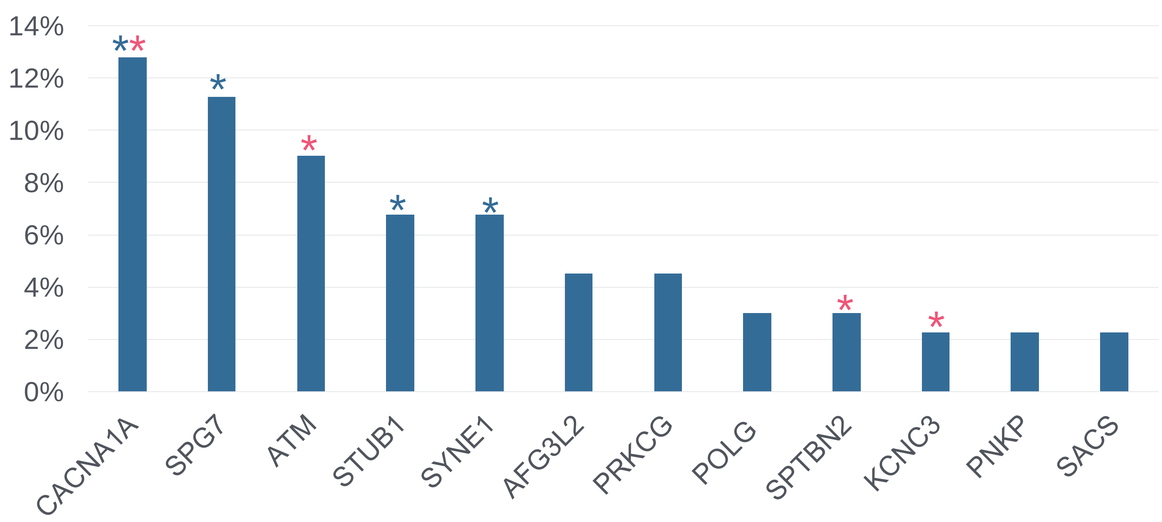


Figure 1. Distribution of LP/P variants by gene, as a proportion of all LP/P variants (%)

Only genes with ≥3 variants reported are shown. * designates LP/P variants identified most in adult patients, * designates LP/P variants identified most in pediatric patients.

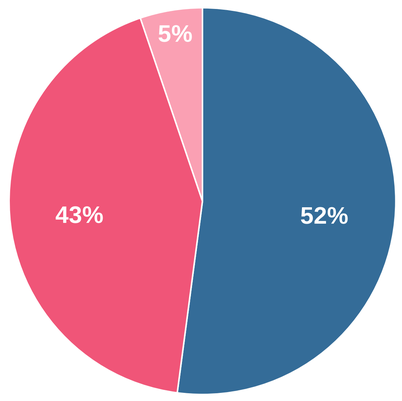


Figure 2a. Distribution of adult informative results by mode of inheritance

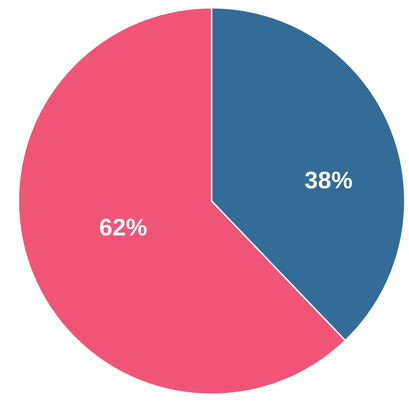


Figure 2b. Distribution of pediatric informative results by mode of inheritance

Conclusion

- NGS multigene panels yielded an informative genetic test result for 1 in 7 patients with a clinical suspicion of HA.
- Of those with informative results, ~4% had a LP/P mtDNA variant and 2% had a LP/P CNV <1,000bp in size.
- Of those with informative results, ~4% had a LP/P variant in a gene that was associated with gene-specific therapy or potential interventional clinical trial eligibility.
- Following repeat expansion testing, NGS panel testing that includes mtDNA analysis and high-resolution CNV analysis may have clinical utility for patients with a suspicion of HA.

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

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