Genetic findings in a cohort of over 600 patients suspected to have hereditary neuropathy tested with a multi-gene hereditary neuropathy panel

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Introduction

Hereditary neuropathies are a group of disorders characterized by chronic sensory polyneuropathy. They are genetically heterogenous, with duplications of *PMP22* explaining up to 50% of cases. A tiered testing approach is suggested, beginning with *PMP22* copy number variant (CNV) analysis, followed by a multigene panel. Treatment is typically symptomatic; however, there may be gene-specific referral/screening recommendations for some individuals.[1,2] The yield of genetic testing in patients with hereditary neuropathy has been documented, but previous studies have not consistently included the mitochondrial genome. We evaluated the yield of genetic testing in a cohort of patients with suspected hereditary neuropathy undergoing concurrent analysis of nuclear and mitochondrial (mtDNA) genes.

Methods

A retrospective review of de-identified data from 661 consecutive individuals who underwent testing via a hereditary neuropathy multi-gene panel was performed. Processed data was fully de-identified and analyzed in aggregate in accordance with GDPR and applicable ethical guidelines. Individuals were included if they were suspected to have hereditary neuropathy based on the clinical history provided. The panel included sequencing and CNV analysis by an exome-targeted next generation sequencing (NGS) assay. Target regions included coding exons (±20 bp from the intron/exon boundary) of up to 116 nuclear genes associated with neuropathy, and up to 43 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. The mitochondrial genome was included on the panel for 136 individuals. Variant classification was performed in accordance with 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 individual's reported phenotype and disease inheritance. Chi-square analyses determined statistical significance (α=0.05).

Results

A total of 661 individuals underwent testing; 78.5% (519/661) were adults (≥18 years of age). Over half were male (58.5%, 387/661). Median age at testing was 43 years (range: newborn to 87 years). In all, 25.1% of individuals (166/661) received an informative result. Children were more likely to receive an informative result (33.8%, 48/142 vs 22.7%, 118/519) (Figure 1).

Genes associated with autosomal dominant, autosomal recessive, and X-linked inheritance accounted for 67.5% (112/166), 19.3% (32/166), and 13.3% (22/166) of informative results, respectively. Of the genes associated with autosomal dominant inheritance, *PMP22* was the most common (n=41). Of the genes associated with autosomal recessive inheritance, *SH3TC2* (n=7) and *HINT1* (n=5) were most frequent. Three genes (*AIRM1*, *GJB1*, and *PRPS1*) accounted for all the X-linked cases. Informative results in X-linked genes were reported in a total of 10 females and 12 males.

Informative variants were reported in 40 different genes, with variants in *PMP22* (44/166, 26.5%), *GJB1* (20/166, 12.0%), *MFN2* (16/166, 9.6%), and *MPZ* (13/166, 7.8%) contributing frequently (Figure 2). CNVs were implicated in 24.7% (41/166) of informative results, with CNVs in *PMP22* responsible for 95.1% (39/41) of all CNVs. Of the CNVs in *PMP22*, 31/39 (79.5%) were copy number gains and 8/39 (20.5%) were copy number losses. CNV size ranged from 2 exons to whole gene, with 31/41 (75.6%) being copy number gains and 10/41 (24.4%) being copy number losses.

Noncoding variants were responsible for 1.2% (2/166) of informative results. Of the 136/661 (20.6%) patients who had the mitochondrial genome included in their analysis, none had a variant identified in an mtDNA gene.

Suspicious variants of uncertain significance (VUS likely to be reclassified to LP following family member testing), were identified in 3.8% (25/661) of individuals.

One in four individuals tested with a hereditary neuropathy gene panel received an informative result.

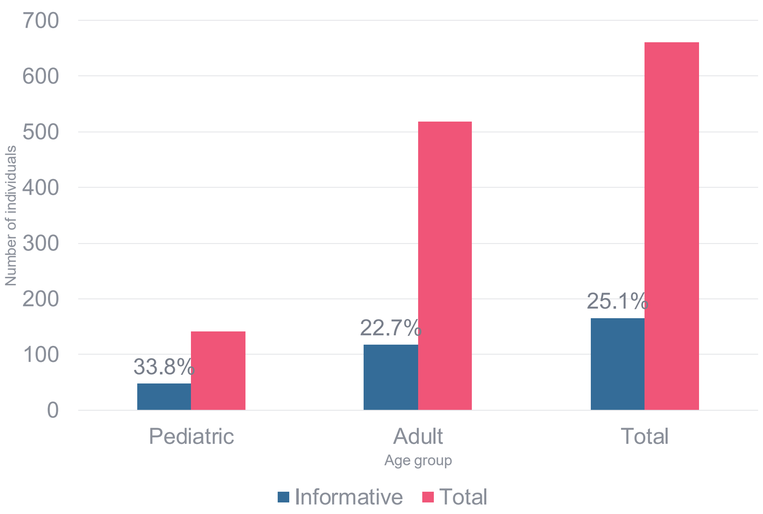

Figure 1. Informative results in the pediatric, adult, and total cohorts.

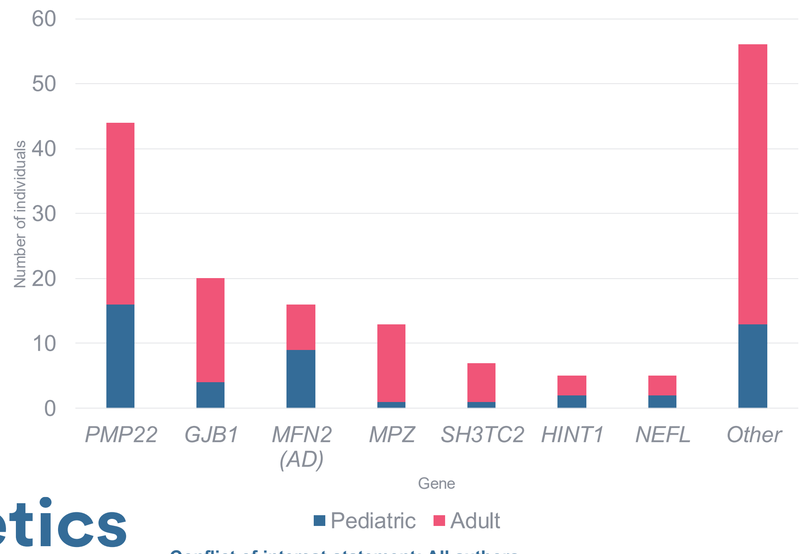

Figure 2. Distribution of informative results by gene in the pediatric and adult population.

Conclusions

- **An informative or potentially informative result was reported for 28.9% of individuals who underwent testing for hereditary neuropathy using a multi-gene panel.**
- **Informative results were reported most often in *PMP22*, *GJB1*, *MFN2*, *MPZ*, *SH3TC2*, *HINT1*, and *NEFL*, comparable to what is reported in the literature. However, 33.7% (56/166) of informative results were due to 33 other genes, highlighting the value of broad multi-gene panel content.**
- **The frequency of *PMP22* CNVs was lower than reported in the literature, possibly reflecting the suggested tiered testing approach.**
- **CNVs in multiple genes (*PMP22*, *ATL1*, and *PRX*), ranging from 2 exons in size to whole gene events, contributed to 1 in 4 informative results, emphasizing the value of CNV assessment for more than just *PMP22*.**
- **Non-coding variants (*GJB1* and *HKI1*) contributed to 1% of informative results.**
- **Variants in mtDNA genes did not contribute to informative results in the 136 individuals who had the mitochondrial genome included in their panel.**

References:

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