The relationship between variant type and phenotype among diseases screened by the Foresight® Expanded Carrier Screen

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INTRODUCTION

- Using a high throughput approach to expanded carrier screening, Myriad Genetics has identified over 37,000 disease-causing sequence variants across genes associated with autosomal recessive and X-linked diseases.
- To gain insight into how different types of sequence alterations (SNVs, indels, CNVs) and their location within a gene (e.g. exonic, intronic, UTR) are distributed across assayed genes, we analyzed total and gene-specific distributions of pathogenic variation by variant type.

METHODS

- The Foresight® Carrier Screening panel uses an NGS-based platform to detect germline sequence alterations within exonic/intronic and UTR regions of assayed genes.
- To characterize the type and distribution of disease-causing genetic alteration in Foresight® genes, we conducted a retrospective review of 37,000 pathogenic variants detected during testing of over 1.2 million patient samples, with pathogenicity assessed according to our carrier screening interpretation guidelines.
- To assess the correlation between variant type and gene, the distribution of pathogenic alteration by variant type was determined for a set of 24 disease phenotypes with significant contribution to overall world-wide disease risk.

RESULTS

- Analysis of pathogenic variation revealed that loss-of-function (LOF) variant types (truncations subject to nonsense-mediated decay (NMD), splice site variants, post-NMD truncations, initiation codon variants, CNV dels) are the predominant variant types observed in a carrier screening population (82% LOF, 18% non-LOF) (Fig. 1).
- Truncations subject to NMD account for 32% of pathogenic variation, followed by canonical splice variants predicted to result in out-of-frame transcripts (23%) and CNV deletions (14%) (Fig. 1).
- Examples of genes with significant (≥90%) distribution of LOF variants detected include *VPS13B* (100%), *DMD* and *BLM* (99% LOF), *IKBKAP* (98%), *DPYD* (96%), *TMEM216* (93%), *FANC* genes (92%), and *USH* genes (90%) (Fig. 2 and Table 1).
- Examples of genes associated with both LOF and non-LOF variants include *PAH* (74% non-LOF), *DHCR7* (44% non-LOF), *ATP7B* (40% non-LOF), and *GAA* (37% non-LOF) (Fig. 3 and Table 1).

Figure 1. Overall distribution of pathogenic variants by variant type.

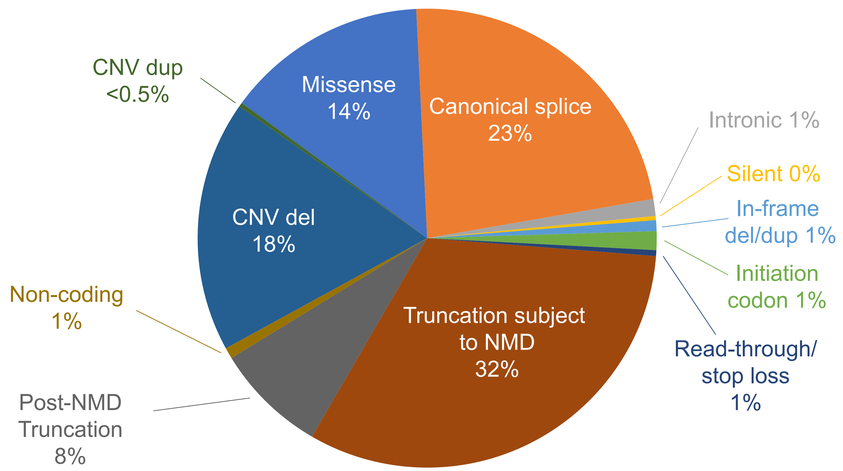

Figure 2. Examples of genes predominantly associated with LOF-type variants.

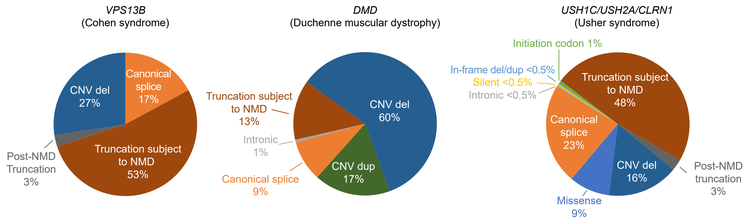

Figure 3. Examples of genes associated with both LOF and non-LOF-type variants.

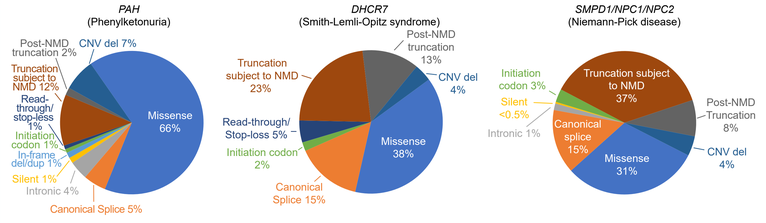

Table 1. Severe/profound recessive disease phenotypes are primarily associated with LOF variant types.

Gene (Disease)	% pathogeneic variants that are LOF-type
VPS13B (Cohen syndrome)	100%
DMD (Duchenne muscular dystrophy)	99%
BLM (Bloom syndrome)	99%
IKBKAP (familial dysautonomia)	98%
DPYD (dihydropyrimidinedehydrogenase deficiency)	96%
TMEM216 (Joubert syndrome)	93%
FANCA/FANCC/FANCG (Fanconi anemia)	92%
USH1C/USH2A/CLRN1 (Usher syndrome)	90%
ALDOB (hereditary fructose intolerance)	89%
MCOLN1 (mucolipidosis IV)	85%
BCKDHA/BCKDHB/DBT (Maple syrup urine disease)	82%
HEXA (hexosaminidase A deficiency)	80%
ABCC8 (familial hyperinsulinism)	77%
G6PC/SLC37A4 (glycogen storage disease type I)	76%
CFTR (Cystic fibrosis)	76%
ASPA (Canavan disease)	73%
ACADM (medium chain acyl-CoA dehydrogenase deficiency)	72%
HBB (beta thalassemia)	71%
SMPD1/NPC1/NPC2 (Niemann-Pick disease)	67%
PMM2 (congenital disorder of glycosylation type Ia)	64%
GAA (Pompe disease)	63%
ATP7B (Wison disease)	60%
DHCR7 (Smith-Lemli-Opitz syndrome)	56%
PAH (phenylketonuria)	26%

LOF variant types
CNV dels/dups
Truncations subject to NMD
Canonical splice
Post-NMD truncations
Initiation codon

Non-LOF variant types
Missense
Intronic
Silent
In-frame del/dup
Read-through/stop-loss
Non-coding

CONCLUSION

- Our analysis shows that LOF variants are the predominant variant type associated with recessive and X-linked diseases in a carrier screening population.
- To our knowledge, this is the largest single cohort study to assess the distribution of pathogenic variation by variant type for recessive and X-linked diseases in a clinical setting.

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