CNV contribution to pathogenic alleles within a healthy population: results from expanded carrier screening of 137k individuals

Samuel Cox, Eerik Kaseniit, Rebecca Mar-Heyming, H. Peter Kang, Saurav Guha

Introduction

Copy number variants (CNVs) are large, exon-level deletions or duplications that require special handling to detect with high accuracy. In conventional expanded carrier screening, specific testing for CNVs is restricted to a subset of genes where a frequent contribution to disease has been established (e.g., DMD) or a founder variant is known. In addition, for a number of established hereditary disorders, CNV analysis is absent from published case studies and is not routinely employed for diagnostic testing. Consequently, the contribution of CNVs remains largely unexplored for a considerable number of genetic disorders. Here we present findings from an expanded carrier screen incorporating panel-wide CNV calling, providing population CNV frequency data across a large number of recessive Mendelian disease genes.

Methods

Counsyl offers an NGS-based expanded carrier screen for 176 recessive diseases that includes panel-wide screening for CNVs. CNVs are identified using custom software that leverages high read-depth values. 1 Subsequently, ACMG-based variant classification is employed. Pathogenic classifications rely primarily on published cases and/or a predicted high-impact deleterious effect on gene function (Fig. 1).

Results

CNVs contribute to population carrier burden across a large number of hereditary diseases

A total of 2,506 pathogenic CNVs were identified, accounting for 1 in 30 detected carriers across the 165 disease genes (Fig. 3A). Furthermore, pathogenic CNVs were detected in 84% (199/165) of genes, surpassing 5% of carriers for a total of 16 diseases (Fig. 3B). The inclusion of panel-wide CNV detection boosts test sensitivity by 2.6% above that with CNV testing for DMD alone, as estimated using modeled fetal disease risk (MFDR) (Fig. 3C).2

Published case evidence for identified CNVs

Among CNV carriers, 18.9% harbored novel pathogenic variants, representing ~300 distinct CNVs not reported in the literature (Fig. 4).

Published CNV diversity varies significantly by gene

For certain genes, e.g., CLN3, CTNS, GALC, HEXB, over 90% of CNV carriers were attributed to a single known founder pathogenic variant. At the opposite extreme, over 30 distinct CNVs were found to contribute to carriers for DMD, FANCA and USH2A (Fig. 5).

Conclusions

CNVs make a considerable and widespread contribution to population carrier burden for serious and clinically actionable Mendelian diseases. For multiple genes, identified pathogenic CNVs were found to be exceptionally diverse and/or absent from the case literature, making them unsuitable for common/founder CNV testing alone. Inclusion of panel-wide novel CNV calling in an expanded carrier screen will, therefore, serve to maximize the detection rate for patients.

References