Newborn Screening, Inborn Errors of Metabolism

AB003. Prevalence of copy number and structural variants across Mendelian disorders

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Background: Exonic copy number variants (CNVs) contribute to disease, but their prevalence is poorly understood.

Methods: We applied a next-generation sequencing method to simultaneously detect single-nucleotide variants and small indels (SNVs) as well as intragenic CNVs in a large population undergoing clinical testing for neurological, pediatric, hereditary cancer, or cardiac disorders.

Results: Testing more than 76,000 unrelated individuals for subsets of 1,002 genes (the equivalent of 2.2 million single-gene tests), we identified 1,307 clinically reportable CNVs in 221 genes. These findings included 830 deletions and 477 duplications that represented 679 unique variants. CNVs were observed in only 1.7% of the patients and accounted for 3% of clinically reported variants, but pathogenic CNVs were present in 9.3% of patients with a positive finding. Most deletions (93%) were pathogenic, but only 46% of duplications were. Moreover, 17% of the unique CNVs included an entire gene and, in several instances, likely represented larger cytogenetic events encompassing several neighboring genes. Pathogenic CNVs were 7.3% of the pathogenic findings in pediatric and rare disorders, 32.2% in neurological disorders, and 4.8% in cardiology. These rates compare with 8.4% in oncology, a rate that has been well documented and helped justify universal del/dup analysis in hereditary cancer tests. We found that CNVs are prevalent in Charcot-Marie-Tooth disease, muscular dystrophy, neurofibromatosis, epilepsy, familial hypercholesterolemia, and other conditions. CNV variants were pathogenic at a rate (72.5%) greater than the fraction of small sequence variants that are pathogenic. In 67 individuals, a CNV was compound heterozygous with an SNV, and in 26 individuals, the two variants together constituted a definitive molecular diagnosis for a recessive disorder.

Conclusions: Our data suggest that universal exon-level CNV analysis is valuable, particularly in pediatrics and neurology, and provides clinicians a better view into CNV prevalence and the disproportionate frequency of CNVs among pathogenic variants.

Keywords: Copy number variant (CNV); Mendelian disorder; genetic testing

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