IN THIS ISSUE

Sequencing offers diagnostic utility for pediatric heart disease patients

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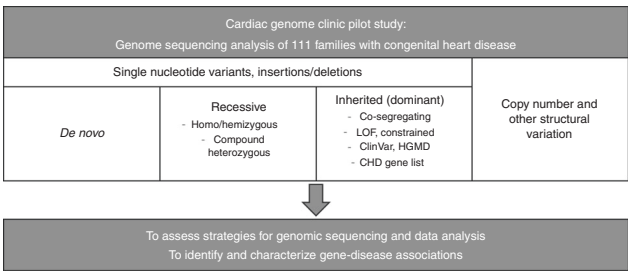

Up to 3% of babies are born with a congenital heart defect, making congenital heart disease (CHD) the most common type of birth defect. CHD encompasses a range of disorders that affect the structure or function of the developing heart. Although evidence from twin studies and familial recurrence rates suggest a genetic contribution, widely accepted formal diagnostic testing guidelines do not exist and families with heart disease are not always offered clinical genetics evaluation. In this issue, Reuter and colleagues demonstrate the diagnostic utility of genomic sequencing for pediatric heart disease patients. The researchers analyzed genomic sequencing data acquired from 111 unrelated probands with pediatric heart disease for variants predicted to be damaging. When possible, the scientists included parents and extended family members, resulting in sequencing information from 328 individuals. The team's analysis uncovered causative variants in 14 of the 111 families (12.6%). They determined that seven of the causative variants were de novo and six were inherited from parents who either did not have heart disease or showed subclinical heart phenotypes. The investigation also revealed two pathogenic copy-number variants. From the analysis, the researchers were able to make 11 diagnoses in patients with extracardiac features and 2 diagnoses in patients with familial heart defects. Additionally, they identified novel gene–disease associations for pulmonary stenosis, hypoplastic left and right heart, congenitally corrected transposition of the great arteries, and early-onset cardiomyopathy. The researchers conclude that the results support genomic sequencing as a first-tier diagnostic test for pediatric patients with CHD, but indicate that larger studies will help determine which patients will most likely benefit from such testing, as findings from this study are not necessarily applicable to a general CHD population. —*V. L. Dengler, News Editor*

RNA splicing analysis sheds light on variants of uncertain significance

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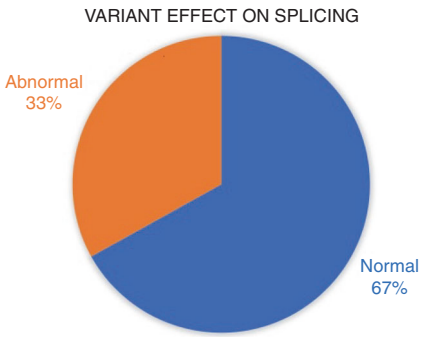

As clinical practices increasingly use sequencing to investigate patients' genetic disorders, the number of identified variants also grows. However, a lack of understanding of the functional effects of variants and genotype–phenotype associations makes determining the pathogenicity of many variants difficult, impacting patient management. Many variants of uncertain significance (VUS) affect RNA splicing. Here, Wai and colleagues assessed splicing defects in a large cohort of VUS and found that routine RNA analysis may aid clinical diagnosis. The researchers collected RNA from blood samples from patients with VUS identified via routine diagnostic genetic testing. Then they analyzed more than 250 coding and noncoding variants for their effect on splicing by targeted reverse transcription polymerase chain reaction (RT-PCR) with Sanger sequencing of the PCR products and agarose gel electrophoresis. The evaluation found that 85 of the 257 assessed variants (33%) were associated with abnormal splicing. Nearly half (39/85) of the detected abnormal splicing variants were associated with skipping of the upstream exon, and only three variants were associated with intron retention. Seventeen samples also underwent transcriptome-wide RNA sequencing analysis that in one case detected a splicing defect that RT-PCR did not catch. Finally, the researchers assessed the variants bioinformatically using the splicing prediction tools Alamut Visual, Human Splicing Finder, and SpliceAI. Although SpliceAI performed the best, with prediction accuracy exceeding 90%, there was still significant miscalling from all tools. The authors conclude that although many genes exhibit tissue-specific expression and splicing, blood RNA analysis has the potential to clarify the functional effects of VUS and improve diagnostics, and as such should at least be considered in genetic disease variant interpretation. —*V. L. Dengler, News Editor*

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