IN THIS ISSUE

Cell-free DNA enables molecular diagnosis of vascular malformations

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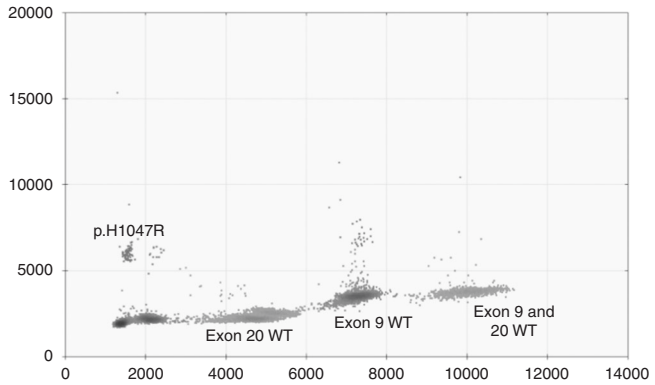

Vascular malformations (VMs) are congenital anomalies that lead to deformed and defective arteries, veins, capillaries, and lymph vessels. These malformations can be painful, cause disfigurement, and are associated with significant morbidity. Pathogenic variants in the PI3K-MTOR and RAS-MAPK pathways cause most VM cases, and targeted therapies exist. However, molecular diagnosis often requires surgery to obtain affected tissue for testing because variants are typically not detected in DNA isolated from blood. In this issue, Zenner and colleagues show that using cell-free DNA (cfDNA) provides a minimally invasive approach for making molecular diagnoses of VM without surgery. The researchers obtained plasma samples from 38 VM patients with known pathogenic variants. Using droplet digital polymerase chain reaction (ddPCR), the team detected variants in cfDNA in two of eight arteriovenous malformation (AVM) patients and one of three venous malformation (VeM) patients. The researchers were unable to detect *PI3KCA* variants from plasma samples from most patients with lymphatic malformations (LMs), a perhaps unsurprising result given that LM has poor connectivity to systemic circulation. When the researchers analyzed cfDNA from cystic samples from LM patients, they detected pathogenic variants in all seven cases analyzed. Next the researchers assessed whether they could prospectively identify variants in LM patients without the need for surgery. The researchers used a multiplex assay to maximize sensitivity on low-concentration samples. They detected three *PI3KCA* variants in four of five individuals and confirmed the variants using singleplex ddPCR. Together the results indicate that pathogenic variants are detectable in plasma in AVM and VeM patients and in cyst fluid from LM patients. The authors conclude that the data support cf-based molecular diagnostics for VMs and may enable molecular therapy without the need for invasive procedures to obtain tissue for molecular testing. —*V. L. Dengler, News Editor*

CNVs underlie inherited heart disease and sudden cardiac death

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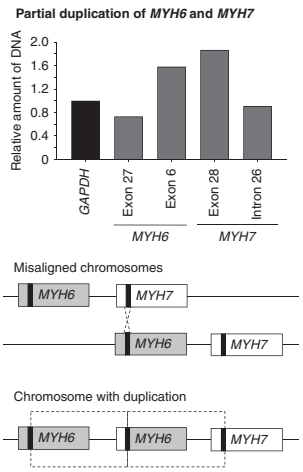

Most genetic heart diseases exhibit autosomal dominant inheritance. However, standard genetic testing in established disease genes does not always identify pathogenic variants, including those that stem from copy-number variants (CNVs) or structural rearrangements such as translocations. Yet, Singer and colleagues report, CNVs underlie some cases of inherited heart disease and unexplained cardiac death. The researchers assessed exome sequencing (ES) results from 690 unrelated probands diagnosed with an inherited heart disease or unexplained sudden cardiac death. They analyzed exome read alignments using eXome Hidden Markov Model software in a panel of 48 established cardiac disease–associated genes to detect CNVs. Careful analysis revealed eight CNVs (1.2%) in eight probands, including five deletions and three duplications that ranged in predicted size from 14 to 795 kb. The team then characterized breakpoint junctions from ES reads and quantitative polymerase chain reaction (qPCR) and PCR analysis. The breakpoint-junction assessments showed that nonhomologous end joining accounted for four deletions and that nonallelic homologous recombination between duplicated sequences was responsible for one duplication. The researchers then used the recently introduced American College of Medical Genetics and Genomics and ClinGen framework to classify the CNVs. They determined that three deletions classified as pathogenic, one deletion and three duplications classified as variants of uncertain significance, and one intragenic deletion classified as benign. The classification characterization uncovered an overall yield of clinically relevant CNVs of 0.4%. The results, according to the authors, demonstrate that CNVs are a rare cause of inherited heart disease and sudden cardiac death that is readily detectable with available sequencing data. The researchers conclude that when standard genetic testing is unable to identify a genetic cause of disease, CNV analysis is advisable. —*V. L. Dengler, News Editor*

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