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NEWS

Noncoding de novo variants contribute to congenital heart disease

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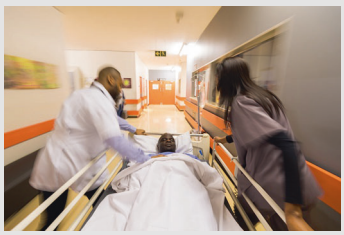
Advances in medical care mean that people with congenital heart disease (CHD) are living longer. Determining the cause of CHD may help to improve quality of life and further extend life expectancy. Previously, researchers discovered that 8% of sporadic CHD cases were attributable to de novo variants (DNVs) in coding regions. Now, in a recent article published in *Nature Genetics* (https://doi.org/10.1038/s41588-020-0652-z), Richter and colleagues report that DNVs in noncoding elements that function during cardiac development also contribute to CHD. The researchers performed genome sequencing on more than 700 probands and their unaffected parents in whom prior exome sequencing (ES) had failed to identify rare damaging missense or loss-of-function coding variants in CHD genes. When the researchers assessed the data at variant-level resolution using a neural network called Heart Effect Neural Network (HeartENN), they found that CHD cases were enriched for potentially biologically meaningful HeartENN scores compared with controls. The researchers then assessed DNVs in regulatory regions associated with human cardiac development. They prioritized more than 21,000 human fetal heart enhancers by pulling out common hits from an H3K27ac chromatin immunoprecipitation of human fetal cardiac tissues and an assay for transposable-accessible chromatin using sequencing to identify open chromatin sequences during cardiomyocyte differentiation of human induced pluripotent stem cells. The analysis revealed 27 genes marginally enriched for DNVs among CHD cases. DNVs were not enriched in any gene in controls. Next the team assessed noncoding DNV effects on post-transcriptional regulation. The researchers analyzed 160 RNA-binding protein (RBP) enhanced cross-linking immunoprecipitation data sets from two ENCODE cell lines and observed a significant enrichment of RBP DNVs overlapping the human fetal heart H3K36me3 active transcription mark, which they used to infer transcriptionally active cardiac binding sites. These DNVs had significant overlap with those in prioritized human fetal heart enhancers among CHD cases but not controls. Finally, the researchers estimated the mean attributable risk to CHD in the cohort. Noncoding DNVs identified via HeartENN contributed to as much as 24% of cases, while those in prioritized human fetal heart enhancers contributed to 12%. DNVs implicated in post-transcriptional disruption contributed to 10% of cases. The researchers conclude that noncoding DNVs in the ES-negative cohort contribute to a fraction of CHD cases equal to or greater than that for damaging coding DNVs identified via ES. *—V. L. Dengler, News Editor*

Genetic susceptibility may predispose African Americans to COVID-19-related arrhythmias, cardiac death



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SARS-CoV-2 has infected millions worldwide, and hundreds of thousands have succumbed to COVID-19. In the United States, deaths from COVID-19 have called out extreme health disparities. Across the nation, mortality rates in predominantly Black counties are sixfold higher than in predominantly white counties. In a recent review article published in the journal *Heart Rhythm* (https://doi.org/10.1016/j.hrthm.2020.04.045), Giudicessi and colleagues indicate that genetic variation may increase risk of cardiac complications and death from COVID-19 in individuals of African descent. The researchers suggest that such underlying genetic susceptibility could contribute to the disproportionate number of COVID-19 deaths in African Americans, while acknowledging that multiple cultural and socioeconomic factors likely contribute to the phenomenon. In particular, the authors highlight the ion channel variant p.Ser1103Tyr-SCN5A, which is seen almost exclusively in individuals of African descent. *SCN5A* encodes the sodium channel NaV1.5, which functions to conduct a small percentage of the current that contributes to the cardiac action potential's plateau phase. Although p.Ser1103Tyr-SCN5A NaV1.5 sodium channels work well under normal physiological conditions, they produce a proarrhythmic rise in persistent/late sodium current when intracellular pH drops in response to hypoxia. As a result, the variant confers an increased risk for ventricular arrhythmia and sudden cardiac death in carriers afflicted with COVID-19 who experience prolonged apnea and hypoxia. Structural heart disease as well as QT-prolonging medication, such as hydroxychloroquine, may exacerbate these proarrhythmic possibilities. For as many as 25% of hospitalized COVID-19 patients treated with chloroquine or hydroxychloroquine and azithromycin, heart rate–corrected QT interval values crossed above the critical 500 ms threshold. Therefore, patients prescribed such "corona cocktails" may be at increased risk of developing drug-induced long QT syndrome with the potential to deteriorate into drug-induced torsades de pointes or sudden cardiac death. In addition, the authors note that increased interleukin-6 (IL-6) levels triggered by SARS-CoV-2 infection also raise arrhythmia risk, notably by inhibiting cytochrome p450 enzymes involved in metabolizing QT-prolonging drugs. The authors conclude that, taken together, the data indicate that in the time of COVID-19, 1 in 13 African Americans may be at substantially increased risk of potentially lethal ventricular arrhythmias. The researchers suggest such actions as investigating the clinical utility of QT-shortening agents and anti-IL6-targeted therapies and avoiding the use of QT-prolonging drugs unless cardiac monitoring is in place. *—V. L. Dengler, News Editor*

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