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Large study of cardiac genetics confirms dubious value of population screening

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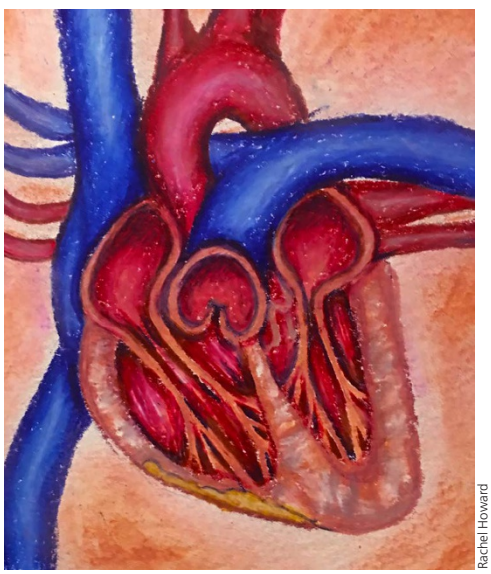
Recently, a spate of studies has called into question the meaning of certain genetic variants that had previously been associated with a variety of inherited diseases. Many of these studies, however, were fairly small and covered only a few variants. As reported in this issue, in a large study of more than 30,000 people who underwent whole-exome sequencing, none of those found to have variants thought to be associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) had any evidence of disease. The patients were all participants in Geisinger Health System's MyCode Community Health Initiative, a precision medicine project. All had electronic health records and had been followed for about 10 years. Investigators focused on the most "radical" putative loss-of-function (pLOF) variants, which would be expected to have a high probability of causing disease. The study flagged 18 study subjects carrying a pLOF variant and researchers reviewed their medical records. None had a documented diagnosis of ARVC. Most (14) had previously undergone an electrocardiogram, and only one of those individuals exhibited a single, minor diagnostic criterion; the others had normal electrocardiograms (EKGs). Of the 184 patients who had variants of uncertain significance (VUS) in an ARVC-associated gene, none had been diagnosed with the condition.



Rachel Howard

The proportion of subjects with VUS with EKG diagnostic criteria did not differ from that of variant-negative controls. Finally, International Classification of Diseases–9 codes showed no difference in defibrillator use, electrophysiological abnormalities, or nonischemic cardiomyopathies in patients with pLOF or VUS compared with controls. The researchers concluded that identification of seemingly pathogenic variants in the general population does not appear to identify individuals at risk for ARVC. Such data convey an important cautionary tale as we begin to do more and more genome-scale sequencing in patients and consider its use in the general population. *—Karyn Hede, News Editor*

Fetal exome sequencing shows utility in select cases

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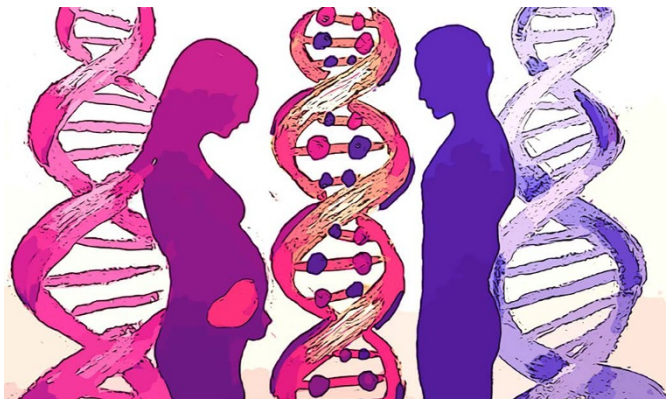

Rachel Howard

Many families dealing with unexplained congenital anomalies during and after pregnancy seek answers from genetic testing. But standard chromosomal screening and follow-up microarray testing provide answers for only about 1 in 10 patients. Exome sequencing, in contrast, has a diagnostic rate of about 30% in infants with certain types of birth defects. Because of its potential to increase the rate of diagnosis, investigators have begun to look to exome sequencing in the prenatal setting. A few small studies have reported that exome sequencing of fetal DNA improves the diagnostic rate when microarray studies provide no answers. However, extending exome sequencing to fetal testing is further complicated by the need to communicate potentially actionable results to pregnant women. Vora *et al*. report their experience communicating results to families in the complex and often ethically fraught realm of fetal DNA testing. The research team evaluated a series of 15 cases of fetal demise in which chromosomal studies and subsequent microarray analysis yielded no diagnosis. Exome sequencing provided a diagnosis in 7 of 15 cases in which multiple congenital defects had been noted in ultrasound studies. It also revealed a candidate gene (*MAP4K4*) for a previously unknown developmental disorder. To better investigate how well women understand the testing process and the results, the researchers also surveyed study participants and interviewed them after results had been returned. They found that, despite pretest genetic counseling explaining the relatively low chance of a positive result, most women had high expectations that the study would return a genetic explanation. The research team concluded that, while promising, exome sequencing is not yet ready for routine use in a prenatal setting and that more research on the most cost-effective and efficient use of this resource is needed. *—Karyn Hede, News Editor*