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Partnership provides genetic diagnoses in undersaved Amish communities

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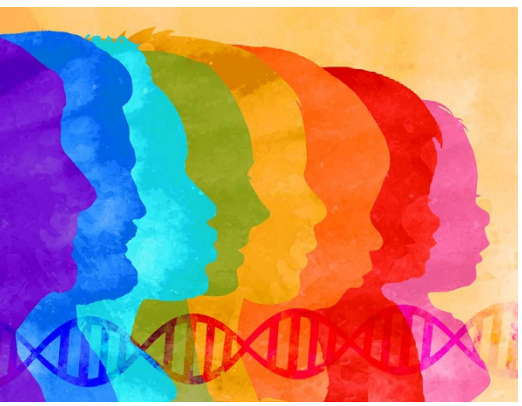
In many areas of the United States, access to advanced genetic and genomic diagnostic services is weak or altogether lacking. In this issue, Strauss *et al.* report the long-term, cost-effective results of a partnership between the Regeneron Genetics Center and the Clinic for Special Children, which serves uninsured members of the Old Order Amish and Mennonite communities in Pennsylvania and surrounding states. Over a 17-year period, 79 patients presenting with complex disorders, and who had gone an average of 3 years undiagnosed after various biochemical and focused genetic studies, were enrolled in the program. The patients received chromosomal microarray analysis (CMA) and whole-exome sequencing (WES; of proband and family members) at no cost. The careful screening process resulted in an overall diagnostic yield of 44–51%. The most common indications for testing were central nervous system disease (64%), auditory or visual impairment (7%), neuromuscular weakness (6%), growth delay (5%), hepatopathy (4%), and skeletal dysplasia (4%). Due to the small size of the endogamous community, "founder" alleles were more common than in larger populations. By recognizing and testing for these founder variants prior to utilizing CMA and WES, the research team obtained molecular diagnoses for more than 40% of patients after one visit, obviating the need for further analysis. For patients who required WES, the researchers returned actionable secondary results to 21 people who opted to receive these results. An economic analysis of the partnership showed that the cost of using a focused genomic strategy for one molecular diagnosis was $8,000, compared with $60,000 per diagnosis using the established diagnostic approach. The researchers concluded that for carefully selected patients, WES can be an efficient and cost-effective path to diagnosis. *—Karyn Hede, News Editor*



Rachel Howard

Naturally occurring gene knockouts can inform previously made associations

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Taking advantage of the unique population of Saudi Arabia, scientists at several Saudi institutions clarified the roles of five genes that had been flagged in genome-wide association studies (GWAS). The genes had been suggested as influencing complex traits but had not been directly implicated in Mendelian diseases. The study, published in this issue, reports five instances in which individuals have various mutations in the five genes, each shedding light on function. The authors observe that in some instances, a knockout phenotype probably represents a Mendelian counterpart to the complex trait reported in previous association studies. This phenomenon was evident in the *TRAF3IP2* gene, with which a Mendelian form of severe eczema could be a more severe variant of the psoriasis susceptibility previously suggested by GWAS. The *BTBD9* gene had been suggested to be involved in susceptibility to restless leg syndrome. Here, it was found be involved in unexplained myopathy. In contrast, the observed phenotypes for *PDXNL* and *RSC1* appear to be unrelated to the phenotypes previously suggested to be associated with these genes. The study provides evidence that naturally occurring knockouts can improve the specificity of GWAS interpretation. However, the authors caution against any firm conclusion that the phenotypes reported are causative, since the knockout events affect such a small number of patients. Nonetheless, they add valuable data regarding potential gene function. *—Karyn Hede, News Editor*

Rachel Howard