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Fetal DNA sequencing of birth defect cases yields novel pathogenic variants

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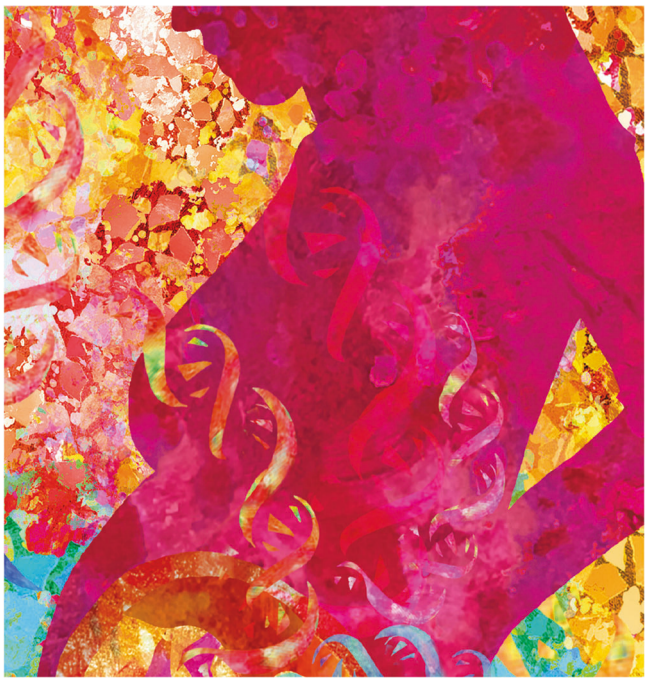

Rachel Howard

A research team studying a series of cases in which fetuses were found to have severe birth defects has discovered several new gene variants, including two in the *GREB1L* gene that cause the affected fetuses to lack kidneys (bilateral renal agenesis). The group, from several Canadian research institutions, investigated 101 fetal cases recruited over a three-year period. All cases had been identified prenatally with severe anatomic anomalies, and either the fetuses were stillborn or the pregnancy had been terminated. The goal of studying cases of severe physical disorders was to explore the precise genetic origins of these less commonly studied birth defects that often become evident during the second trimester of pregnancy. Currently, the genetic basis of the rare fetal malformations is not well understood. Knowing that the diagnostic yield of chromosomal microarray analysis for investigation of these types of defects is low, the researchers wanted to evaluate the added value of exome sequencing for the investigation of these anomalies. The findings, reported in this issue, shed light on a unique set of disorders. The group's diagnostic yield of 19% was in line with similar studies. They found likely pathogenic variants in genes (*DSTYK*, *ACTB*, and *HIVEP2*) previously associated with disorders quite dissimilar to those observed in the fetal cases. Two variants in *GREB1L* led to bilateral renal agenesis, a discovery that would likely not have been made in another setting because the condition is associated with a lethal malformation; this patient group is excluded from studies in liveborn children. —*Karyn Hede, News Editor*

Discovery of undetected balanced translocations in a public DNA database

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When chromosomal segments rearrange without causing any changes that can be detected using traditional chromosomal banding assays, identification of those changes becomes problematic. Genomic sequencing tends not to detect such changes. So, it was perhaps not surprising that a global collaboration applying a new, publicly available analytical tool found several examples of inversions and balanced translocations among the samples available through the 1000 Genomes Project, an international effort to establish a public database that catalogs human genetic variation in detail. The findings, reported in this issue, brought to light four cases of balanced translocations—two female and two male, from different ethnic populations—as well as four cases of inversions, all male. Chromosomal analysis did not identify the translocations, likely due to the pattern and size of the exchanged segments. Further, six of the eight breakpoints in the four cases with balanced translocations contained gene disruptions. While all individuals included in the 1000 Genomes Project were apparently healthy at enrollment, at least one of the disrupted genes found, *NRXN3*, is known to be associated with autism spectrum disorder in heterozygous deletion. The investigators speculate that reduced penetrance could explain the result in a healthy individual. The methods used in the study could help usher in an era of improved cytogenetic analysis. —*Karyn Hede, News Editor*