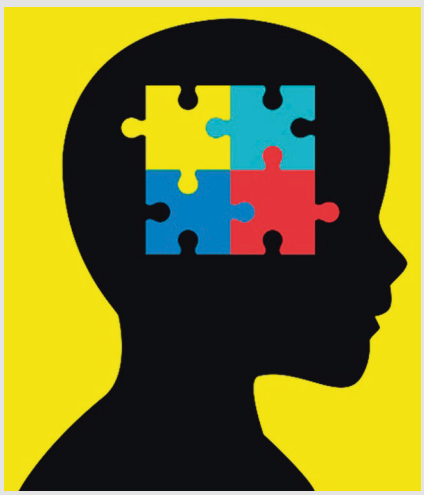
NEWS

Variants in "junk DNA" may contribute to autism



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Researchers are making substantial advances in understanding the genetics of autism spectrum disorder (ASD), a developmental disorder that impacts children's communication and sociability. De novo variants that affect protein-coding genes are important contributors to the condition yet explain only about 30% of simplex cases. Most de novo variants are in fact located in intronic and intergenic regions, but little is known about the contribution of noncoding variants to ASD or other complex diseases. In a recent article in *Nature Genetics* (https://doi.org/10.1038/s41588-019-0420-0), Zhou et al. use a deep-learning framework to identify influential noncoding variants in ASD. Drawing on genome sequencing data from 1790 families in the Simons Simplex Collection (SSC), researchers used biochemical data between DNA- and RNA-binding proteins and their targets to train a deep, convolutional neural network–based framework. The framework then predicted the effect of de novo variants in the collection. The analysis revealed an increased burden of variants that disrupt regulatory processes such as transcriptional and RNA-binding protein regulation in ASD probands. The researchers identified new candidate variants that might affect ASD via gene expression control, including variants near *HES1* and *FEZF1* that impact activator activity. To quantify the impact of the variants, the scientists trained a regularized linear model with a selection of regulatory variants identified in human disease from the Human Gene Mutation Database and variants from healthy people in the 1000 Genomes populations. The model produced a predicted disease impact score (DIS) for each autism variant. Compared with unaffected siblings, all de novo variants had a higher functional impact in probands, Zhou and colleagues found. The scientists also noted individuals with higher ASD risk carried a higher load of meaningful de novo variants. In total, de novo noncoding variants explained 4.3% of ASD cases in the SCC cohort. Loss of function and missense variants in contrast contributed to 5.4% and 3.1% of cases, respectively. Together the analysis provides evidence that de novo noncoding regulatory variants play a causal role in ASD, according to the researchers. They also note their approach may prove useful in predicting disease phenotypes from genetic information such as de novo variants. —*V. L. Dengler, News Editor*

Triple whammy: three genetic variants combine to cause early heart disease

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Congenital heart disease is the most common type of birth defect. Genetic causes that underlie the condition, however, remain elusive. In a recent article in *Science* (http://science.sciencemag.org/content/364/6443/865), Gifford et al. describe a rare combination of heterozygous variants that led to heart disease in a nuclear family. The discovery reveals how oligogenic inheritance and genetic modifiers can contribute to complex diseases such as congenital heart disease. A 2-month-old infant presented with congestive heart failure that required mechanical ventilation and pharmaceutical support. Echocardiography revealed that the child suffered a type of cardiomyopathy known as left ventricular noncompaction (LVNC). The family's medical history reported a sibling that had died at 24 weeks gestation. When the researchers examined histologic sections from the autopsy, they found that biventricular noncompaction had afflicted the fetus. Imaging of immediate living family members revealed LVNC in a 4-year-old sibling and suggestive signs in the father. The scientists then performed exome sequencing on the nuclear family. They focused their analysis on inherited private and/or rare nonsynonymous variants inherited from the father. Of 30 identified single-nucleotide variants of interest, only 2 were prominently expressed in heart tissue and predicted to be damaging. One was a missense variant in myosin heavy chain 7 (*MYH7*) and the other was a variant in the transcription factor MKL2. Both variants were previously described and heterozygous, and each variant resulted in an amino acid substitution at a highly conserved residue. The researchers then repeated the analysis on variants from the mother. This analysis revealed a rare heterozygous missense variant in *NKX2-5*, a key transcriptional regulator in cardiac development. Again the variant led to an amino acid substitution, but it was not predicted to be damaging. Gifford and colleagues then used CRISPR/Cas9 gene editing to generate mice with the triple-compound heterozygous variants. The mice exhibited deep trabeculation in the left ventricular wall similar to the affected family members. When the researchers increased pressure load on the left ventricle, the triple-compound heterozygous mice displayed worse cardiac function than wild-type mice. Together the results suggest that inheritance of the three heterozygous variants in *MYH7*, *MKL2*, and *NKX2-5* is sufficient to recapitulate the LVNC phenotype, in which the *NKX2-5* variant acts as a genetic modifier. The authors conclude that genetic modifiers may elucidate why variants in the same gene can lead to a broad array of diseases. —*V. L. Dengler, News Editor*

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