IN THIS ISSUE

Recurring variants uncover de novo pathogenic variants

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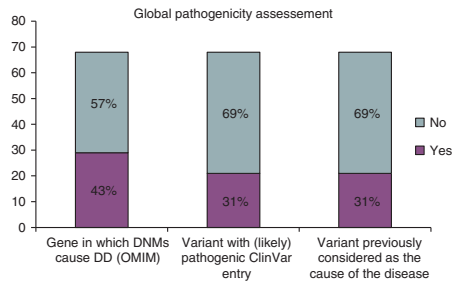

De novo variants influence many developmental disorders including intellectual disability, autism, and epilepsy. However, recognizing pathogenic de novo variants remains challenging. In this issue, Lecoquierre and colleagues demonstrate that detection of the same missense variant in two unrelated individuals with similar clinical presentations uncovers novel pathogenic variants. The researchers created a data set of about 7200 unique missense variants of interest that they pulled from a publicly available database called denovo-db. The data set contained de novo missense variants identified in at least one individual with a developmental disorder and were selected from clinical subcohorts associated with pediatric developmental disorders including autism, intellectual disability, developmental disorder, epilepsy, neural tube defects, and acromelic frontonasal dysostosis. To identify recurring variants, the scientists compared this data set with one derived from exome sequencing a local cohort of nearly 1300 probands with a developmental disorder. The researchers excluded variants found in the general population and compared the local probands' phenotypic data with information from the clinical cohort from denovo-db. The strategy identified 67 ultrarare good-quality missense variants: 32 identical variants, 12 distinct variants affecting the same nucleotide, and 23 variants affecting the same codon. When the team ran the variants through the OMIM database, they found that 43% were known to be involved in a developmental disorder caused by de novo pathogenic variants. Additionally, nearly a third (21/67, 31%) had been annotated as pathogenic or likely pathogenic in the ClinVar database. Furthermore, 21 of the variants had been previously identified by the researchers as responsible for disease in the corresponding affected patients. The findings suggest variant recurrence is an efficient means to detect pathogenic variants. In total, the analysis uncovered ten newly discovered de novo missense variants implicated in pediatric developmental disorders. The researchers conclude that variant recurrence will be central for future identification of new ultrarare diseases and may offer an unbiased approach to discovering new phenotype–genotype relationships in genes known to cause a specific disease. —*V. L. Dengler, News Editor*

Exome sequencing is cost-effective for patients with monogenic disorders

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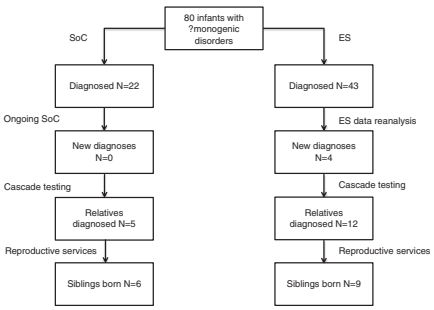

Growing evidence demonstrates that genomic tests such as exome sequencing (ES) provide high diagnostic and clinical value in rare genetic disease cases. However, few studies have investigated the long-term cost-effectiveness of such tests when diagnosing patients with suspected monogenic disorders. Now, Schofield and colleagues show that ES not only benefits these patients but also proves increasingly cost-effective when first-degree relatives and parental reproductive outcomes are included. The researchers recruited from Royal Children's Hospital in Melbourne, Australia, a cohort of 80 infants who likely had a monogenic disorder based on clinical presentation such as multiple congenital abnormalities and dysmorphic features or skeletal dysplasias. The researchers performed ES on cohort patients in parallel with typical diagnostic care. The team then built on previous studies to model the incremental cost-effectiveness of ES in the cohort by projecting over a 20-year time horizon. Using current ES prices of AU$3100, the researchers estimated an average ES diagnostic pathway cost of AU$7013 per patient. Forty-eight of the 80 patients received a diagnosis, including 26 diagnosed by ES alone. The remaining 22 diagnoses were made via the traditional diagnostic pathway. Nearly 90% of eligible first-degree relatives underwent cascade testing. When considering the cost and health outcomes of cohort participants, the team's models indicate that ES led to an increase of 7.39 quality-adjusted life-years (QALYs), a combined assessment of longevity and quality of life outcomes attributed to a particular intervention. Each QALY came at an incremental cost-effectiveness ratio (ICER) of about AU $31,000. When factoring in cascade testing of first-degree relatives, both QALY and cost-effectiveness benefited, raising QALYs to 11.62 and lowering the incremental cost to just under AU$21,000. Finally, when parental reproductive outcomes were also taken into account, QALYs increased again to 36.00 and incremental cost decreased to just over AU$14,000. The researchers acknowledge that the cost of ES testing and analysis can vary substantially depending on location, but conclude that the use of ES in patients with suspected monogenic disorders is very cost-effective. —*V. L. Dengler, News Editor*

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