NEWS

Untargeted metabolomics screening improves IEM diagnostic yield

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Inborn errors of metabolism (IEMs), a group of more than 500 heterogeneous disorders, are individually rare, but cumulative incidence is about 1 in 800 live births. Many IEMs are treatable, making early detection and diagnosis critical. Currently the Recommended Uniform Screening Panel (RUSP) covers 49 metabolic conditions, but it does not include many treatable conditions. Traditional metabolic screening draws on results from biochemical testing such as plasma amino acids, plasma acylcarnitine profile, and urine organic acids. In contrast, clinical metabolomics is a comprehensive chemical analysis of body fluids that can detect multiple metabolites across a wide range of biochemical pathways in a single test. In a recently published study in *JAMA Network Open* (https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2781912), Liu and colleagues found that an untargeted metabolomic screening approach improves diagnostic yield compared with traditional metabolic screening. To determine whether untargeted metabolomics could serve as a primary initial screen for IEMs, the researchers performed a cross-sectional study that compared a traditional screening cohort including nearly 1,500 patient samples and a clinical metabolomic cohort including 2,000 clinical patient plasma samples that underwent untargeted metabolomic profiling. Traditional screening identified biochemical abnormalities in 11% of tested families, 12% of which were considered diagnostic for an IEM. Positive diagnostic yield from traditional metabolic screening was 1% (19 of 1,483 cases). In total, traditional screening identified 14 IEMs, 11 of which are listed on the RUSP. Untargeted metabolomic screening identified 912 families with substantially abnormal profiles. Further analysis confirmed 128 (14%) positive cases, yielding a diagnostic rate of 7%, approximately sixfold higher than that of traditional metabolic screening. The untargeted screening identified key diagnostic or related secondary metabolites for 70 IEMs, of which only 21 are currently listed on the RUSP. Of the remaining 49 conditions, 26 are not covered by a traditional screening approach and 7 are currently treatable. The findings indicate that early screening by clinical metabolomics may identify disorders early and in some cases facilitate treatment, thereby reducing morbidity and mortality. Compared with traditional screening, clinical metabolomics screened for and identified a larger number of metabolic disorders, supporting the use of this approach as a first-line screening tool for IEMs. The authors conclude that the results support a broader screening approach for IEMs using clinical metabolomics. —*V. L. Dengler, News Editor*

C2orf69 deficiency causes fatal autoinflammatory Mendelian disorder

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Open reading frame 69 on chromosome 2 (*C2orf69*) encodes a two-exon gene of unknown function. Wong and colleagues recently reported in the *American Journal of Human Genetics* (https://www.cell.com/ajhg/fulltext/S0002-9297(21)00187-7) that *C2orf69* loss is responsible for a fatal autoinflammatory Mendelian disorder in humans. The researchers identified two brothers who presented with failure to thrive, global developmental delay, and periodic fevers among other features within 3 months of age. By 12 months of age, both experienced recurrent seizures and one exhibited severe microcephaly. Exome sequencing from one brother, who died at 18 months of age from pneumonia, revealed a germline homozygous frameshift variant in *C2orf69*. The researchers found that both neurotypical parents are heterozygous for the variant, which conforms to Mendelian expectations for an autosomal recessive trait. Collaborators recruited 18 similarly affected children from 7 additional families. All affected children displayed brain atrophy with progressive leukoencephalopathy and recurrent seizures, infection, inflammation, and failure to thrive. Sequencing from 12 children uncovered homozygous damaging variants in *C2orf69*. A BLAST search found that *C2orf69* is a highly conserved eukaryotic gene, and structure modeling indicated that it may encode an esterase or lipase enzyme. A series of cellular assays revealed that C2orf69 localizes to the mitochondrial outer membrane. When the researchers knocked out *C2orf69* in zebrafish, they saw that by 8 months of age the fish were smaller in both weight and length compared with wild type. Knockout fish experienced brain inflammation and died between 8 and 10 months of age from spontaneous epileptic seizures. The results indicate that C2orf69 is essential for brain development. Examination of a muscle biopsy from an affected child exposed changes such as subsarcolemmal mitochondria accumulation and mild cytochrome c oxidase deficiency suggestive of mitochondrial myopathy. Diastase-resistant periodic acid–Schiff staining pointed to polyglucosan body accumulation, characteristic of glycogen storage disease type IV caused by defects in *GBE1*. *C2orf69* knockout in human cells depleted GBE1 levels by about half. The researchers also found an accumulation of polyglucosan bodies in C2orf69 knockout zebrafish, further indicating a link between glycogen metabolism and C2orf69 deficiency. Altogether, the results revealed that C2orf69 deficiency results in an autoinflammatory Mendelian disorder that disrupts immune and central nervous system development. —*V. L. Dengler, News Editor*

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