New test to screen newborns for rare genetic disorders paves the way for earlier diagnosis and treatment

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Credit: Evgeny Atamanenko

A newly developed test to screen for three rare genetic disorders simultaneously in newborns was feasible, reliable and scalable, according to a new study.

The research, led by the Murdoch Children's Research Institute (MCRI), reported that screening for Prader Willi, Angelman and Dup15q syndromes using the new type of test would open new avenues for earlier diagnosis and treatment, paving the way for the three chromosome 15 imprinting disorders to be added to newborn bloodspot screening programs (heel prick test) for the first time.

The study, published in the *Journal of the American Medical Association Network Open,* was the first to validate the use of a low-cost, specialized screening method called Methylation Specific-Quantitative Melt Analysis (MS-QMA), developed by MCRI researchers, for these disorders at a large scale.

The one-step test can be used to screen for the three conditions simultaneously, by looking at the number of chemical modifications or marks called methylation added to affected genes, which are not present at such high or low levels in children without these disorders.

The State Government provided a $100,000 grant to MCRI as part of the 2018 Victorian Medical Research Acceleration Fund to support the development of the new screening method for the rare disorders. Medical Research Minister Jaala Pulford visited MCRI recently to see how the test worked and to learn more about its potential.

The study first checked for accuracy, with the test correctly distinguishing most of the 167 samples from people who had one of the disorders. It was then tested on 16,579 newborns in Victoria with the test identifying two with Prader Willi, two with Angelman and one with Dup15q.

The three disorders are characterized by varying degrees of intellectual disability, autism, behavioral problems, seizures and/or severe obesity. About 135 babies are born with one of these disorders each year in

Australia, but the disorders are not included in newborn screening programs, and many go undiagnosed in the first year of life.

MCRI Associate Professor David Godler said a key reason why these disorders were not included in current newborn screening programs was the lack of a test with low laboratory costs that could work at a population scale.

"Tests are currently only performed on those suspected of having these disorders, and only if features are recognized by a child's doctor, and subsequently referred for appropriate testing," he said. "This is not the case with newborn screening where testing is performed on all newborns before symptoms become apparent."

Associate Professor Godler said the study found the cost, disorder prevalence and accuracy of MS-QMA as a first-tier test were in line with other conditions currently included in newborn screening programs.

The study reported that in the 16,579 newborns screened, the probability of those with a positive screening test truly having the disease using MS-QMA was 67 percent, 33 percent and 44 percent for Angelman, Prader Willi and combined detection of chromosome 15 imprinting disorders, respectively.

"Having a high positive predictive value is important for newborn screening as it ensures that there is lower number of false positive results that need to be repeated, leading to lower overall laboratory costs, less work for maternity services in obtaining a repeated blood sample and minimizes the psychological effect on families," Associate Professor Godler said.

MCRI Professor David Amor said that if these findings were replicated in future independent studies, adding these chromosome 15 imprinting

disorders to newborn screening programs would allow for earlier diagnosis and using targeted interventions as they emerge, such as gene therapy for Angelman syndrome.

"For Prader Willi, diagnosis in infancy allows for early initiation of growth hormone treatment to improve long term health outcomes," he said. "For Angelman and Dup15q, most infants do not receive an early diagnosis that would allow intervention in the first year of life. But such early diagnosis, if available through newborn screening, could prevent the diagnostic odyssey, reduce medical costs and the significant stress and anxiety currently experienced by the families while they await a diagnosis."

Chrissy Cimino's son Elliott, 4, was diagnosed with Angelman syndrome at 14 months.

As a baby, Elliott couldn't sit upright, never cried or babbled and struggled to put on weight. After searching for a diagnosis for months, Chrissy said she was relieved to finally have the answer.

"There were a lot of red flags that were missed, and I knew in my gut that something wasn't right," she said. I kept persisting with medical appointments and I did my own research. It was such a relief to have that diagnosis so we could finally start medical interventions."

But Chrissy said if Elliott had been diagnosed through a newborn screening program, his motor and cognitive skills wouldn't be as poor.

"We couldn't get him on the NDIS until he was two and half so we missed out on years of intensive physio and speech and occupational therapies. He is almost five and he still isn't walking. If he was diagnosed earlier we could have helped him a lot sooner."

Doris Hamilton-Brown's son Lewis, 2, was diagnosed with Prader Willi at four weeks of age.

Doris said due to being born small for gestational age, Lewis was taken to the neonatal unit but failed to improve.

"After Lewis failed to get better the doctors started to look at genetic reasons," she said. "The diagnosis was unexpected and tough to hear but getting answers meant we could intervene early."

Lewis started growth hormone treatment at seven months, which will help with muscle bulk, reduce fat mass, increase physical activity levels and improve attainment of developmental and cognitive milestones.

"He has just started walking and while he is non-verbal he can understand verbal cues and communicate what he needs," Doris said.

She said having a test for Prader Willi and other chromosome 15 imprinting disorders on newborn screening programs would remove a lot of angst, guilt and uncertainty for parents.

"We were lucky that Lewis was able to start treatments and therapies fairly early on but for many families the diagnosis can come late and intervention is delayed," Doris said.

More information: David E. Godler et al, Feasibility of Screening for Chromosome 15 Imprinting Disorders in 16 579 Newborns by Using a Novel Genomic Workflow, *JAMA Network Open* (2022). DOI: 10.1001/jamanetworkopen.2021.41911

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