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SEQUENCE
Decoding news and trends for the medical genetics community

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RESEARCH UPDATE

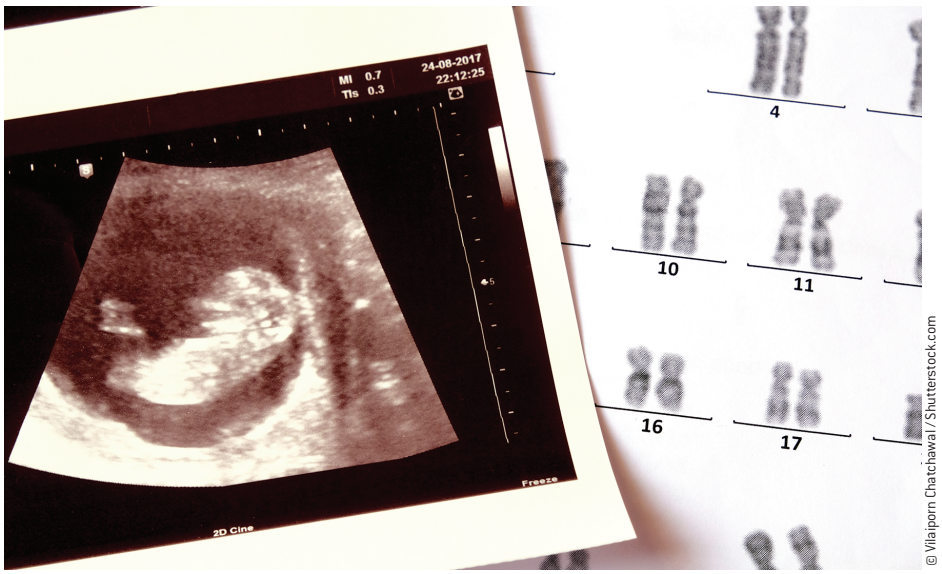
NEW DEFINITION OF UNEXPLAINED REGRESSION IN DOWN SYNDROME PROPOSED

Establishing a clinical definition will support future research and investigation of an underlying mechanism

Down syndrome (DS), caused by trisomy of chromosome 21, is the most common genetic cause of intellectual disability in the US, and it has long been associated with multiple congenital malformations and medical complications. However, it is increasingly recognized that adolescents and young adults with DS may experience functional deterioration, an apparent regression of cognitive ability that is characterized by reduced speech and psychomotor activity and a loss of autonomy and daily skills. Symptom onset for this regression can be sudden and acute, or evolve and progress over a period of months or years. The age of onset ranges from 4 to 30 years, and some reports describe individuals developing psychiatric/neurologic findings such as psychosis, aggression, and catatonia.

According to a recent database review, the causes of "unexplained regression in Down syndrome" (URDS) are largely unknown (Santoro et al, 2019). A clear pathophysiologic mechanism has not been identified, and because the etiology continues to remain unclear, recommendations for medical evaluation, management, and treatment of URDS are limited.

The same type of regression has been observed among individuals with autism, which occurs concurrently in 16% of those with DS, and in Alzheimer's disease, which is also seen in 80% of individuals with DS above the age of 65 years. However, there are distinct differences between regression in DS related to autism and regression in DS related to Alzheimer's disease, and now URDS appears to represent an entity all its own. Based on case-control evidence, researchers propose a separate definition for URDS, which they say will provide a foundation for future research and investigation of underlying mechanisms (Santoro et al, 2019).



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Researchers have identified 28 clinical and core features of patients with unexplained regression in Down syndrome.

"We began this study to establish a definition of regression," says Stephanie Santoro, MD, a clinical geneticist and Assistant in Pediatrics at Harvard Medical School. "We hoped that this would create consistency in how we think about this entity."

The Study

To address the challenges of diagnosing and managing URDS, a working group was created within the Down Syndrome Medical Interest Group (DSMIG-USA), which, in turn, generated a definition that includes 28 core and common clinical features of URDS. Researchers created a database that included both patients with unexplained regression and matched controls. Standardized data on clinical symptoms and tiered medical evaluations were collected, and a total of 35 patients with DS and unexplained regression were identified, with a mean age at regression of 17.5 years. Cases of URDS were compared with age- and sex-matched controls for clinical features, depression and stressor screens, and medical evaluations.

Study results showed that diagnostic features between the 2 cohorts differed substantially. The group with URDS had 4 times as many mental health concerns ($p < 0.001$), 6 times as many stressors ($p < 0.001$), and 7 times as many depressive symptoms ($p < 0.001$) as the group with URDS. In addition, abnormalities were identified in vitamin D 25-OH levels, polysomnograms, thyroid peroxidase antibodies, and screening for celiac disease.

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Overall, patients with URDS demonstrated an average of 15.4 of the 28 core and common features of the proposed diagnostic criteria compared to patients in the control group, who averaged 1.3.

"On the clinical side, we now have an established definition to use when we meet with families who wonder if their child may have this entity," says Dr. Santoro. "Using the score, we can say with more certainty if this diagnosis fits. In the past we relied on our experience and clinical gestalt." She also notes that this score could, prospectively, be used to follow children over time and help to foresee which children are at higher risk for URDS, although she adds that this possibility should also be studied before being put into clinical practice. Researchers still do not know how an individual patient's score may change over time, whether scores increase over time for patients with URDS, and whether the score itself would actually predict who will develop regression.

Weighing In

One of the key takeaways of this work is that patients with URDS have many more stressors, depressive symptoms, and mental health concerns than those without. "On the clinical side, I am [now] more attuned to stressors for my patients, and more apt to refer to psychiatry, psychology, or neuropsychology when there appears to be a co-occurring mental health condition," says Dr. Santoro. "Although we can't be certain without knowing the interplay/mechanism for URDS, it seems prudent to take steps to minimize and treat these factors for all of our patients with Down syndrome."

Paul Kruszka, MD, MPH, clinical geneticist at the Medical Genetics Branch at the National Human Genome Research Institute in Bethesda, Maryland, observes that the researchers were able to define the clinical characteristics of URDS by adding their 35 cases to the 79 cases that have already been published. "URDS is a recognizable and potentially treatable component of Down syndrome as it occurs in adolescence and adulthood, thus presenting a potential opportunity for intervention," he says. "I agree with the authors' prediction that this manuscript will help guide future research into the pathophysiology of this condition and hopefully therapeutic targets, and that it will raise awareness of URDS and assist researchers with establishing the prevalence of this condition."

However, it should be noted that larger cohorts of URDS are needed in order to more accurately evaluate comorbid and possibly contributing conditions, such as sleep apnea and thyroid disease. As an example, Dr. Kruszka points out that even though abnormal polysomnograms are twice as prevalent in URDS as in controls (60% vs. 33%), the study is underpowered to evaluate this difference. "This study was 86% white, and I do not see that any Asians were included," he says. "A more diverse population of Down syndrome will be important for future studies."

Reference

Santoro SL, Cannon S, Capone G, et al. Unexplained regression in Down syndrome: 35 cases from an international Down syndrome database. Genet Med. 2019 Nov 26; doi:10.1038/s41436-019-0706-8. [Epub ahead of print.]

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RESEARCH UPDATE

PHENOTYPE-BASED CRITERIA INCREASES DIAGNOSTIC IMPACT OF EXOME SEQUENCING IN NEONATES

Throughout the US, newborn screening programs, which generally screen for 30 to 50 treatable genetic disorders, have had success in preventing mortality or life-long morbidity. Newborns who are admitted to intensive care units, however, may also present with features suggestive of an underlying genetic disorder. Such clinical presentations can vary widely, from major anatomic malformations or pronounced biochemical abnormalities to subtler signs and symptoms. In these cases, trying to reach a diagnosis by traditional methods is a potentially lengthy and costly process, and so was genetic testing when it was performed serially gene by gene. Next-generation sequencing (NGS), however, significantly altered that paradigm.

With NGS, large panels of genes can be rapidly scanned at the same time, at a much lower cost, and with a higher probability of an accurate diagnosis. Exome and genome sequencing (ES/GS) are increasingly being used to accelerate diagnosis in the neonatal intensive care unit (NICU), and some studies have found diagnostic yields in the 21–60% range (Gubbels et al, 2019). Still, it remains unclear which patients are most likely to derive optimal benefit from ES/GS sequencing, because enrollment criteria in studies tend to rely on expert opinions from specialized teams typically composed of medical and metabolic geneticists and neurologists. Without expert opinion or any type of stratification, the diagnostic yield tends to be lower: One randomized trial found that when NICU patients were sequenced in the absence of any specific inclusion criteria, a diagnosis was made in only 1 of 29 cases (Ceyhan-Birsoy et al, 2019).