Unexplained intellectual disability explained by state-of-the-art genetic analysis

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A research team reported that next generation sequencing of the exome, the 1 to 2% of the DNA containing the genes that code for proteins, enabled the identification of the genetic causes of unexplained intellectual disability in over 50% of patients in a study conducted at Radboud University Medical Centre in Nijmegen, The Netherlands.

"Through next generation sequencing, we were able to discover mutations in genes that had not been previously linked to causing intellectual disability," said Marjolein Willemsen, M.D., Ph.D., who presented the research today (Nov. 8) at the American Society of Human Genetics 2012 meeting in San Francisco.

Correctly diagnosing children with intellectual disability (ID) can lead to early intervention and special education programs, vocational training and health screenings for associated conditions that will enable them to reach their full potential, said Dr. Willemsen of Radboud's department of human genetics.

Genetic diagnosis "is of major importance for the care and counseling of patients and families," Dr. Willemsen said. "Proper diagnosis provides insight into associated health and behavioral problems, prognosis and recurrence risk."

The cause of intellectual disability is unknown in more than half of patients with learning and other intellectual disabilities, which affect about 2% of the population, said Tjitske Kleefstra, M.D., Ph.D., also of

Radboud University Medical Centre's human genetics department.

Participating in the Radboud University study were 253 patients with unexplained intellectual disability, most of whom were adults. They underwent a multidisciplinary clinical evaluation and a metabolic screen. Genome-wide analysis of each patient's DNA was also conducted, and specific genetic diagnostic tests were performed as needed.

Because they used both genetic tests and clinical evaluations, the researchers were able to correlate the biological as well as the behavioral features of each patient's intellectual disability with the DNA findings.

Intellectual disability can be a challenge to diagnose because a wide range of features characterizes these disorders, and the underlying genetic causes can vary widely, Dr. Kleefstra said. "As a result, many parents go from one doctor to another in search of a diagnosis and treatment for their child," she added.

In the first part of the study, a diagnosis was made in over 18% of the patients as a result of the combination of clinical evaluation and application of genetic diagnostic technologies that are now routinely used in clinical genetic practice.

Many of the identified mutations were chromosomal abnormalities, and 5% were mutations in single genes that already had been linked to ID. One of these genes, EHMT1, was discovered in 2006 by Dr. Kleefstra as the cause of what is now known as the Kleefstra syndrome, which is characterized by intellectual disability, hypotonia (low muscle tone) and distinctive facial appearance.

The researchers then performed next generation sequencing (NGS) in a subset of the patients who remained undiagnosed after the first analysis. In this second part of the study, the exomes of the included patients were

analyzed.

In 17 of the 47 patients (36.2%) in whom NGS was applied, the likely pathogenic genetic causes were identified. The total yield of both parts of the study thus totaled over 54%.

Because intellectual disability syndromes caused by several novel genes were identified, the study has expanded scientific knowledge about the range of genetic causation in intellectual disability, Dr. Willemsen said.

More information: The researchers' abstract is titled, "Making headway with the molecular and clinical definition of rare genetic disorders with intellectual disability."

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