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## **Unexplained intellectual disability explained by state-of-the-art genetic analysis, researchers reported at ASHG 2012**

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 likely genetic causes of unexplained forms of intellectual disability in over 30% of a group of patients, a research team in The Netherlands reported today (Nov. 8) at the American Society of Human Genetics 2012 meeting in San Francisco.

“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., of the department of human genetics at the Radboud University Medical Centre in Nijmegen, The Netherlands.

Correctly diagnosing children with intellectual disability 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.

Genetic diagnosis “is of major importance for the care and counseling of patients and families,” she 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, said Tjitske Kleefstra, M.D., Ph.D., also of Radboud University Medical Centre’s human genetics department.

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.

Exome sequencing was conducted on the DNA of 47 patients, a subset that remained undiagnosed after genome-wide analysis of 253 individuals. The 253 individuals represented 234

*(more)*

families. Because participants from the same family were counted as one patient, index patients totaled 234, Dr. Willemsen explained.

The 234 index patients, most of whom were adults, underwent a multi-disciplinary 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.

Using both genetic tests and clinical evaluations, Dr. Willemsen and her colleagues correlated the biological as well as the behavioral features of each patient's intellectual disability with the DNA findings.

In the first part of the study, 18.4% of the index patients were diagnosed as a result of the combination of clinical evaluation and application of genetic diagnostic technologies that are now routinely used in clinical genetic practice, Dr. Willemsen said.

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

In part two of the study, the scientists performed next generation sequencing of the exomes of the 47 patients who remained undiagnosed after the first analysis. In 17 (36.2%) of the 47 patients, the likely pathogenic genetic causes were identified. The total yield of both parts of the study thus totaled 54.6%, Dr. Willemsen said.

However, because only 47 (24.6%) of the 191 patients who remained undiagnosed in the first phase of the study were selected for the part two exome sequencing studies, the diagnostic yield of the total cohort was 26.1% (61 out of 234), Dr. Willemsen said.

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, she added.

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

### **About ASHG**

The American Society of Human Genetics is the primary professional membership organization for nearly 8,000 human genetics specialists worldwide. The ASHG Annual Meeting is the world's largest gathering of human genetics professionals and a forum for renowned experts in the field.

**NOTE to journalists:** please note the following ASHG 2012 news release about another study on the genetics of intellectual disability: "Exome sequencing: potential diagnostic assay for unexplained intellectual disability, scientists report at ASHG 2012"