

Exome sequencing: Potential diagnostic assay for unexplained intellectual disability

November 8 2012

Research findings confirming that de novo mutations represent a major cause of previously unexplained intellectual disability were presented on Nov. 8 at the American Society of Human Genetics 2012 meeting in San Francisco.

Josep de Ligt, M.Sc., bioinformatician and Ph.D. student in human genetics at Radboud University Nijmegen Medical Centre in The Netherlands, also reported findings lending support to the use of exome sequencing, which deciphers over 21,000 protein-coding genes and not the entire [human genome](#), as a diagnostic assay to determine whether one or more [genetic mutations](#) explain a patient's [intellectual disability](#).

The cause of intellectual disability, which represents a wide range of phenotypes, or observable biological characteristics, is unknown in at least 50% of patients.

Most individuals with intellectual disability without a known cause are the only members of their families with the condition. Because the cause of their child's cognitive impairment is unknown, parents are often baffled.

The child with a [cognitive disability](#) is often an "isolated case without family history of the condition," said de Ligt, adding that intellectual disability occurs in about 1% of the population,

By exome sequencing of 100 patients with unexplained [cognitive](#)

[impairment](#), de Ligt and his colleagues uncovered 79 genes with unique de novo mutations.

These de novo mutations were present in the DNA of the patients but not in that of their parents whose exomes also were sequenced.

"All de novo as well as X-linked mutations identified in this study were interpreted in the context of the [clinical diagnosis](#)," de Ligt pointed out.

The diagnostic interpretation revealed that 16 of the 100 mutations were causative, or pathogenic. Ten of these mutations occurred in genes already known to be involved in intellectual disability, and three X-linked maternally-inherited mutations were identified.

In addition, de novo mutations were uncovered in three novel [candidate genes](#), which after follow-up were found to be more frequently mutated in patients with intellectual disability.

"Comparison of these patients showed clear overlapping [phenotypes](#), thereby establishing pathogenicity for these three new genes," said de Ligt.

Furthermore, disruptive de novo mutations were identified in 19 additional genes with a functional link to intellectual disability. Because 19 genes were found in only a single patient, de Ligt said that a conclusive diagnosis based on these findings could not be made.

Additional studies in larger patient cohorts will likely to confirm a considerable proportion of these as true intellectual disability genes, raising the diagnostic yield of this approach, he added.

"This study confirms that de novo mutations represent a major cause of previously unexplained intellectual disability," said Joris Veltman, Ph.D.,

associate professor in human genetics, Radboud University Nijmegen Medical Centre. "Because of the availability of large scale sequencing strategies, these mutations can now be readily revealed."

de Ligt said that the results of the study recommend "exome sequencing as a diagnostic assay for patients with unexplained intellectual disability."

More information: The researchers' abstract is titled, "Diagnostic exome sequencing in patients with intellectual disability of unknown cause."

Provided by American Society of Human Genetics

Citation: Exome sequencing: Potential diagnostic assay for unexplained intellectual disability (2012, November 8) retrieved 14 July 2023 from <https://medicalxpress.com/news/2012-11-exome-sequencing-potential-diagnostic-assay.html>

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