Intellectual disability is rarely inherited—risk for younger siblings is low

19 April 2021

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The prevalence of intellectual disabilities, which means difficulties with learning and understanding new things, is roughly 1-2% in the population. People with a severe intellectual disability need help from others in daily activities throughout their lives.

Such disabilities can be caused by genetic changes or external factors. According to estimates, roughly 2,500 genes underlie intellectual disability, of which approximately half remain unidentified.

In recent years, the diagnostics for intellectual disabilities have improved thanks to advancements in techniques that make it possible to sequence the entire genome. These techniques can also help to identify causes of intellectual disability not found in other medical examinations and tests. Exome sequencing, that is, the sequencing of the protein-coding regions of genes in the genome, enables the identification of new pathogenic gene variants as well. Identifying genes is a prerequisite for identifying disease mechanisms and developing treatments.

The study conducted at the University of Helsinki utilized exome sequencing to determine the potential genetic background of intellectual disability. The study participants included Finnish families with family members with delayed cognitive development for which no clear cause had been identified. The results were recently published in the *Human Genetics* journal.

It was found that in 64% of the study participants the cause of their developmental disorder was a known intellectual disability gene. The majority of these variants, 75%, was the result of random mutations taking place during fetal development (de novo), and variants not found in the parents' genome. An inherited mutation was identified in no more than a quarter of the pathogenic genes studied. More large-scale structural variants, which are usually not inherited, were found in only 8% of the families.

"Based on our findings, the risk of recurrence of intellectual disability in the next child of individual families is usually low," says Docent Irma Järvelä. According to Järvelä, this is a significant and relieving piece of information for many families.

She believes the use of exome sequencing as a primary method of examination in the diagnostics for intellectual disabilities is well justified. The technique makes it possible to investigate the cause of disability faster than before, which alleviates the uncertainty and concern felt by families, as well as generates savings in healthcare.

"The more familiar we are with the factors underlying intellectual disabilities and their hereditary nature, the better we are able to help families that encounter these serious disorders," Järvelä adds.

Human settlement history does not increase the prevalence of inherited diseases

The Finnish population has become known for its recessively inherited severe diseases caused by single gene defects known as founder variants, with some 40 of such diseases known so far.

The recently published study demonstrated that de novo variants created in early fetal development are the most common cause for intellectual disabilities also in the Finnish population. Known variants associated with recessive diseases were identified in only 5% of the families included in the study, a result in line with other European populations.

"In spite of the isolated nature of our population, Finns are not different from other European populations in terms of the inheritance of intellectual disabilities," Järvelä says.

A distant family connection going back 7 to 10 generations reduces the risk of establishing an recessively inherited disease even in small populations.

"In the light of contemporary gene research, the Finnish disease heritage appears an increasingly rare find. Related research in Finland is of a high medical standard," Järvelä emphasizes.

In the recently published study, nine new candidate genes were identified, of which a handful were found to be recessive. In further research, one of these genes could turn out to be a previously unknown gene enriched in the Finnish population.

The study was conducted in cooperation with Finnish doctors involved in the treatment of people with intellectual disabilities and the Department of Medical Genetics at the University of Helsinki as well as Columbia University and the Baylor College of Medicine in the United States.

More information: Irma Järvelä et al, Exome sequencing reveals predominantly de novo variants in disorders with intellectual disability (ID) in the founder population of Finland, *Human Genetics* (2021). DOI: 10.1007/s00439-021-02268-1

Provided by University of Helsinki