A syndrome combining intellectual disability, epilepsy and hypotonia results from the failure of a single gene

March 17 2016

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The objective of genetic medicine is to analyze all the genes that make up the human genome, in order to identify as many genetic diseases as possible. Indeed, each gene variation has the potential to trigger specific defects. Among all genetic conditions, diseases known as "recessive" occur only when both the father and the mother are healthy carriers of the same defective gene which can be passed down to their children. This category includes a disease that combines intellectual disability, epilepsy and hypotonia. In order to identify the cause of this disorder, researchers at the University of Geneva (UNIGE) sequenced the genomes of families presenting these symptoms, and identified the responsible gene: PIGG. In collaboration with a Japanese team, they were able to confirm its crucial role in the onset of this disease, opening the door to specialized diagnostics and prevention. Results can be read in *The American Journal of Human Genetics*.

The human genome is composed of 20, 000 genes. As of today, 3,200

are known to cause diseases, of which 1,700 are associated with recessive diseases. In the idea of finding the cause of a specific intellectual disability with hypotonia and epileptic seizures, Periklis Makrythanasis, lead author of the study and a researcher in the Department of Genetic Medicine and Development at the UNIGE Faculty of Medicine, looked into the cases of consanguineous families presenting this disorder. Why consanguineous? "Because the probability of suffering from a recessive disease is then higher, since both parents must carry the same genetic defect. There is therefore a higher chance of identifying a gene responsible for this syndrome by studying the members of an affected consanguineous family," he answered. This disease, however, does not only affect inbred groups; these populations are simply at higher risk of being affected.

The UNIGE researchers studied families in which several members presented these three symptoms. Using genome sequencing, they identified one gene which likely caused this intellectual disability. This gene, known as PIGG, is an important element in the protein production chain. Indeed, its role is to encode an enzyme that processes the modification of other proteins. If it dysfunctions, it prevents some of these proteins from being processed normally, and thereby causes intellectual disability, epilepsy, and hypotonia, which characterizes this syndrome.

But once the gene was identified, the team still needed to confirm that it indeed caused the disease. "We entered PIGG into an international database, known as Matchmaker, in order to see if other researchers had also noticed this gene's involvement in people with similar symptoms. Luckily, Japanese and British scientists gave us a positive answer!" explained Stylianos Antonarakis, head of the laboratory which conducted this study.

In collaboration with researchers from the University of Osaka, led by

Yoshiko Murakami, last author of this study, the scientists conducted in vitro experiments on the gene's biochemistry, which allowed them to confirm its role in provoking the disease.

This discovery is significant for the research and prevention of recessive genetic diseases. Indeed potential defects in the PIGG gene can be detected by sequencing patients from consanguineous families or any family and this analysis can even be performed prenataly. "As personalized genetic diagnosis becomes possible, this disease will be identified among other people presenting the same symptoms. These results also pave the way for futur new treatment. To solve a problem, you need to identify the cause, which is what we have done here," concluded Periklis Makrythanasis.

Provided by University of Geneva

Citation: A syndrome combining intellectual disability, epilepsy and hypotonia results from the failure of a single gene (2016, March 17) retrieved 19 April 2024 from https://medicalxpress.com/news/2016-03-syndrome-combining-intellectual-disability-epilepsy.html

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