Spontaneous mutations important cause of mental retardation

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New research by Dutch geneticists affiliated with the Radboud University Nijmegen Medical Centre demonstrates that spontaneous mutations are an important cause of mental retardation. The majority of mental retardation is caused by spontaneous mutations in paternal sperm or maternal egg cells, the scientists say.

With this conclusion, the researchers have not only resolved an important paradox but have also caused a small revolution in the world of medical genetics. They present their work in the journal *Nature Genetics*.

Mental retardation is a severe disorder that affects approximately two percent of the general population. Over the last few years, several genes have been identified to cause this disorder, but these have so far only explained a limited number of cases. The main genetic cause, referred to as the 'missing heritability', still awaits discovery. But what is this missing heritability for mental retardation?

Dutch researchers affiliated with the Radboud University Nijmegen Medical Centre, under supervision of Joris Veltman and Han Brunner, show in their article in Nature Genetics that newly generated (de novo) mutations explain a large portion of mental retardation. As such, mental retardation is not transmitted from one generation to the next, but occurs through spontaneously arisen genetic changes in the egg or sperm cells of the parents; The child has a defect in one of the genes, which still shows a normal function in both parents.

The researchers read the genetic code of all 20.000 genes for 10 patients with mental retardation. A similar analysis was performed for their healthy parents. By comparing the genetic codes obtained, differences in genes between parents and child could be precisely determined.

For nine out of ten children, the researchers indeed found such changes, each time in a different gene. For three children, the change identified was irrelevant to their disorder. But more important, for the remaining six children, they found two changes that are definitely relevant to their disorder and the four other changes are most likely related to their disorder. Geneticist Joris Veltman: "Apparently, the mental retardation observed in six of these ten children can be explained by a novel genetic change, a de novo mutation. This is more than half of all - so far - unexplained mental retardation!"

In the world of medical genetics, mental retardation reflects an intriguing paradox. Individuals with mental retardation seldom have children themselves; as such, they do not pass their impairment on to the next generation. Nonetheless, the frequency of mental retardation in the general population balances and remains around two percent. How can this be possible? Then what is the cause of mental retardation? This question has never been answered to full satisfaction.

Veltman and Brunner now offer a surprising resolution for this paradox. A majority of mental retardation occurred by chance; by novel mutations in the genetic code of the children. It is expected that approximately 1,000 of all 20,000 genes can cause mental retardation. When a de novo mutation hits one of these genes, it will result in mental retardation.

Parents of children with mental retardation often want to understand the cause of the mental retardation, but also want to estimate their recurrence risk for future pregnancies. Clinical geneticist Han Brunner: "In more than half of the cases we could not answer this question as we

did not know the cause. With this approach, it is now possible to elucidate up to sixty percent of all currently unsolved causes. In addition, we can now determine the recurrence risk for those families in which a de novo mutation caused the mental retardation. This risk will be only marginally increased compared to the general population. For many parents this is a reassuring message which may play a role in their decision making process for additional children."

On average, one new mutation will appear during the process that copies all parental genes to their child. With 1,000 of all 20,000 genes potentially playing a role in mental retardation, the chance of having a child with mental retardation is relatively high. A similar scenario is likely to be true for other diseases in which a large number of genes play a role, such as schizophrenia and autism. The concept of de novo mutations might be equally important for these diseases.

These findings may cause a small revolution for genetic research, a shift in paradigm. Veltman: "So far, mental retardation was thought to be caused by an interaction of multiple genes. We describe this as complex genetics. Indeed, in the general population mental retardation can be caused by as many as thousand genes. But on an individual level, each case -- as we now found -- is caused by a mutation in a single gene. This newly generated mutation can be readily identified by reading the genetic code of the parents and their child, because there is only one distinguishing factor, which is the causative mutation. This opens a new window of opportunity to look at disease, diagnostics, therapy and prevention."

This research has only now been made possible due to recent technological developments. Brunner: "At the beginning of this year, the department of human genetics heavily invested in state-of-art sequencing equipment. This machine does not read the genetic code of a single gene, but enables the readout of all 20,000 genes in a single experiment. This

enormous acceleration of analyzing the genome, which is referred to as 'Next Generation Sequencing', has caused a revolution in genetics. With this, personal genomics will become feasible, both from a financial aspect as well as from the time span needed to complete such an experiment. Our research is a nice example of this."

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