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Intellectual disabilities caused by protein defect

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Intellectual disabilities are often caused by a mutation that damages a gene, preventing the associated protein from functioning properly. However, a mutation can also change the function of a gene. As a result, the gene in question acts in a completely different way. Researchers from Radboudumc discovered this mechanism in fifteen genes playing a role in the development of intellectual disabilities. Their research results published in the *American Journal of Human Genetics* on 31 August 2017 show that these changes in function play a more prominent role than previously thought.

Genes are responsible for protein production in cells. A common cause of intellectual disabilities is a de novo mutation (i.e. a mutation present in a child, but not in its parents) damaging a gene so severely that it is no longer able to produce functional proteins. The resulting protein defect will cause illness. In a number of disease-related genes, it is shown that a de novo mutation does not eliminate the gene, but probably alters its function. These mutations are only located on specific parts of the gene.

Change in function

In order to find out how often this mechanism is involved, researchers from Radboudumc have combined the gene mutations in Dutch patients with a large international database comprising de novo mutations in patients. This research project was led by geneticist Christian Gilissen. "With our method, we were able to detect genes in which mutations not

so much eliminate as affect the gene in another way. We found fifteen genes in which mutations cluster closely together, twelve of which being associated with developmental disorders. We also found three new genes that are likely to play a role in the development of intellectual disabilities as well", according to Gilissen.

Interactions

The de novo mutations that were found only change a very small part of a protein. The function of the protein remains largely, but not entirely the same. Gilissen says: "The mutations are more likely to affect superficial parts of the proteins. These disturb interactions with other proteins and cause problems. Although mutations eliminating genes were often thought to be the main cause of intellectual disabilities, mutations altering the function of genes are now shown to be an important factor as well. That is a surprising finding."

Clustering mutations

Why are the de novo mutations that were found specifically clustered? Gilissen says: "There can be several explanations for that. Firstly, these genes show little natural variation. If such a gene is completely eliminated, a person may not be born. Only mutations located on very specific parts of the gene are viable. Consequently, only these mutations can be found. Another explanation can be that the mutations provide growth benefits to the sperm in which they develop. In that case, only these mutations would be able to survive."

New possibilities

The three newly-discovered genes playing a role in the development of intellectual disabilities provide new diagnostic possibilities for patients.

Gillissen says: "It is important that we have discovered a mechanism that has not yet been a focus of study. We expect this mechanism to play a role in a much larger proportion of patients with intellectual disabilities."

More information: Stefan H. Lelieveld et al. Spatial Clustering of de Novo Missense Mutations Identifies Candidate Neurodevelopmental Disorder-Associated Genes, *The American Journal of Human Genetics* (2017). DOI: 10.1016/j.ajhg.2017.08.004