Newly discovered gene variants lead to autism and mental retardation

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Researchers working with Professor Gudrun Rappold, Director of the Department of Molecular Human Genetics at Heidelberg University Hospital, have discovered previously unknown mutations in autistic and mentally impaired patients in what is known as the SHANK2 gene, a gene that is partially responsible for linking nerve cells. However, a single gene mutation is not always enough to trigger the illness.

In some cases, a certain threshold of mutation must be exceeded. The researchers conclude from their results that a correct inner structure of the nerve cell synapses is necessary to enable the normal development of language, social competence, and cognitive capacity. Essential for the success of the project were the studies by the Heidelberg research team with the doctoral student Simone Berkel and collaboration with a Canadian research team headed by Steve Scherer. The study has already been published online in the leading scientific journal *Nature Genetics*.

Autism is a congenital perception and information-processing disorder of the brain that is often associated with low intelligence, but also with above-average intelligence. The disease is characterized by limited social communication and stereotypical or ritualized behavior. Men are affected much more frequently than women. Autism and mental retardation can occur together but also independently of one another and are determined to a great extent by hereditary factors. Some of the responsible genes have already been identified but the precise genetic mechanisms have not yet been explained.

Genetic makeup of hundreds of patients analyzed

Professor Rappold and her team focused their studies on the SHANK2 gene, which encodes a structural protein at the nerve cell synapses. It is responsible for the mesh structure of the basic substance in the postsynapse. Only when the postsynapse is properly structured can nerve impulses be correctly transmitted. The researchers analyzed the genetic material of a total of 396 patients with autism and 184 patients with mental retardation. They found different mutations in their SHANK2 genes in the area of individual base pairs, but also variants in the number of gene copies. The mutations led to varying degrees of symptoms. None of the observed gene variants occurred in healthy control persons. "Apparently an intact postsynaptic structure is especially important for the development of cognitive functions, language, and social competence," explained Professor Rappold.

Identical mutations as the cause of different diseases

Some of the genetic mutations identified were new occurrences of mutations that were not inherited from the parents, but some of the mutations were also found in one parent. Since there are also healthy carriers of gene variants, we must assume that a certain threshold of gene mutations must be exceeded for the disease to appear. "Moreover, the same mutation can be present in an autistic patient with normal intelligence and in a mentally impaired patient," said Professor Rappold. There is some overlap in the clinical symptoms of mental retardation and autism, which can now be explained by a common genetic cause.

More information: Mutations detected in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. S Berkel, CR Marshall, B Weiss, J Howe, R Roeth, U Moog, V Endris, W Roberts, P Szatmari, D Pinto, M Bonin, A Riess, H Engels, R Sprengel,

SW Scherer, GA Rappold, Nature Genetics, 2010 in press (tracking number NG-LE27550R1; manuscript ID 589) Doi:10.1038/ng.589