MedicalXpress

How does the brain develop in individuals with autism?

November 12 2014

Geneticists at Heidelberg University Hospital's Department of Molecular Human Genetics have used a new mouse model to demonstrate the way a certain genetic mutation is linked to a type of autism in humans and affects brain development and behavior. In the brain of genetically altered mice, the protein FOXP1 is not synthesized, which is also the case for individuals with a certain form of autism. Consequently, after birth the brain structures degenerate that play a key role in perception. The mice also exhibited abnormal behavior that is typical of autism. The new mouse model now allows the molecular mechanisms in which FOXP1 plays a role to be explained and the associated changes in the brain to be better understood.

"While these kinds of results from basic research cannot be directly translated into treatment, they are still quite valuable for the affected individuals or in this case, for their parents and family. For many of them, it is important to be able to specifically put a name to the disorder and understand it. It can make dealing with it easier," said Professor Gudrun Rappold, Head of the Department of Molecular Human Genetics at Heidelberg University Hospital and senior author of the article. The results have now been published in a preliminary online version in the journal *Molecular Psychiatry* in cooperation with Miriam Schneider, Institute of Psychopharmacology at the Central Institute of Mental Health in Mannheim, and Dr. Corentin Le Magueresse, German Cancer Research Center (DKFZ) and Professor Hannah Monyer, Department of Clinical Neurobiology, Heidelberg University Hospital and DKFZ in Heidelberg.

Autism is a congenital perception and information-processing disorder in the brain that is frequently accompanied by intellectual disability and in rare cases, superior intelligence and special gifts such as photographic memory. The disorder is characterized by limited social interaction, repetitive behavior and language impairment. Furthermore, a wide range of other disturbances can occur. "Today, in addition to the defect in the FOXP1 gene, we are familiar with other genetic mutations that cause autism or increase the risk of this kind of disorder. However, we are only able to understand how they affect the molecular processes in the neurons, brain development and behavior for a few of these mutations," Rappold said.

This is also the case for FOXP1. Back in 2010, clear signs that structural flaws in this protein play a role in autism and mental disability had been discovered. But what role does it play in the healthy brain? What signal pathways is it involved in? Which other proteins does it interact with and exactly what damage is caused by its absence? The new mouse model has helped to shed light on these questions. The researchers discovered that the mice were born with a normally developed brain for the most part. During the course of the first weeks of life, the striatum, which is important for perception and behavior, degenerates. In a centrally located brain structure as well - the hippocampus - which is indispensable for developing long-term memory and recall, microscopically visible changes occur that can also impact signal processing. It could be proven, for example, that in the affected neurons the impulse conduction is changed through which signals are transmitted between neurons.

In addition to the striatum, the ventricles of the brain are degenerated; these are adjacent structures in the murine brain. "Enlarged ventricles were also detected in humans with a FOXP1 mutation," explained Dr. Claire Bacon, who works in the Molecular Human Genetics Department and is first author of the publication. The changes also trigger abnormal

behavior that is comparable to the symptoms of autistic patients. The mice barely noticed their fellow mice and did not attempt to make contact to them. Further symptoms include stereotypical compulsive repetitive behaviors, hyperactivity and disturbed nestbuilding behavior.

The researchers now intend to study to what extent the communication of noise by FOXP1 mice (mice communicate via noises in the ultrasonic range) is impaired and whether there are also parallels to the disturbances in patients with FOXP1 mutation in this area as well. In addition, they plan to characterize the newly identified genes impacted by the FOXP1 in the brain and find out which signaling cascades and response paths are disrupted. In this way, they hope to find starting points for a specific treatment. "However, we first have to understand exactly how these changes occur before we can develop treatment concepts," Rappold stressed.

More information: Brain-specific Foxp1 deletion impairs neuronal development and causes autistic-like behaviour. Bacon C, Schneider M, Le Magueresse C, Froehlich H, Sticht C, Gluch C, Monyer H, Rappold GA. Mol Psychiatry. 2014 Sep 30. DOI: 10.1038/mp.2014.116. [Epub ahead of print]

The distinct and overlapping phenotypic spectra of FOXP1 and FOXP2 in cognitive disorders. Bacon C, Rappold GA Hum Genet. 2012;131(11):1687-98.

Provided by Heidelberg University Hospital