Mutations in the gene DLL4 cause Adams-Oliver syndrome

Adams-Oliver syndrome (AOS) is a rare hereditary disorder that occurs in 1 in 225.000 individuals and is characterized by the presence of both scalp and limb defects. Congenital anomalies of the heart and blood vessels are also frequently observed. Mutations (genetic errors) in five different genes (coding parts of the genome) were identified as a cause for AOS prior to this report. These genes contain the code for the production of proteins, essential building blocks of the human body. Mutations in those genes lead to errors in the corresponding proteins. These proteins act together in networks and are important in de development of different cells and tissues. Because three of the previously identified proteins interact with each other, we hypothesized that other proteins working in the same network, could lead to the same disease. Because AOS patients often also have cardiovascular problems, we specifically selected from this network a protein, called DLL4, that is essential in blood vessel development. We analyzed the coding parts of the *DLL4* gene in 91 independent families that had no mutations in the currently known five genes. In total, we identified nine families with mutations in *DLL4*. All these genetic errors are predicted to lead to a reduced function or altered structure of the protein and as such cause the disease.

The individuals that carry a mutation in *DLL4* show wide variability in the severity of symptoms. Some patients only have a small bald area on the scalp and short fingers, while others are born with absence of skin on parts of the scalp, defects of the skull bones and complete absence of fingers or toes. Even within the same family, affected family members who carry the same mutation can present with important differences in severity of the symptoms. These observations indicate that mutations in DLL4 cannot completely explain the disease in the affected individuals and thus most likely other genetic and/or environmental factors must be involved as well.

The identification of *DLL4* as a cause of AOS is important for the genetic counseling of patients. Affected individuals can now be checked for mutations in *DLL4* and get an accurate confirmation of clinical diagnosis by a genetic diagnosis. If an affected parent wants to have a baby, the chance of the child being affected is as high as 50%. We have provided new insights into a specific group of interacting proteins that is important in the development of this disease. In the long run, we anticipate these results will contribute to the development of new drugs to help AOS patients.

Publication

Heterozygous Loss-of-Function Mutations in DLL4 Cause Adams-Oliver Syndrome.
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