Research team enlightens the reasons for severe blindness

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People suffering from a severe retinal disease will sooner or later lose their eyesight considerably or even become completely blind. Those affected, family members, researchers and doctors hope that this fate might be avoided one day by a better understanding of the reasons for this disease.

Coordinated by the geneticist Ronald Roepman from Nijemegen, an important step has now been made in this direction by an international research team with the participation of the GSF - National Research Center for Environment and Health: they identified a further gene for the inherited retinal disease Leber Congenital Amaurosis (LCA) and discovered first evidences how it functions. This represents new opportunities for gene therapy, which especially for LCA, is considered as very promising since the disease is caused by a single mutation.

LCA causes blindness very early on – often shortly after or within a few months of birth. The disease can be caused through a single mutation in different genes; with the newly discovered LCA5 gene, ten disease-causing genes had been identified so far which are responsible for approx. 60 % of all LCA diseases. “All these deficiencies lead in the end to the same symptoms, however, in order to treat the disease efficiently with the individual patient, it is important to know which gene mutation occurred in the specific case and what it causes”, underlines Dr. Marius Ueffing (GSF Institute for Human Genetics), who leads the project at GSF.

The LCA5 gene encodes the lebercilin, a so far unknown protein. Through proteomic methods, Ueffing's team could demonstrate that lebercilin specifically interacts with other proteins which play a role in the protein transport in the cells. Thus the scientists concluded that lebercilin is relevant for the protein transport within the optical cell: as shown by electro-microscopic pictures, within the optical cell described as the photoreceptor, lebercilin binds the most to the so-called cilium, the connection point between the interior and exterior segments of the photoreceptor. Through this "molecular transport belt", the optical crimson must be also transported into the exterior segment of the optical cell. The light reception takes place exactly here. If the lebercilin synthesis is disturbed, the already used optical crimson in the exterior segment cannot be replaced anymore and the eyesight is lost, according to the researchers' hypothesis.

Very similar transport processes also play a role in other body parts, e.g. in the kidneys. Lebercilin is part of a complex network of proteins which controls ciliary transport processes, or directly take part in them. Disruptions in the cooperation of such molecular networks at the protein interaction level often build the molecular basis of diseases. In the case of ciliary diseases (ciliopathies), the restricted functionalities of cilium cause deafness, blindness or even severe syndrome diseases. LCA is therefore a good model which also enables to gain more knowledge over other difficultly treatable diseases in the long term.

LCA itself is so far incurable. However, patients and doctors set their hopes high on gene therapy: since each type of LCA is caused by the mutation of a single gene, the affected persons could be helped by exchanging this gene. Such a LCA gene therapy has been already successfully implemented for dogs who naturally suffer from LCA: the treated dogs regained their permanent eyesight due to this therapy. A clinical study of twelve human patients is currently being carried out at a large-scale London hospital with encouraging results. If these findings

prove to be withstandable, there will also be gene therapy available for LCA5 gene deficiencies in five to ten years time, says Ueffing. “The affected persons urge for a faster procedure” underlines Ueffing, “but researchers and doctors assume a big responsibility concerning the development and implementation of gene therapies. Therefore, very high safety standards must be set in this field.”

Source: GSF - National Research Center for Environment and Health