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New mechanism for febrile seizures in young children discovered

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Febrile seizures are among the most dreaded complications of infectious diseases in small children. An international research team composed of experts from the Universities of Tübingen, Leuven and Luxembourg has now made a breakthrough by demonstrating the existence of a previously unknown cause for this most frequent form of epileptic attacks in small children. As a study just published in the medical journal *Nature Genetics* shows, mutations in the STX1B gene are responsible for the children's pathological reactions to fever. The gene mutations lead to an impaired regulation in the release of certain nerve cell messenger substances. The consequence of this is an increase of involuntary electrical discharges in the brain, accompanied by epileptic febrile seizures. In the long run, the newly discovered gene alterations can also be the source of serious epilepsy and mental disability. The scientists now hope to develop new forms of therapy on the basis of their discoveries.

Febrile seizures are the most frequent form of childhood epileptic attacks and affect roughly two to four per cent of all children worldwide. They often occur between the ages of three months and five years and can even appear upon mild hyperthermia. What is apparently even more decisive than the fever level, however, is the speed with which the fever rises. "This explains why children can experience a febrile seizure even before the parents have noticed that the child is ill," says Professor Holger Lerche, M.D., Director of the Hertie Institute for Clinical Brain Research (HIH) and Medical Director of the Department of Neurology and Epileptology at the University of Tübingen. Parents naturally

become worried when a small child shows a tendency to fever attacks. However, the prospects in most cases are good: the attacks subside by the time of school age, and damaging aftereffects remain present only in rare and exceptional cases.

The factors which contribute to the development of epilepsy from simple febrile seizures are still largely unknown. "Genetic predisposition plays an important role. But up to now there has been an inadequate understanding of which genomic mutations are involved in detail," says the study's co-initiator, Professor Yvonne Weber, M.D., Assistant Medical Director of the Department of Neurology and Epileptology at the University of Tübingen.

The team of researchers came upon the track of these genetic mutations via exome sequencing, a special technique for examining a partial section of the genetic material. Even though the exome makes up only about one per cent of the human genotype, it also contains most of the pathogenic genetic alterations (mutations) which have been found to date. Analysis of genetic material first revealed STX1B mutations in two large families whose members are prone to both febrile seizures and epileptic attacks. The analysis was then widened to include further patients, which led to the discovery of four further mutations. Here too, the affected persons suffered from febrile seizures and serious epileptic attacks, which had resulted over and above this in mental disabilities. "In other words, the STX1B mutations gave us an important clue: they do more than trigger epileptic febrile seizures, which of themselves often subside in these small patients by the time of the first school year; the mutations may also be the cause of serious cases of epilepsy, with consequent impairment of intellectual development", as Lerche explains. The researchers now hope to turn these insights to practical advantage in the form of better methods of treatment and even, in the ideal case, to successfully prevent the development of epilepsy.

Together with experts in the field of zebrafish research from the University of Leuven, Belgium and the University of Luxembourg's Centre for Systems Biomedicine (LCSB), the neuroscientists were able to confirm the impact of the newly discovered STX1B mutations with the aid of a model system. Zebrafish provide an excellent model for the study of epilepsy. In the zebrafish, the development of organs such as the brain takes place at the level of molecular mechanisms in much the same way as in humans. "We were able to show not only that similar patterns of epileptiform attacks also occur in zebrafish with genetically altered STX1B genes, but also that brainwave changes appeared which were clearly aggravated by hyperthermia - as in the case of fever," says Dr. Camila Esguerra, the principal investigator who led this part of the study at the University of Leuven and is now in the process of forming a new research team at the University of Oslo, Norway.

Zebrafish are also especially well-suited for the development of new avenues of treatment. Together with Dr. Alexander Crawford (Luxembourg), Dr. Esguerra has already found a substance which can prevent the most violent form of attacks in zebrafish. "We hope that from this we will be able to develop a new drug in a few years which will prevent the development of certain forms of serious epilepsy in childhood," says Crawford. In addition, a search for new substances will also be carried out in STX1B mutations.

The project also included clinical and genetic experts of the EuroEPINOMICS Consortium, a European Science Foundation network initiated and directed by scientists in Tübingen, Kiel and Antwerp and funded in Germany with 2.5 million Euros from the German Research Foundation. This has brought clinicians together with scientists in the field of basic research to study both the genetic mechanisms of epilepsy and avenues for new methods of therapy. Still another network, "IonNeurONet" is part of this project and is carrying on a search for the causes of rare forms of epilepsy and other nervous disorders (e.g. rare

forms of migraine as well as retinal and muscular diseases). With the help of the German Federal Ministry for Education and Research (BMBF), which has provided support for the network, patients with the corresponding impairments have been gained as test subjects for the study. Such large-scale networks, with the corresponding numbers of patients, are essential for the discovery and confirmation of new genetic defects. They are also a prerequisite for later clinical trials to confirm research results in patients. The work described here has brought the scientists and physicians of the present study a step closer to a discovery of new therapeutic options.

More information: Mutations in STX1B, encoding a presynaptic protein, cause fever-associated epilepsy syndromes; Nature Genetics, DOI: 10.1038/ng.3130

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