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Researchers map previously unknown disease in children

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Two children from Europe and one from Canada, aged four, six and 10, suffer from a previously unknown disease that causes epileptic seizures, loss of magnesium and reduced intelligence. There is currently no way to treat or alleviate their symptoms.

But researchers in an international consortium have now discovered the

cause of their illness. Professor Bente Vilsen and her research group at the Department of Biomedicine at Aarhus University, Denmark, are part of the consortium, which also includes researchers from universities in Germany, England, Austria, the Netherlands and Canada. The research results have been published in the *American Journal of Human Genetics*.

Using a genetic analysis, the researchers have discovered that the disease is caused by a newly occurring mutation in one of the sodium-potassium pump's four forms, known as Alpha-1. Even though the children have exactly the same three symptoms, they do not have the same genetic defect, as the amino acids in the pump protein which are genetically altered are different, explains Bente Vilsen.

"It turns out that the form of sodium-potassium pump that mutates is found in both the kidneys and the brain. The mutation leads to the kidneys, which normally absorb magnesium, instead secreting the substance in the urine; however, it is not the loss of magnesium that triggers the epileptic seizures. The convulsions occur because the sodium-potassium pump is also extremely important for the brain's functions, meaning that giving extra magnesium supplements won't prevent the seizures," says Bente Vilsen.

She adds that the third frightening sign of the disease, mental retardation , should probably be attributed to a lack of oxygen to the brain during the seizures.

Jens Christian Skou received the Nobel Prize in Chemistry in 1997 for discovering these molecular pumps, which are mutated in all three children. This knowledge is important, because understanding the role of the sodium-potassium pump is the first step toward developing effective treatment methods. The research group is now working toward this goal, even though the disease is rare.

"But three cases have turned up in two different places in Europe and in Canada, and they're not likely to be the only ones," says Bente Vilsen. She explains that the new knowledge about the disease will probably mean that medical doctors will in future be more aware that loss of magnesium in combination with epilepsy may be caused by genetic defects in the sodium-potassium pump.

"I believe that we will find many more children with the disease, and that this is a good example of why international research cooperation is absolutely necessary—there are simply too few cases of the disease for a single country to carry out the research alone," says Bente Vilsen.

She points out that in future, it will be possible to replace sick genes with healthy ones, and that it is therefore important to know precisely which gene is affected by a mutation. She also points out that the understanding of the disease mechanisms causing rare diseases often lead to better treatment of patients with related but far more commonly occurring diseases.

Jens Chr. Skou's sodium-potassium pump is best known as the membrane pump that is needed for the normal functioning of nerve cells, kidney cells and most of the body's other cells.

The pump works like a battery, separating sodium and potassium on either side of the membrane. This creates an electrical current across the cell membrane that drives many other processes such as, e.g., electric conduction along the nerve cells and the absorption of magnesium and a range of nutrients from the urine into the kidney cells, so that they are not normally lost in the urine.

Jens Christian Skou, who died in early summer at the age of 99, originally had the idea that mutations in the sodium-potassium pump would be incompatible with life. But it has since been found that serious,

non-fatal diseases can originate from genetic defects in the sodium-potassium pump—exactly the case with the disease afflicting the three children.

This is due to two factors. First, there are several variants of the sodium-potassium pump in different body tissues which are able to supplement each other if one of the forms does not work. And, secondly, humans have genetic material from both parents, so even in the kidneys, which in contrast to the brain contain only one variant of the sodium-potassium pump (Alpha-1), not all of the sodium-potassium pumps will be defective, but only those derived from one of the two parents.

Therefore, in both the brain and kidneys, there will be a reduced number of functioning sodium-potassium pumps, but not a total absence of pumps—because if this was the case, the children would have died before birth, as predicted by Jens Christian Skou.

The patients were discovered by medical doctors working in clinical practice. Bente Vilsen's group contributed their expertise in examining sick sodium-potassium pumps by inserting the diseased gene in cultured cells that originally come from monkey kidneys, making it possible to measure their pump function in the laboratory. As it turned out, the three mutations each in their own way caused the pump to be unable to transport sodium and potassium.

There is a long way to go before the research results benefit the patients, as the discovery is still basic research. However, Bente Vilsen explains that Postdoc Rikke Holm from her research group recently discovered how it was possible to use an additional mutation—a so-called 'rescue' mutation—to nullify the effects of the disease mutations on the pump's binding of sodium.

"This provides an insight into the molecular mechanism that we in the

research group are working to use to improve the pump's transport activities, meaning that we can possibly one day develop a drug with a similar rescue effect. In any event, that's our hope. The fact is that it's basic research that generates the knowledge that forms the basis for the development of the vast majority of drugs and forms of treatment," says Vilsen.

More information: Karl P. Schlingmann et al, Germline De Novo Mutations in ATP1A1 Cause Renal Hypomagnesemia, Refractory Seizures, and Intellectual Disability, *The American Journal of Human Genetics* (2018). DOI: 10.1016/j.ajhg.2018.10.004

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