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Researchers at MedUni Vienna have discovered the genetic cause of a rare disease characterized by life-threatening "liver crises" in early childhood and subsequent manifestation of neurological symptoms, such as neuropathy and ataxia (a movement disorder), when they reach school age. In 2007 the same researchers published a mutation in the Scyl1 gene in a naturally occurring mouse mutant with similar symptoms. Using next-generation sequencing techniques, they have now succeeded in identifying the first cases of a corresponding condition in humans. This marks the successful end to a search that started in the Neuromuscular Research Department (Center for Anatomy and Cell Biology of MedUni

Vienna) more than ten years ago.

So-called mdf ("muscle deficient") mice have an atrophic cerebellum and display symptoms such as muscular atrophy, ataxia (gait disorders) tremor and thinning of the optic nerves. This is due to a mutation in the Scyl1 gene of the mouse, which was discovered more than 10 years ago and first described in 2007 by the group of researchers led by Wolfgang M. Schmidt and Reginald E. Bittner (Neuromuscular Research Department at the Center for Anatomy and Cell Biology of MedUni Vienna). Scyl1, which is highly conserved in evolutionary terms, is an important molecule for intra-cellular transport. For the first time, using modern DNA sequencing techniques (Next Generation Sequencing) it has now become possible to identify mutations in the human SCYL1 gene in patients with similar clinical symptoms.

First patients identified

"Due to the rapid technological advances in the field of Next Generation DNA-Sequencing over the last few years, it is now possible to make a quicker and more comprehensive analysis of the human genome", says the corresponding author of the present publication, Reginald E. Bittner. "Because of the enormous improvement in sequencing output, which produces more than 100 million sequences per individual analyzed, we were able to identify mutations in the SCYL1 gene of three patients for the very first time. The three subjects, two siblings and a girl from a different family, are suffering from symptoms similar to those of the mdf mice. Apart from the neurological manifestations, such as tremor, muscle weakness and ataxia due to cerebellar atrophy, the subjects also repeatedly suffered life-threatening crises with acute liver failure in their early years," says Bittner, describing the human SCYL1 disorder.

Genetic diagnosis helps

"Our discovery will help those affected, their families and their treating physicians to understand the molecular genetic cause of this condition. In this case, we only managed to do this because we comprehensively analyzed all the subjects' genes – even those that had previously not been thought to be linked to a genetic condition," explains lead author Wolfgang Schmidt (also from the Neuromuscular Research Department). "Even with this rare condition, it is only when patients have an accurate molecular genetic diagnosis that they can potentially participate in a specific therapeutic trial," says Schmidt.

More information: Wolfgang M. Schmidt et al. Disruptive SCYL1 Mutations Underlie a Syndrome Characterized by Recurrent Episodes of Liver Failure, Peripheral Neuropathy, Cerebellar Atrophy, and Ataxia, *The American Journal of Human Genetics* (2015). DOI: 10.1016/j.ajhg.2015.10.011

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