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Genetic cause of severe nerve damage in older adults with inability to walk deciphered

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Congenital gene mutations lead to afflicted persons of advanced age developing severe nerve damage (polyneuropathy) with paralysis, loss of sensation and pain. The illness can advance rapidly and lead up to the inability to walk with wheelchair dependency. The affected gene was now identified by an international team of researcher under the guidance of the Medical University Vienna and the University Munich.

"The gene mutation leads to an enzyme deficiency which probably triggers nerve damage. In future, the balance of the reduced enzyme activity could represent a novel therapy approach which could cause the disease to be stopped," says Michaela Auer-Grumbach of the University Clinic for Orthopaedics of the MedUni Vienna. Polyneuropathy occurs in 2-3 percent of the population and in 7 percent of those over the age of 65; currently, the cause is still unclear in up to 50 percent of the affected people and a causal therapy is not yet available for this group of patients.

The origin of this discovery was three unrelated Austrian families, where several family members between the age of 55 and 80 initially noticed a loss of sensation and discomfort in the toes, which spread to the knees within just a few months. This was often accompanied by pain as well as a relatively quickly advancing muscle weakness when lifting toes and feet. Auer-Grumbach: "After a few years, walking freely was often no longer possible." Despite extensive research, the cause could initially not be clarified.

"Due to the rapid deterioration of the symptoms, some patients were

initially treated with unsuitable medication, which showed no improvement, but often caused considerable side effects. Based on the poor response to anti-inflammatory medication, but also due to the familial accumulation of polyneuropathy, we ultimately assumed a genetic cause, even though the late start of the disease seemed rather atypical for inherited polyneuropathy. An analysis of the entire exome of the patients, i.e. the sections of the genetic makeup which encrypt proteins, subsequently resulted in a serious genetic deviation in the MME gene, which is responsible for the formation of the Neprilysin enzyme," explains the researcher from MedUni Vienna, who is also the lead author and manager of the study.

Together with Jan Senderek of the Friedrich-Baur-Institute of the Neurological Clinic and Polyclinic of the University Munich, who is also aware of similar patients in Germany, the MME gene was tested in other patients. Following the incorporation of further European and American work groups, mutations could be identified in 28 patients from 19 families. A further confirmation of these research results were subsequently provided by the results of the measurements of the enzyme Neprilysin in the blood and fatty tissue, which was significantly lower than in control persons. An additional study from Japan, which also describes sever polyneuropathy at a complete lack of the Neprilysin enzyme, confirms the study results of the work groups from Vienna and Munich, which has now been published in the current edition of the magazine *American Journal of Human Genetics*.

Lack of enzyme leads to the development of severe Polyneuropathy

"The discovery of the cause of this disease allows the specific genetic diagnostic and consultancy of afflicted patients and their families and shall avoid ineffective therapies, which are stressful due to undesirable

side effects in the future," summarises Michaela Auer-Grumbach. "If further studies confirm that the deficiency of Neprilysin leads to the formation of polyneuropathy, there is justified hope that an effective therapy can be developed in the near future, either by enzyme replacement or with active ingredients, which are already known for raising the Neprilysin level.

The authors of the study (which was made possible due to a FWF project) are now planning further epidemiological examinations of patients with unclear polyneuropathy to discover whether mutations in the MME gene are also of significance in the sporadic (not family-cumulative) appearance of polyneuropathy. "Polyneuropathy from the age of 50 is frequent, but the cause can currently only be clarified and a therapy initiated in approx. 50 %. We hope that an MME/Neprilysin quick-test can lead to a quick diagnosis in the future and that this also accelerates the development of a therapy," so Michaela Auer-Grumbach.

More information: "Rare variants in MME, encoding metalloprotease neprilysin, are linked to late-onset autosomal dominant axonal polyneuropathies." *American Journal of Human Genetics*. dx.doi.org/10.1016/j.ajhg.2016.07.008.

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