Researchers discover a novel gene involved in primary lymphedema

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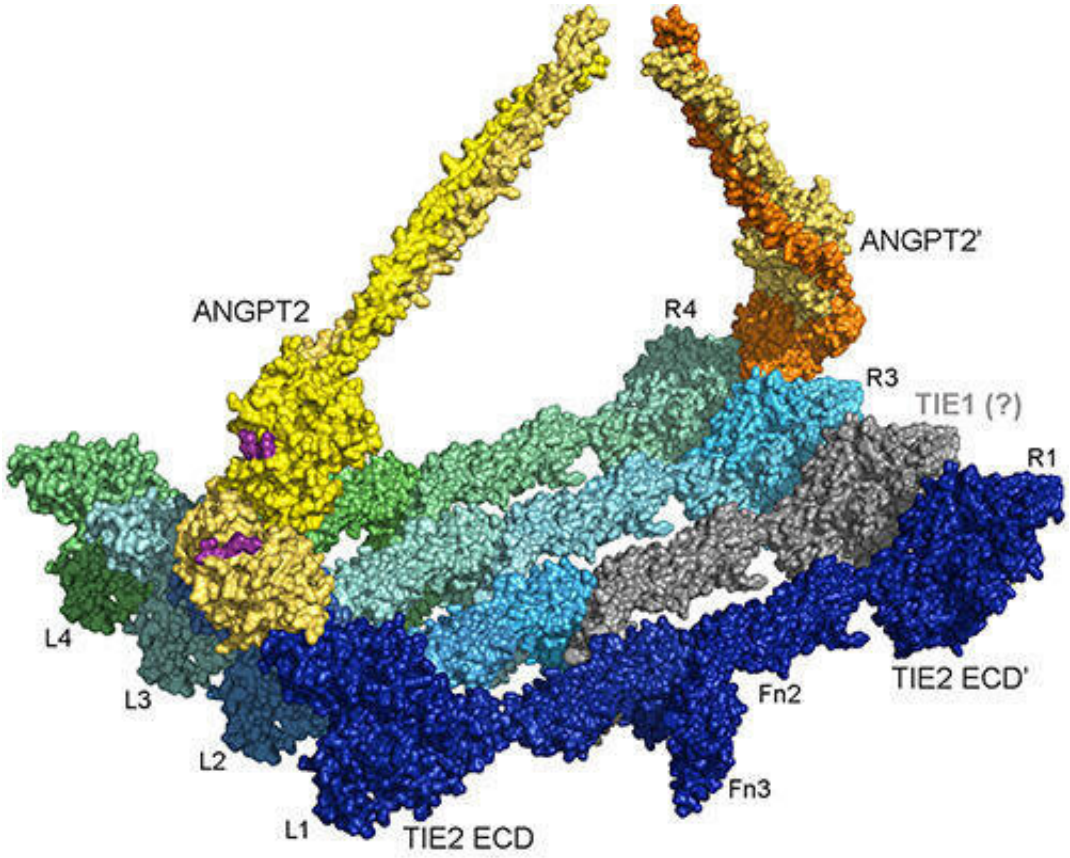

A new model of ANGPT2-mediated TIE2 and TIE1 clustering and activation at atomic resolution. Credit: VM Leppanen et al., *Sci. Transl. Med.* 12, eaax8013 (2020)

The Human Molecular Genetics laboratory of the de Duve Institute

(UCLouvain), headed by Professor Miikka Vikkula, recently identified mutations in a novel gene, ANGPT2, responsible for primary lymphedema. Together with the Wihuri Research Institute and its director, Professor Kari Alitalo at the University of Helsinki, the laboratories could show how these mutations cause the disease.

"The mutations result in loss of the normal function of the ANGPT2 protein that is known to play a role in lymphatic and blood vessel maturation. This important discovery opens possibilities for the development of improved treatments of lymphedema," explains Professor Alitalo.

The discovery is recently published in *Science Translational Medicine*.

Influence of the ANGPT2 gene mutations causing lymphedema shown in humans for the first time

Lymphedema is a strongly invalidating chronic disease resulting from abnormal development or function of the lymphatic system. In the patients, lymph is poorly drained from tissues, and thus accumulates in the extremities, causing swelling and fibrosis, limiting the mobility of the affected body part and increasing the likelihood of infections. Lymphedema can be either primary, which has no known underlying cause, or secondary, when it results from removed or damaged lymph vessels, e.g., after surgery, infection or cancer treatment. Primary lymphedema is often inherited.

The team of the de Duve Institute with its large international network of collaborators, including the Center for Vascular Anomalies and the Center for Medical Genetics of the Saint-Luc hospital in Brussels, has collected samples from almost 900 patients suffering from primary lymphedema, also collecting samples from their family members. By

using whole-exome sequencing (i.e., the sequencing of all the coding parts of the genes in the genome), mutations in ANGPT2 were discovered in lymphedema patients from five families.

The ANGPT2 encodes the angiopoietin 2 protein, a growth factor that binds to receptors in blood and lymphatic vessels that were first identified in Professor Alitalo's laboratory.

"ANGPT2 has previously been shown to influence lymphatic development in mice, but this is the first time when mutations in this gene were found to cause lymphedema in humans," says Professor Alitalo.

New information on mechanisms that lead to lymphedema

Among the identified mutations, one deletes one copy of the entire gene, whereas the four others are amino acid substitutions. The researchers showed that three of the mutants are not properly secreted from cells that normally produce the protein, and this also decreases the secretion of the protein produced from the remaining normal allele. Thus, the mutations had a so called dominant-negative effect. The fourth mutant was hyperactive in inducing increased proliferation of dilated lymphatic vessels. This mutant demonstrated altered integrin binding.

The mutations that resulted in primary lymphedema in patients provided important insights into the function of the ANGPT2 protein and mechanisms that lead to lymphedema.

Identifying the genetic causes crucial for a better management of the disease

In Europe, over 1 million people are affected by lymphedema. Therapy is limited to repeated manual lymphatic massage and use of compressive garments intended to decrease tissue swelling. In some cases, surgery may be helpful. Another lymphatic vessel growth factor, VEGF-C, is currently undergoing clinical trial in combination with surgery for the treatment of lymphedema in patients whose lymph nodes in the armpit have been removed due to breast cancer metastasis. So far, no cure exists for lymphedema and it resolves or ameliorates with time only in a minority of cases.

"Identifying the genetic causes is crucial for a better management of the disease. It makes a more precise and reliable diagnosis possible, where today, many people with the disease are still not diagnosed. As the newly published study shows, research on lymphedema leads to insight in the underlying cellular mechanisms, which may be targets for the development of new therapies," Professor Alitalo says.

More information: Veli-Matti Leppänen et al. Characterization of ANGPT2 mutations associated with primary lymphedema, *Science Translational Medicine* (2020). DOI: 10.1126/scitranslmed.aax8013

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