# Discovery of new genetic mutation in aortic disease allows better diagnosis

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Thoracic aortic aneurysm and dissection (TAAD), an enlargement or tearing of the walls of the aorta in the chest, is, together with abdominal aortic aneurysms, responsible for about 2% of all deaths in Western countries. The aorta is the largest artery in the body, and carries blood from the heart. About one out of every five patients with TAAD has a family member with the same disorder, therefore indicating a genetic cause. However, the relevant genetic mutations discovered so far only explain about 30% of all cases. Through the study of a large family with TAAD features, an international team of genetic researchers have now discovered that a mutation in the TGFB3 gene is also responsible for the condition.

Elisabeth Gillis, MSc, a PhD student in the Centre for Medical Genetics at Antwerp University Hospital, Antwerp, Belgium, will tell the annual conference of the European Society of Human Genetics today (Saturday) that she and colleagues from seven other countries are the first to link this particular genetic mutation to serious aortic disorders. This is important, she says, because it means that the TGFB3 gene can be included in diagnostic screening. "Armed with this knowledge, we can screen patients with symptoms of TAAD, and also family members without symptoms. Early identification of a risk of aortic aneurysm formation will allow us to implement preventive treatment with medication aimed at slowing down the process of aneurysm and, ultimately, replacement of the aorta before a significant risk of dissection arises", she will say.

An aortic aneurysm occurs where there is a weakness in the walls of the aorta, creating an outward bulge. Weakness in the aorta is dangerous, because it can lead to rupture (dissection) which is life-threatening.

The researchers studied 9 patients from a large Flemish-Dutch family with the cardiovascular, skeletal and facial features typical of a form of TAAD, called Loeys-Dietz syndrome. They screened DNA from each family member without finding any genetic mutations known at that stage to be connected with TAAD. However, further investigation revealed two candidate genomic regions that appeared to be involved, one of which contained the TGBF3 gene. "This gene was an obvious candidate because it has previously been shown that the TGFbeta-signalling pathway has a key role in the formation of aortic aneurysm," says Ms Gillis.

After sequencing the gene, the researchers identified a mutation that was present in all affected family members. Finally, 470 TAAD patients were screened for TGFB3 mutations, and causal mutations were found in ten other families.

"This is an important finding because incidence of TAADs may be much higher than currently reported," says Ms Gillis. "Acute aortic dissections may be disguised as heart attacks, and we know that the genetic component of TAAD is strong - in about 20% of patients, it is also found in family members. Therefore anything we can do to enable early identification of people at risk will help. However, aortic aneurysm formation is not yet fully understood, so reversing the risk of dissections remains a challenge, even though effective treatments are available."

The choice of treatments for TAAD depends on a number of factors, such as size/location of the aneurysm and rate of growth. Current therapies include surgery, for example replacing the weakened part of the aorta, and medical treatments such as beta-blockers or angiotensin

receptor blockers.

"Research on the TGFbeta-pathway in TAAD is far from finished. In addition to investigating further the role of these mutations in the condition, the discovery of new TGBF3 patients will help us improve follow-up guidelines for them. We hope that the identification of these new genetic factors will speed progress towards truly personalised medicine. The more we can link mutated genes to specific patients, the more we can identify the right symptoms and link specific therapies to them," Ms Gillis will conclude.

Provided by European Society of Human Genetics