Medical Xpress

More people in the UK at risk of hereditary heart disease than previously thought

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More people in the UK are at risk of a hereditary form of cardiac amyloidosis, a potentially fatal heart condition, than previously thought, according to a new study led by researchers at UCL (University College London) and Queen Mary University of London.

The study, published in *JAMA Cardiology*, used data from the UK Biobank to analyze the genes of 469,789 people in the UK and found that one in 1,000 possessed genetic variants with a likely link to cardiac transthyretin (ATTR) amyloidosis.

Among study participants with African ancestry, incidence was much higher, with one in 23 (4.3%) having genes thought to be linked to the disease.

Cardiac amyloidosis is where abnormal proteins, called amyloid, build up in the heart tissue, making the heart stiff and less able to pump blood. If left untreated, it is likely to be fatal within four to six years.

Senior author Dr. Luis Lopes, from the UCL Institute of Cardiovascular Science, said, "We found a higher than expected number of people in the UK with potentially harmful genetic variants linked to cardiac ATTR amyloidosis, an often fatal condition.

"Many people with these variants will not go on to develop disease. However, it is important to try to identify those who do as early as we can, as there are promising new medicines that can effectively treat the condition, and acting earlier with these medicines is likely to help patients more."

The first author, Dr. Nay Aung, from the William Harvey Research Institute, Queen Mary University of London, said, "Our study showed that people carrying these potentially harmful variants have a two-to-three-fold increase in the risk of heart failure and cardiac rhythm issues. This again highlights the need for early detection and monitoring for disease progression."

Previously, ATTR amyloidosis was considered rare, affecting between one in 120,000 and one in 830,000 people globally. In recent years in the

UK, however, the number of people being diagnosed has increased, partly due to improvements in imaging pioneered at the UCL Center for Amyloidosis.

ATTR amyloidosis can be hereditary, caused by a mutation in the transthyretin (TTR) gene, but it can also occur as people age without a genetic basis.

The hereditary form is known to be much more common in certain geographic clusters of populations in Portugal, Japan and Sweden, and among individuals with Black African ancestry.

The new study, in contrast to previous research looking at the prevalence of one genetic variant linked to ATTR amyloidosis (Val142Ile), estimated the prevalence of 62 variants identified as having a possible link to the disease.

Looking at an average of 12 years of data from the UK Biobank participants, the research team found that people with these variants had a higher risk of heart failure, thickening of the heart muscle, and heart rhythm problems, which held true after adjusting for factors such as age, sex, BMI and cardiovascular risk factors.

Hospital data suggested a relatively low proportion, 2.8%, of this group had been diagnosed with cardiac amyloidosis. The UK Biobank participants were aged 57 on average and the researchers said the disease may develop later in life or still be in its earliest stages during the time of the study.

The proportion doubled when researchers looked for extra-cardiac symptoms associated with the hereditary form of ATTR amyloidosis, suggesting under-recognition of the disease in its early stages.

These symptoms included carpal tunnel syndrome (pressure on a nerve in your wrist causing tingling, numbness and pain in your hand and fingers) and lumbar stenosis (the narrowing of the area of the spine that contains the nerves or spinal cord, leading to aching, cramping and tingling in the legs brought on by walking or standing).

The researchers called for greater clinical vigilance for possible hereditary ATTR amyloidosis among people with these symptoms or with unexplained thickened heart muscle.

A next step, the researchers said, would be to prospectively investigate the proportion of people with these variants who developed disease. This could help to inform possible screening strategies. Genetic tests are currently offered to people with symptoms or people whose family members have the disease.

Among the promising new treatments for ATTR amyloidosis is a gene-editing therapy developed at the UCL Center for Amyloidosis. Early trial results of the therapy, a single intravenous infusion of NTLA-2001, indicate it may stop disease progression.

The therapy is one of several new treatments that aim to tackle the amyloid build-up in the heart. Previously, treatments for the condition sought to relieve the symptoms of heart failure (which may include fatigue, swelling in the legs or abdomen, and shortness of breath with activity), but did not address the underlying cause.

More information: Nay Aung et al, Prevalence, Cardiac Phenotype, and Outcomes of Transthyretin Variants in the UK Biobank Population, *JAMA Cardiology* (2024). DOI: 10.1001/jamacardio.2024.2190