Study finds link between inherited DNA sequences and heart disease

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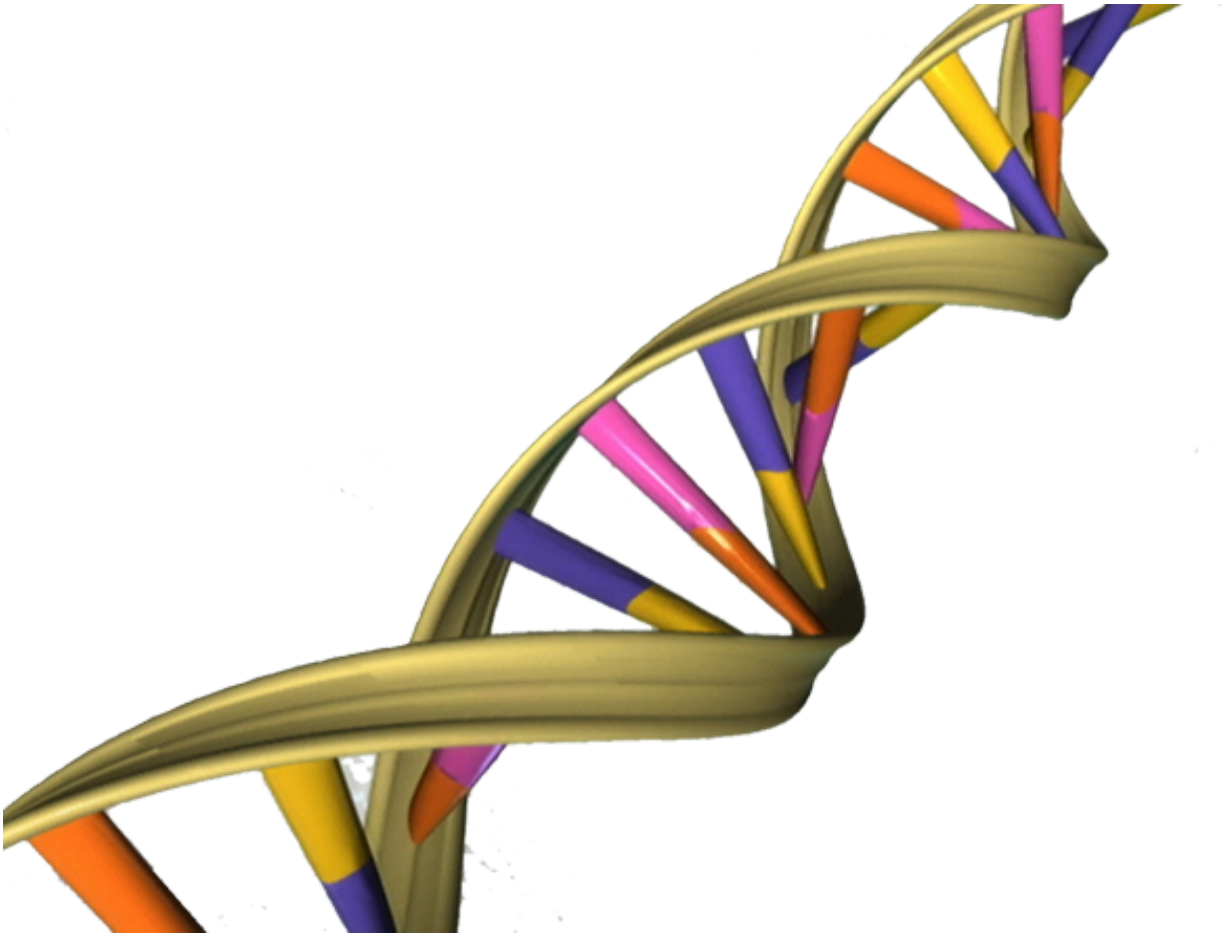

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

A study to examine recessively inherited genome-wide DNA sequences has for the first time discovered a potential link with Britain's biggest killer - Coronary Artery Disease (CAD).

The research led by a team from the University of Leicester was the first time that recessively inherited DNA sequences in the whole genome called Runs of homozygosity (ROHs) were examined for a connection to the disease.

The study appears in the *American Journal of Human Genetics*.

CAD is a terminal clinical manifestation of cardiovascular disease and is the leading cause of death worldwide and is the UK's single biggest killer. Nearly one in six men and one in ten women die from CAD. CAD is a complex, multifactorial disorder originating from a complicated interplay of multiple genetic and environmental factors.

Paraskevi Christofidou, from the Department of Cardiovascular Sciences, at the University of Leicester, said: "ROHs are regions of the genome with identical copies inherited from parents and traced back to a common ancestor.

"There is no study that has examined whether genome-wide homozygosity levels are a risk factor for CAD and whether ROHs might play a role in regulation of gene expression within cells of key importance to atherosclerosis."

"Contributions of ROHs to the genetic architecture of CAD are not known. The primary goal of this project was a comprehensive analysis of association between genome-wide homozygosity measures and CAD in individuals of white European ancestry. A secondary aim was to explore the association of ROHs and gene expression in human monocytes and macrophages."

Paraskevi Christofidou added that the team analysed 24,320 individuals from 11 populations of white European ethnicity. This revealed statistically significant differences in homozygosity levels between individuals with CAD and control subjects.

She said: "On average, individuals with CAD had 0.63 ROHs more than control subjects. The average total length of ROHs was approximately 1046.92 kb greater in individuals with CAD than control subjects.

"We were able to qualify a measure of genome-wide homozygosity levels in relation to CAD - an estimated 13% increase in CAD per 1 standard deviation increase in the proportion of the autosomal genome covered by ROHs.

"Individual ROHs showed significant associations with monocyte and macrophage expression of genes located nearby.

"Our findings are important because they provide evidence for an excess of ROHs as a potential contributor to CAD and therefore support a theory on the role of recessive component in the genetic architecture of CAD.

"Additional work is needed to unravel the exact synergistic role of multiple recessive variants, homozygosity levels and their association to CAD."

This project was part of Dr Christofidou's PhD under Dr Maciej Tomaszewski's and Professor Nilesh Samani's supervision.

Dr Tomaszewski, who is Clinical Senior Lecturer in Cardiovascular Medicine at the University & Honorary Consultant Physician at Leicester's Hospitals , said: "We would like to thank the participants and our collaborators within CARDIoGRAM and Cardiogenics consortia

who have been extremely supportive of this project."

This study was supported by the Alumni Association of University of Leicester PhD studentship and International Mentoring Travel Award by American Heart Association to Paraskevi Christofidou.

Chris Shaw from the University's Development and Alumni Relations Office, said: "Dr Christofidou was the University of Leicester's first ever recipient of an Alumni-funded Postgraduate Research Scholarship. The outcomes from this major study clearly demonstrate how philanthropy supports individual academics and also makes a major contribution towards tackling chronic disease."

Professor Jeremy Pearson, Associate Medical Director at the British Heart Foundation, which helped fund the research, said: "This Leicester team, led by BHF Professor Samani, are at the cutting-edge of genetic research to understand the key genes that increase a person's risk of premature coronary heart disease, which can lead to a sudden heart attack. With BHF funding, they have previously found over 40 such genes.

"For the first time they have now shown that having more stretches of DNA containing the same version of a gene, one inherited from each parent, is associated with increased heart disease risk.

"By targeting this aspect of our genetic instruction manual, the team has also found several new genes that could help increase a person's risk of developing coronary heart disease and having a heart attack.

"Research to improve our understanding of how our genes can increase our risk of a heart attack is helping us find new ways to target the effects of those genes, which could lead to new drugs to prevent these deadly events."