Major global study reveals new hypertension and blood pressure genes

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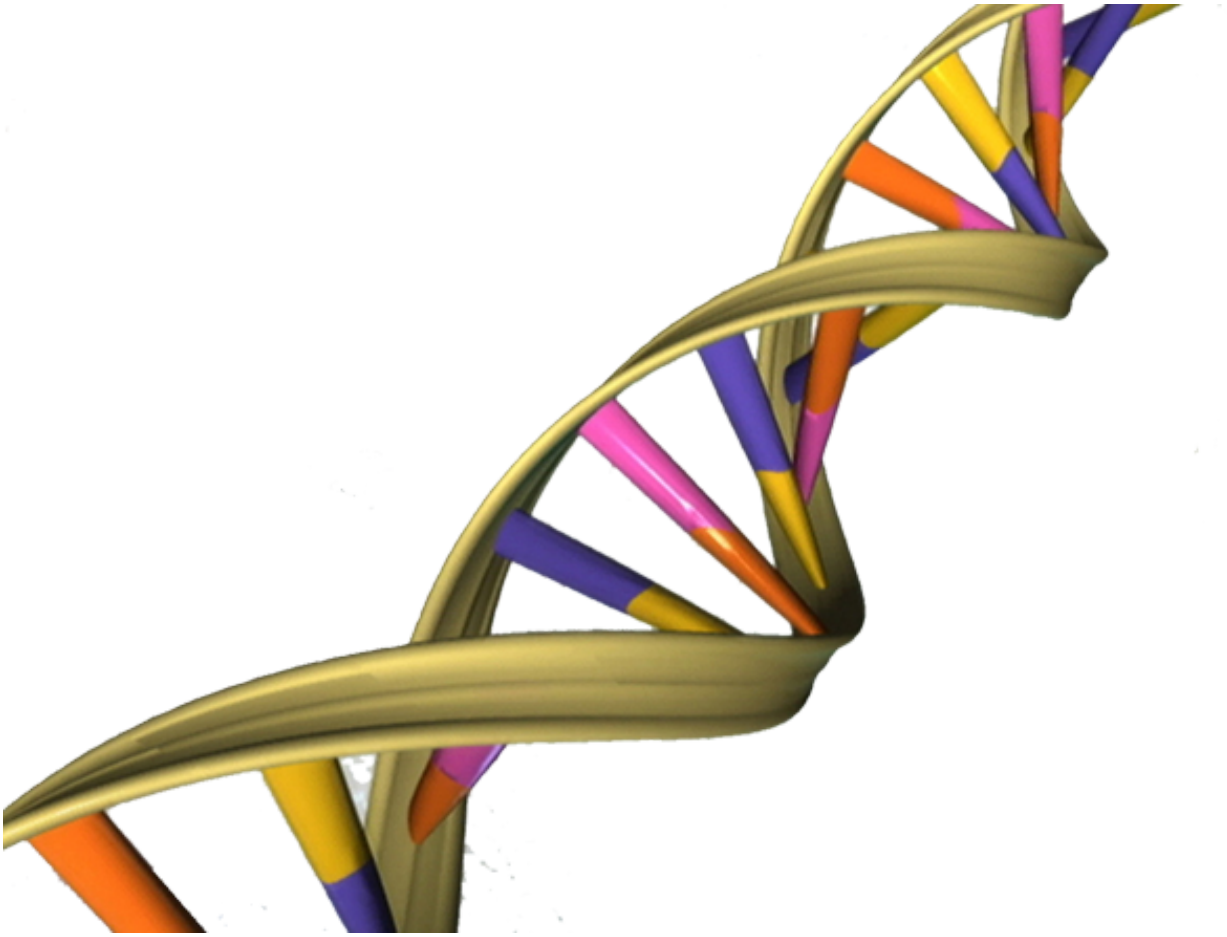

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Thirty-one new gene regions linked with blood pressure have been identified in one of the largest genetic studies of blood pressure to date, involving over 347,000 people, and jointly led by Queen Mary University of London (QMUL) and the University of Cambridge.

The discoveries include DNA changes in three genes that have much larger effects on blood pressure in the population than previously seen, providing new insights into the physiology of hypertension and suggesting new targets for treatment.

High blood pressure or hypertension is a major risk factor for cardiovascular disease and premature death. It is estimated to be responsible for a larger proportion of global disease burden and premature mortality than any other disease risk factor. However, there is limited knowledge on the genetics of blood pressure.

The teams investigated the genotypes of around 347,000 people and their health records to find links between their genetic make-up and cardiovascular health. The participants included healthy individuals and those with diabetes, coronary artery disease and hypertension, from across Europe, (including the UK, Denmark, Sweden, Norway, Finland and Estonia), the USA, Pakistan and Bangladesh. The study brought together around 200 investigators from across 15 countries.

Study author Professor Patricia Munroe from QMUL said: "We already know from earlier studies that high blood pressure is a major risk factor for cardiovascular disease. Finding more genetic regions associated with the condition allows us to map and understand new biological pathways through which the disease develops, and also highlight potential new therapeutic targets. This could even reveal drugs that are already out there but may now potentially be used to treat hypertension."

Most genetic blood pressure discoveries until now have been of common

genetic variants that have small effects on blood pressure. The study, published in *Nature Genetics*, has found variants in three genes that appear to be rare in the population, but have up to twice the effect on blood pressure.

Study author, Dr Joanna Howson from the University of Cambridge said: "The sheer scale of our study has enabled us to identify genetic variants carried by less than one in a hundred people that affect blood pressure regulation. While we have known for a long time that blood pressure is a risk factor for coronary heart disease and stroke, our study has shown that there are common genetic risk factors underlying these conditions."

RBM47 is a gene that encodes for a protein responsible for modifying RNA. RRAS is involved in cell cycle processes and has already been implicated in a syndrome related to 'Noonan syndrome' which is characterised by heart abnormalities. COL21A1 is involved in collagen formation in many tissues, including the heart and aorta. COL21A1 and RRAS warrant particular interest since both are involved in blood vessel remodelling, with relevance to hypertension.

The team also found a mutation in a key molecule ENPEP that affects blood pressure. This gene codes for an enzyme that is a key molecule involved in regulating blood pressure through the dilation and constriction of blood vessels, and is currently a therapeutic target.

Professor Jeremy Pearson, Associate Medical Director at the British Heart Foundation which part-funded the research, said: "Large scale genetic studies continue to expand the number of genes that may contribute to the development of heart disease, or risk factors such as high blood pressure. But so far most of the genes discovered in these studies individually have only very small effects on risk - though they may still provide valuable clues for new drug targets.

"This study has increased the number of genes implicated in control of blood pressure to almost 100 and, in the process, has also identified three genes that have larger effects on blood pressure than previously found."

The study was also funded by the National Institute for Health Research (NIHR), National Institute of Health (NIH), Wellcome Trust and the Medical Research Council.

A complementary study in *Nature Genetics*, co-led by Patricia Munroe (QMUL) and Christopher Newton-Cheh (Harvard Medical School), finds 17 new gene regions involved in blood pressure regulation that play a role in tissues beyond the kidneys.

More information: 'Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension'. Surendran et al. *Nature Genetics* 2016. DOI: 10.1038/ng.3654

'The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals'. Ehret et al. *Nature Genetics* 2016. DOI: 10.1038/ng.3667

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