Systems-wide genetic study of blood pressure regulation in the Framingham Heart Study

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A genetic investigation of individuals in the Framingham Heart Study may prove useful to identify novel targets for the prevention or treatment of high blood pressure. The study, which takes a close look at networks of blood pressure-related genes, is published in the journal *Molecular Systems Biology*.

More than one billion people worldwide suffer from high blood pressure and this contributes significantly to deaths from cardiovascular disease. It is hoped that advances in understanding the genetic basis of how blood pressure is regulated will improve the prediction of susceptibility to cardiovascular disease and also provide insight into how individually tailored treatments for high blood pressure can reduce the risk of disease.

"For more than 50 years the Framingham Heart Study has been an invaluable source of research findings on the contributions of high blood pressure, high cholesterol, smoking and other factors to the development of cardiovascular disease," says Daniel Levy, director of the Framingham Heart Study. "More recently we have launched a major initiative to identify and study the genes underlying cardiovascular and other chronic diseases in individuals taking part in the Framingham Heart Study since we believe that this research could lead to new treatments and better strategies for disease prevention."

Dissecting genetic data to identify molecular alterations that lead to or cause disease is very challenging. In the present work, the authors

developed a strategy that combines multiple types of large-scale genetic and molecular data. Specifically, the scientists first looked at a vast collection of gene expression data from 3679 individuals who were not receiving any drug treatment for high blood pressure. As a starting point, they combined information on likely genetic differences contributing to elevated blood pressure by incorporating genome-wide association studies with the gene expression data for all of the individuals they studied. As a next step, the researchers worked from the hypothesis that it would be the surrounding network of certain disease-causing genes that would have the most impact on blood pressure and disease susceptibility.

Scientists have known for some time that looking at each gene in isolation is not a powerful enough way to determine how different genes underlie blood pressure and other complex traits. By looking at multiple genes and how they interact, the researchers were able to find four groups of genes linked to blood pressure that warranted further study to reveal key driver genes controlling blood pressure regulation.

"Our work was able to pinpoint several gene networks closely linked to the regulation of blood pressure," says Tianxiao Huan, one of the lead authors of the study. "As a proof-of-concept, we validated one of these key driver genes, Sh2b3, and demonstrated its relationship to hypertension in mice."

The researchers revealed that mice lacking the Sh2b3 gene had normal blood pressure but showed an exaggerated blood pressure response to treatment with angiotensin-II, a naturally occurring hormone that causes blood vessels to contract. Adding further confidence that Sh2b3 can play a causal role in the dysregulation of blood pressure in humans, the scientists found that the genes predicted to be affected by Sh2b3 greatly overlapped with the set of genes whose expression is indeed affected in the mice that lack the Sh2b3 gene.

"Moving forward, it should be possible to study additional key driver genes in this way, which should help in our efforts to identify novel targets for the prevention and treatment of hypertension," says Huan.

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