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Genetic variation linked to heart disease risk through RNA machinery

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Researchers have pinpointed a new mechanism of how natural variation in our DNA alters an individual's risk for developing heart disease by interfering with the ability of a developmental gene to interact with a specialized type of RNA. This work expands on previous work identifying the "hidden" causes of complex disease risk, with the goal of unlocking new pathways and potential drug targets for cardiovascular disease.

This latest study led by Thomas Quertermous, MD at Stanford University and Georg Sczakiel, PhD at the University of Lübeck (Germany) was a joint effort between human geneticists and molecular biologists. Postdoctoral scholar, Clint Miller, PhD was the lead author of the study published online in *PLOS Genetics* on Mar 27.

Humans share approximately 99.9% of their DNA. The remaining differences in our DNA sequences arise though natural mutations during evolution. The most common form of variation is known as a single nucleotide polymorphism (SNP). After the completion of the Human Genome Project, SNPs became powerful tools to define the genetic basis of complex traits. Ultimately, large-scale scanning or genome-wide association studies (GWAS) revealed ~50 regions linked to coronary heart disease. But it has been challenging to understand exactly why individuals harboring distinct DNA sequences are more likely than others to develop heart disease.

Previous studies have focused on how genetic variations alter

interactions with DNA binding proteins, or transcription factors. Here, the researchers explored how a particular disease variant in the developmental gene TCF21 confers risk by altering RNA binding and stability. This variant disrupted the normal interaction with a small non-coding RNA (microRNA), and this disruption changed the levels of TCF21 in human vascular cells and diseased arteries. This represents the first report of a heart disease variant disrupting microRNA interactions.

"Atherosclerosis is a cumulative process that develops over a lifetime. While one's environment can be modified to reduce risk, this work highlights the role of genetics and epigenetics. Our genes are exquisitely controlled such that subtle changes in key switches can cause our system to go haywire," said Dr. Miller. "This work increases our understanding of heritable disease risk, as we move towards prevention of cardiovascular disease."

More information: Miller CL, Haas U, Diaz R, Leeper NJ, Kundu RK, et al. (2014) Coronary Heart Disease-Associated Variation in TCF21 Disrupts a miR-224 Binding Site and miRNA-Mediated Regulation. *PLoS Genet* 10(3): e1004263. DOI: 10.1371/journal.pgen.1004263