

Diabetes and heart disease linked by genes, study reveals

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Type 2 diabetes (T2D) has become a global epidemic affecting more than 380 million people worldwide; yet there are knowledge gaps in understanding the etiology of type-2 diabetes. T2D is also a significant risk factor for coronary heart disease (CHD), but the biological pathways that explain the connection have remained somewhat murky. Now, in a large analysis of genetic data, published on August 28, 2017 in *Nature Genetics*, a team, led by researchers in the Perelman School of Medicine

at the University of Pennsylvania, has first looked into what causes T2D and second clarified how T2D and CHD - the two diseases that are the leading cause of global morbidity and mortality, are linked.

Examining genome sequence information for more than 250,000 people, the researchers first uncovered 16 new diabetes genetic risk factors, and one new CHD genetic risk factor; hence providing novel insights about the mechanisms of the two diseases. They then showed that most of the sites on the genome known to be associated with higher diabetes risk are also associated with higher CHD risk. For eight of these sites, the researchers were able to identify a specific [gene variant](#) that influences risk for both diseases. The shared [genetic risk factors](#) affect biological pathways including immunity, cell proliferation, and heart development.

The findings add to the basic scientific understanding of both these major diseases and point to potential targets for future drugs.

"Identifying these gene variants linked to both type 2 diabetes and CHD risk in principle opens up opportunities to lower the risk of both outcomes with a single drug," said study co-senior author Danish Saleheen, PhD, an assistant professor of Biostatistics and Epidemiology. "From a drug development perspective, it would make sense to focus on those pathways that are most strongly linked to both diseases," Saleheen said.

The researchers started by examining sets of genome data on more than 250,000 people, of South Asian, East Asian or European descent. In this large, multi-ethnic sample they were able to confirm most of the known diabetes "risk loci"— sites on the genome where small DNA variations have been linked to altered, usually higher, diabetes risk—and uncover 16 new ones.

With their analyses of the genome data, the scientists were also able to

identify eight specific gene variants that are strongly linked to altered risk for both diseases. Seven of these gene variants, as expected, appeared to increase risk for both diseases.

The eighth, a variant of the gene for the cholesterol-transport protein ApoE, turned out to be associated with higher diabetes risk but lower CHD risk—a finding that is somewhat puzzling, Saleheen said, though he noted that it is consistent with data from statin trials showing that pharmacologically lowering LDL cholesterol can modestly increase diabetes risk.

The researchers found evidence that, on the whole, the genetic link between the diseases appears to work in one direction, so that risk [genes](#) for type 2 diabetes are much more likely to be associated with higher CHD risk than the other way around. Additionally, there could be some pathways where pharmacological lowering of one disease increases the risk of the other.

"Using evidence from human genetics, it should be possible to design drugs for type-2 diabetes that have either beneficial or neutral effects on CHD risk; however it is important to identify and further de-prioritize pathways that decrease the risk of type-2 diabetes but increase the risk of CHD"; said Saleheen.

The scientists also found that diabetes-linked gene variants tend to differ in their apparent effects on CHD risk, depending on their mechanisms. Variants that increase the chance of obesity or high blood pressure, for example, appear to boost CHD risk more strongly than variants that alter insulin or glucose levels.

The scientists discovered that the genomic regions implicated as dual diabetes-CHD risk loci encompass targets of some existing drugs. One such drug is icosapent, an omega-3 fatty acid component of some fish

oils, which lowers cholesterol and is sold in concentrated form as a prescription pharmaceutical.

The dual-effect risk loci also include the region covering the gene FABP4, which is already being investigated for its potential as a diabetes and heart-disease drug target. In mouse studies, inhibition of this gene's protein has been shown to have anti-atherosclerotic, i.e., helps fight thickening and hardening with fat on the inside of arteries and anti-diabetic effects.

Saleheen, co-senior author Benjamin F. Voight, PhD, an associate professor of Genetics, and their colleagues now plan further investigations of the dual-risk genes uncovered in the study.

"I'm hopeful that with the advanced genomic engineering techniques now available, we'll be able to quickly convert our human genetics observations into concrete details regarding the molecular mechanisms involved in both heart disease and [diabetes](#)," said Voight.

The researchers also hope to learn more about the biology of the newly discovered dual-risk genes by studying people who have mutations in those genes, Saleheen said.

More information: Identification of new susceptibility loci for type 2 diabetes and shared etiological pathways with coronary heart disease, *Nature Genetics* (2017). [DOI: 10.1038/ng.3943](https://doi.org/10.1038/ng.3943)

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