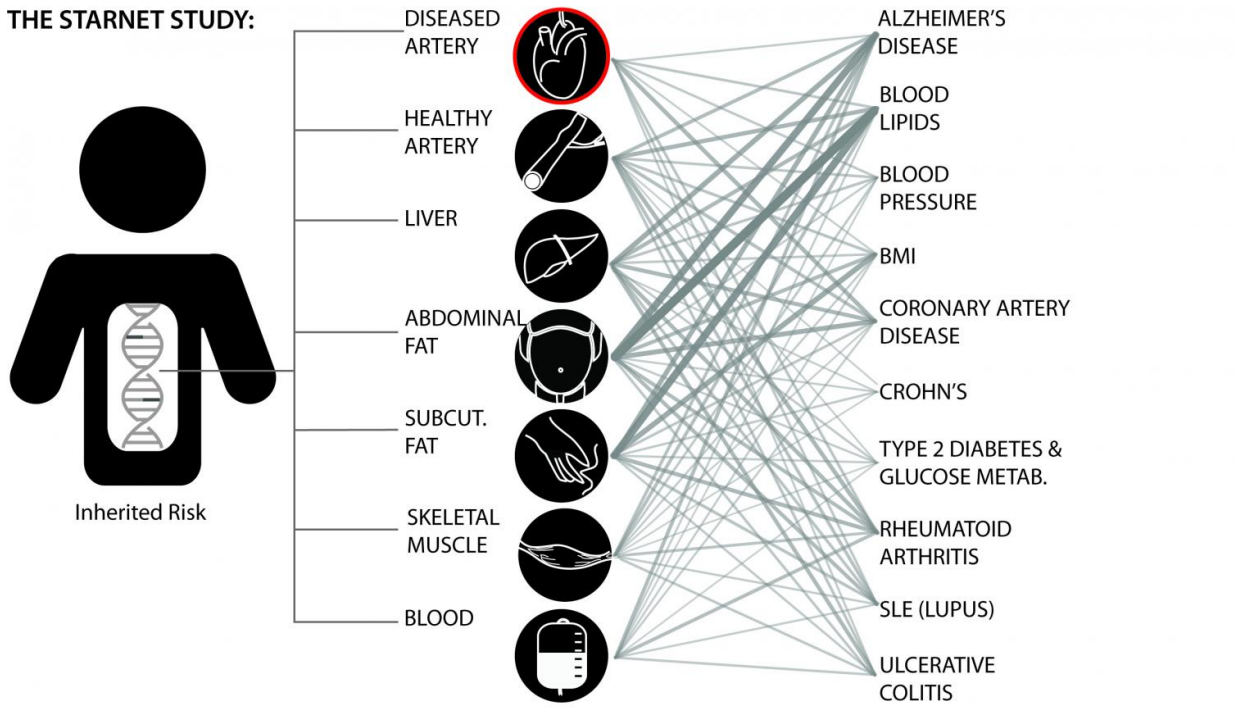
Team identifies genes responsible for CMD risk

August 18 2016



In seven key tissues from patients with coronary artery disease, the Stockholm-Tartu Atherosclerosis Reverse Network Engineering Task (STARNET) study examined genotypes together with global gene expression to successfully identify thousands of genes associated with a multitude of diseases. Many of the genes were shared across the various types of tissues and diseases, as indicated by the abundance of crossover lines above, suggesting genetic links among different types and locations of disease. Credit: Ariella Cohain

In a study being published in the August 19 issue of *Science*, researchers from the Icahn School of Medicine at Mount Sinai, in collaboration with scientists from Tartu University Hospital in Estonia, the Karolinska Institutet and Science for Life Laboratory (SciLifeLab) in Sweden, and AstraZeneca, have identified a profound new level of complexity and interaction among genes within specific tissues responsible for mediating the inherited risk for cardiometabolic diseases, including processes that lead to heart attack and stroke.

"By analyzing gene-expression data from multiple tissues in hundreds of patients with coronary artery disease, we were able to identify disease-causing genes that either were specific to single tissues or acted across multiple tissues in networks to cause cardiometabolic diseases," said Johan Björkegren, MD, PhD, senior author of the study, Professor of Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai, visiting professor at the University of Tartu and senior investigator at the Karolinska Institutet.

The ground-breaking research was done as part of the STARNET study, the first systematic analysis of RNA sequence data from blood, vascular, and metabolic tissues from patients with coronary artery disease (CAD). RNA sequences are copies of the DNA in each cell that serve as templates for protein synthesis and determine whether a tissue remains healthy or becomes diseased.

"Genome-wide association studies (GWAS) have identified thousands of DNA variants increasing risk for common diseases like CAD," said Dr. Björkegren. "However, while GWAS was an important first line of investigations of the genetics of CAD, in order to translate these risk markers into opportunities for new diagnostics and therapies, we must now move into a new phase of discovery and identify the genes perturbed by these DNA variants responsible for driving disease development. Furthermore, we also need to understand in which tissues,

pathways, and molecular networks these disease genes are active. Unraveling disease-driving genes with their tissue-belonging, as we have started to achieve using STARNET, will also be a prerequisite for developing precision medicine with individualized diagnostics and therapies."

STARNET was launched in 2007 by Dr. Björkegren and Arno Ruusalepp, MD, PhD, Chief Cardiac Surgeon at Tartu University Hospital and senior co-author on the study. Unlike similar studies, STARNET obtained samples of several key tissues from 600 clinically well-characterized patients with CAD during coronary artery bypass surgery. By using sophisticated data analysis techniques, the researchers found that the gene expression data from STARNET were highly informative in identifying causal disease genes and their activity in networks not only in CAD but also for other cardiometabolic diseases as well as Alzheimer's disease.

"One unexpected and thus potentially important finding of the study was that besides the liver, abdominal fat emerged as a key site for regulation of blood lipid levels," said Oscar Franzén, MSc, PhD, Postdoctoral Fellow at the Icahn School of Medicine at Mount Sinai, first author of the study, and computational biologist in Dr. Björkegren's laboratory. "For example, a gene called PCSK9, which is implicated in controlling plasma levels of low-density lipoprotein (LDL)—the so-called bad cholesterol—was found to do so by acting in abdominal fat, not in the liver where blood levels of LDL are mainly regulated." PCSK9 has lately gained substantial attention as the latest target for lipid-lowering drugs now reaching the market.

"The STARNET project is fundamentally relevant for studies of the causes of CAD and other complex diseases," said Eric Schadt, senior co-author on the paper and the Jean C. and James W. Crystal Professor of Genomics at the Icahn School of Medicine at Mount Sinai, and Founding

Director of the Icahn Institute for Genomics and Multiscale Biology. "We were not only able to assign a high number of individual genes to DNA markers previously identified by GWAS but also, and quite unexpectedly, we found that many of these downstream genes appeared in disease-causal gene regulatory networks that were shared across tissues and diseases."

In collaboration with AstraZeneca and the SciLifeLab team, Dr. Björkegren's team has also used STARNET to try to improve drug target development. "We are excited about our joint project with Dr. Björkegren's team at the Karolinska Institutet and AstraZeneca, which now with the *Science* report has delivered the first wave of ground-breaking data that we have supported for the past 3 years," said Li-Ming Gan, MD, PhD, a co-author of the study, Senior Medical Director and collaboration lead at AstraZeneca. "During the course of our project we have found that Dr. Björkegren's datasets including STARNET provide essential translation information to help us identify new drug targets, as well as informing on existing targets in cardiovascular and metabolic diseases, a main therapy area for AstraZeneca."

"The PCSK9 finding together with the unexpected cross-tissue and even cross-disease activity of many disease-causing genes shows how little we currently understand about the cause of CAD," said Dr. Ruusalepp. "As a cardiac surgeon actively treating CAD patients, I am confronted by the massive global burden of CAD and the toll it takes on our society every day. STARNET has opened the door to a new era of understanding in CAD, and brings exciting new hope for future therapies."

More information: "Cardiometabolic risk loci share downstream cis- and trans-gene regulation across tissues and diseases," *Science*, science.sciencemag.org/cgi/doi … 1126/science.aad6970

Provided by The Mount Sinai Hospital