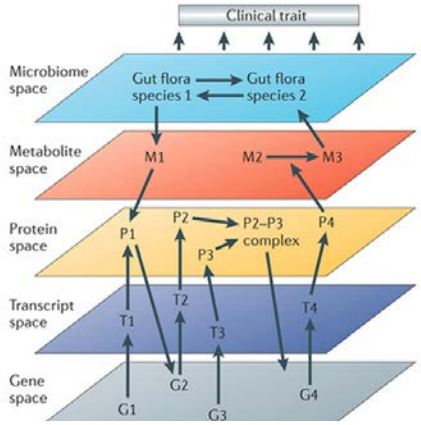

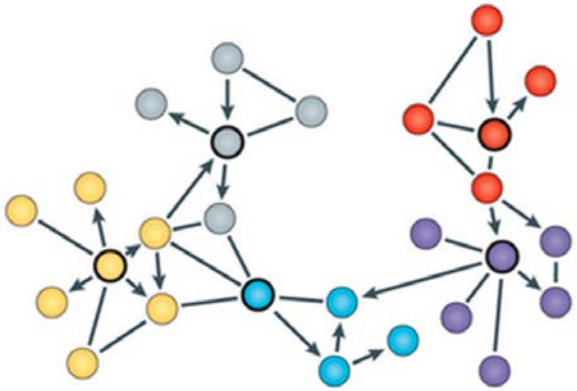

Systems Genetics Laboratory

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"Using big data analytics to understand the molecular pathways of disease. Developing personalized medicine approaches to cardiovascular and metabolic disorders."

The goal of our laboratory is to understand the genetic mechanisms that lead to increased susceptibility to cardiovascular and metabolic diseases. The interactions among hundreds of genes and gene networks along with environmental factors such as diet affect our health status. We use systems genetics to uncover this complexity. We use a range of experimental and computational methods to quantitate and integrate intermediate phenotypes, such as transcript, protein or metabolite levels, in human and mouse populations. We also test our predictions using standard biochemistry and molecular biology approaches in cell cultures and animal models. Our results provided insights into both the molecular underpinnings of complex traits and the understanding of common, complex diseases.

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Genetic Regulation of Adipose Gene Expression and Cardio-metabolic Traits

Genome-wide association studies (GWASs) have identified many loci for complex metabolic and cardiovascular traits, yet the underlying genes and mechanisms by which they affect disease remain poorly characterized. The genetic analysis of gene expression by identification of expression quantitative trait loci (eQTLs) in relevant tissues has proven useful to predict candidate genes at GWAS loci and biological pathways that are perturbed in affected individuals. Subcutaneous adipose tissue serves as a buffering system for lipid energy balance, particularly fatty acids and might play a protective role in metabolic and cardiovascular disease risk. We are studying the adipose tissue biopsies from participants of the Metabolic Syndrome in Men (METSIM) study that is being conducted in Kuopio, Finland. This population is extensively characterized for metabolic traits that are relevant to the development of Metabolic Syndrome, Type 2 Diabetes, and Coronary Artery Disease. We have measured the DNA variation, mRNA and microRNA variation and studied the genetic regulation of the transcript variation. We are working on understanding how several candidate genes identified in this study are affecting metabolic traits.

Integrative Genomics of Vascular Smooth Muscle Function

Atherosclerosis which develops in the arterial wall is the underlying process that leads to heart attacks and stroke. Nearly three quarters of the GWAS loci associated with atherosclerosis have unknown functions in the disease process. These novel genomic loci provide a solid foundation to unravel disease mechanisms at the molecular level. Translating these loci into genes and pathways will help to provide novel insight into disease susceptibility that will ultimately lead to personalized treatments for patients with differing genetic makeup and the discovery of new drivers of disease that can be therapeutically targeted. Numerous studies have shown the involvement of endothelial cells, which line the blood vessels, and smooth muscle cells (SMCs), which make up bulk of the vessel wall, in the disease process. We are studying aortic endothelial and smooth muscle cells from heart transplant donors for variation in cellular phenotypes that are relevant to the development of atherosclerosis, variation in transcript levels, and variation in their DNA sequences. We aim to identify which atherosclerosis-relevant genomic loci lead to subtle changes in the atherosclerosis-relevant cellular functions and the expression levels of a large number of genes in highly connected gene networks.

RECENT RESEARCH DEVELOPMENTS

- Recent work elucidated the effect of genetic variants on adipose tissue gene expression and identified nearly 100 genes that had not been implicated in cardio-metabolic disorders.
- Recently we identified two miRNAs that play an important role in regulating inflammatory signaling in endothelial cells

RECENT GRANTS

- NIH – Systems Genetics Analyses of Cardiometabolic Trait Loci in Humans and Mice
- Ralph E. Powe Junior Faculty Enhancement Award

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