Integration of genetic colocalizations with physiological and pharmacological perturbations identifies cardiometabolic disease genes


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Insulin resistance (IR) leads to type 2 diabetes (T2D) and other diseases, but is hard to study directly.

T2D

Fasting glucose, Insulin

“Clamp” or IST

Beta Cell Function

Glycemic or other traits (HDL, Tg, Waist, Rette, BMI)

Uniquely colocalized IR and T2D loci show various patterns of tissue and trait sharing

Loci with single colocalized genes show tissue-specificity patterns according to trait cluster

Genetic associations were integrated across 9 IR-related traits and 5 IR- or T2D-relevant human tissues

9 GWAS traits
- multiple phenotypes
- multiple traits
- multiple loci
- multiple co-localizations

5 QTL traits (eQTL and sQTL)
- co-localization
- same causal variant
- same causal variant
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- same causal variant

Colocalization analysis found 1366 genes associated with 470 IR-related GWAS loci

Tissue-specific genes and splicing-specific genes exist

Candidate causal genes show varied patterns of response to a panel of 21 perturbations in fat, liver, and muscle cells

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A generalized version of the hashtag-producing code is available at https://github.com/mjgloudemans/post-coloc-toolkit.

For further questions about this project or about applying the methodology to your own diseases of interest, contact me at mjgloud@stanford.edu.