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Genetics of CAD and related
phenotypes

Insulin sensitivity (resistance)

- GENESIS (GENETics of Insulin Sensitivity)
 - 2500 subjects with insulin clamp genotyping
 - Whole genome genotyping
 - GWAS complete
 - Replication in expanded cohort w/ Hispanic/Latino cohort

Insulin sensitivity (resistance)

- GENESiPS (GENESIS iPSC study, NIH NextGen consortium)
- 200 subjects – 1000 iPSC lines
- 500 RNAseq runs on iPSC lines 100 subjects
- Differentiation to vascular (endothelial, smooth muscle) cells
- Differentiation to metabolic (skeletal muscle, adipose) cells
- Analyses – assessment of variation iPSC, gene networks of insulin sensitivity

Collaborations genetics of CAD

- CARDIoGRAM+C4D
- TaiChi - ~20,000 East Asians –
 - CAD, T2DM phenotypes
 - Regeneron, BROAD, exome, WGS

Mechanisms of CAD GWAS association

- Mapping of causal variation in smooth muscle
- Human coronary artery smooth muscle cells
 - 60 lines
 - WGS
 - RNAseq
 - Histone mods (H3K27Ac, H3K4me1, H3K4me3, H3K27me3)
 - ATACseq, etc.

Mechanisms of CAD GWAS association

- Causal variant, causal gene
- Variant mechanism, gene mechanism
- 9p21.3 – CDKN2B
- 6q23.2 – TCF21
- 2q22.3 - ?
- 1p36.33 - ?