Disclosure Slide

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Gene-level analysis of LOF variants in 246,730 whole exome sequences reveals a novel association of GIGYF1 with diabetes

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Introduction
- Sequencing of large cohorts offers an unprecedented opportunity to identify predicted loss of function \((pLOF)\) genetic variants and to find novel contributors to human disease.
- We identified 15,610 genes carrying more than one rare \((\text{MAF} < 1\%)\ pLOF\) variant called as high confidence by LOFTEE in 246,730 exome-sequenced White British participants in the UK Biobank (UKBB).
- We performed SKAT-o and other gene-level tests to examine the association \(pLOF\) in these genes with glucose, HbA1c and type 2 diabetes (T2D) controlling for age, sex and genetic ancestry via 12 principal components.

\(pLOF\) in GIGYF1 and GCK associates with glucose, HbA1c and T2D
- SKAT-o on all aggregated \(pLOF\) variants showed associations of just two genes, GCK and GIGYF1, with both glucose and HbA1c levels.
- Burden tests revealed that GCK and GIGYF1 \(pLOF\) also associate with increased incidence of T2D diagnosis \((n=16,392\) cases).
- Of 88 carriers of a \(pLOF\) in GIGYF1, 22 had been diagnosed with T2D and 45 had either a medical diagnosis, self-report, or family history of diabetes \((n=63,628\) cases).

PheWAS of GIGYF1 \(pLOF\) reveals associations with IGF-1, cholesterol and hypothyroidism
- We performed a phenome-wide association study (PheWAS) testing GIGYF1 \(pLOF\) for association with 131 quantitative traits and 548 ICD10-coded diagnoses.

Common variants at GIGYF1 associate with glucose, T2D and GIGYF1 expression
- An independent common variant signal for glucose and T2D was identified at the GIGYF1 locus and these associations replicated in additional datasets (Biobank Japan and FinnGen).
- rs221783 is the best eQTL or correlated with the best eQTL \((R^2>0.8)\) for GIGYF1 in several tissues including pancreas, adipose and thyroid (GTEx v8.0).

Conclusions
- We detected a novel association between \(pLOF\) in GIGYF1 and increased diagnosis of T2D as well as increased glucose and HbA1c levels.
- GIGYF1 \(pLOF\) also associated with decreased levels of IGF-1 and cholesterol as well as an increased risk of hypothyroidism.
- An independent common variant signal for glucose and T2D was identified at GIGYF1 and these associations replicated in additional datasets.
- GIGYF1 encodes GRB10 interacting GYF protein 1. GRB10 is an adapter protein that binds both the insulin and IGF-1 receptors. Our results highlight the role of GIGYF1 in regulating insulin signaling and protecting from diabetes.

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