Disclosure Slide

Financial Disclosure for:
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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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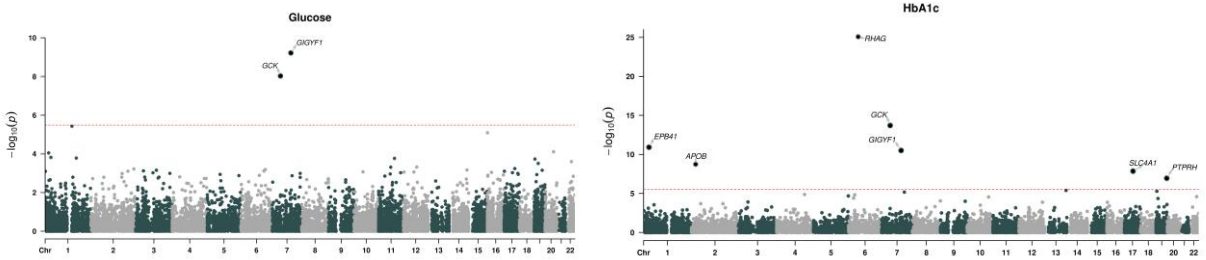
Introduction

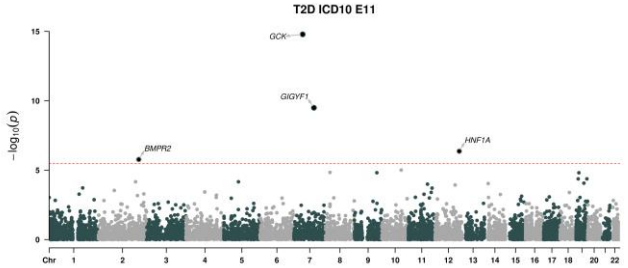
- Sequencing of large cohorts offers an unprecedented opportunity to identify predicted loss of function (pLOF) genetic variants and to find novel contributors to human disease.
- We identified 15,610 genes carrying more than one rare (MAF <1%) pLOF variant called as high confidence by LOFTEE in 246,730 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). *GCK* is known to be involved in Mendelian forms of diabetes but *GIGYF1* has not previously been implicated by genetics in diabetes.
- Out 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).

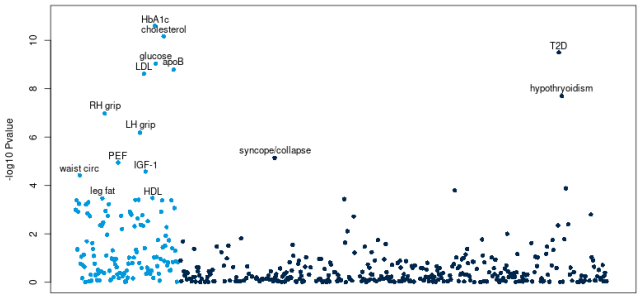


Associations of pLOF in *GCK* and *GIGYF1* with diabetes

gene	phenotype	P-value	OR (95% CI)	n carrier	n carrier cases	n expected
GIGYF1	T2D (ICD10 E11)	$3.17x10^{-10}$	4.92 (3.00,8.09)	88	22	5.85
GIGYF1	Diabetes (including self-report & family history)	$4.41x10^{-7}$	2.96 (1.94, 4.52)	88	45	22.69
GCK	T2D (ICD10 E11)	$1.62x10^{-15}$	26.60 (11.87, 59.63)	28	17	1.86
GCK	Diabetes (including self-report & family history)	$1.45x10^{-6}$	7.57 (3.32, 17.24)	28	20	7.22

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.



Selected associations from PheWAS

gene	phenotype	P-value	Beta/OR
GIGYF1	Cholesterol	$6.82x10^{-11}$	-0.70
GIGYF1	IGF-1	$2.67x10^{-5}$	-0.44
GIGYF1	Right hand grip strength	$1.06x10^{-7}$	-0.39
GIGYF1	Hypothyroidism	$2.03x10^{-8}$	4.99
GIGYF1	Syncope and collapse	$7.24x10^{-6}$	4.11

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).

dataset	phenotype	chr	pos (hg38)	Ref (effect allele)	Alt	rsid	P-value (meta)	effect in SD or OR (95% CI)
UKBB+Biobank Japan	Glucose	7	100695291	T	C	rs221783	$4.33x10^{-14}$	-0.03 (-0.04, -0.02)
UKBB+FinnGen	T2D	7	100695291	T	C	rs221783	$1.73x10^{-5}$	0.95 (0.93, 0.97)

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.

Acknowledgements

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