Disclosure Slide

Financial Disclosure for:
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Phenome-wide association study of predicted loss of function variants and 34 biomarkers in 255,873 UK Biobank whole exome sequences

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Objective

- To characterize the association of rare predicted loss of function (pLOF) variants in UK Biobank with 30 serum and 4 urine biomarkers

Methods

- We performed a large-scale phenome-wide association study of rare (MAF < 1%) pLOF variants identified through exome sequencing of 255,873 UK Biobank participants
- pLOF variants were defined as stop-gained, frameshift, or splice acceptor/donor mutations called as high confidence by the LOFTEE algorithm
- We tested a total of 34 biomarkers measured from serum and urine collected at UK Biobank baseline visit
- Analyses were performed separately in the White, Black and Asian subpopulations of UK Biobank defined based on a combination of self-report and genetic ancestry
- Analyses were performed using SKAT-o controlling for age, sex, and genetic ancestry via 12 principal components
- A Bonferroni-corrected p-value of 3.2×10^{-6} was considered statistically significant

Results

- Analyses included 246,731 individuals of European ancestry, 5,176 individuals of Asian ancestry and 3,966 individuals of African ancestry

	Number of variants
Stop-Gained	176,497
Frameshift	224,900
Splice Donor/Acceptor	137,444
Total	538,841

Table 1. Rare (MAF <1%) pLOF variants in 255,873 UK Biobank whole exome sequences

- Over half (59.9%) of rare pLOFs were observed in only one subject

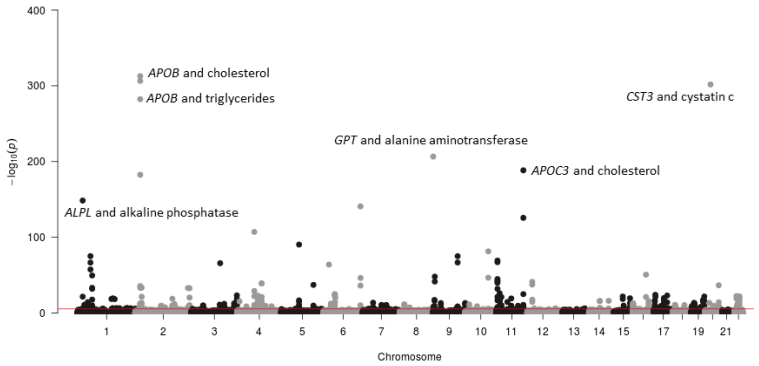

Figure 1. PHEWAS of rare (MAF <1%) pLOF variants and 34 serum and urine biomarkers

Gene	Chr	Phenotype	Pvalue
PCSK9	1	LDL cholesterol	6.9×10^{-76}
ABCA1	9	Apolipoprotein A	7.9×10^{-76}
SLC22A12	11	Urate	5.2×10^{-20}
LPL	8	Triglycerides	2.3×10^{-12}
CASR	3	Calcium	6.4×10^{-12}

Table 2. Significant results validating existing drug targets

- SKAT-o analysis revealed a total of 178 significant associations of pLOF variants with measured biomarkers, including both the replication of many established associations and novel associations
- A total of 3,080 variants from 2,309 genes were homozygous pLOF (putative human “knockouts”)

Conclusions

- Using a phenome-wide association study of pLOF variants, we demonstrate the utility of focusing on rare protein-altering variants to identify therapeutic targets, including the validation of existing drug targets

Acknowledgements

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