

# Proteome Association Studies in Populations of Diverse Ancestries

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## Introduction

Most genome-wide association studies (GWAS) have been conducted in populations of European ancestries, but these results do not reflect the global population or replicate well in non-European populations. Additionally, investigating traits at the proteome level may provide more insight to biological mechanisms than at the genome level. Using data from the Trans-Omics for Precision Medicine (TOPMed) consortium, we have built protein models to perform proteome-wide association studies (PWAS) using S-PrediXcan in published multiethnic GWAS data from the Population Architecture using Genomics and Epidemiology (PAGE) study (Wojcik et al 2019). This output reveals significant associations between genes and a variety of complex traits in non-European populations.

## Methods

- S-PrediXcan: statistical analysis software, takes GWAS summary statistics, protein level models, and phenotype data to find associations between proteome and traits
- Bonferroni significance threshold used to find the most significant associations
- The PAGE study: the most diverse GWAS to date, collecting data in 28 phenotypes in a sample size of ~50,000 non-European individuals; publicly available summary statistics used for our discovery population

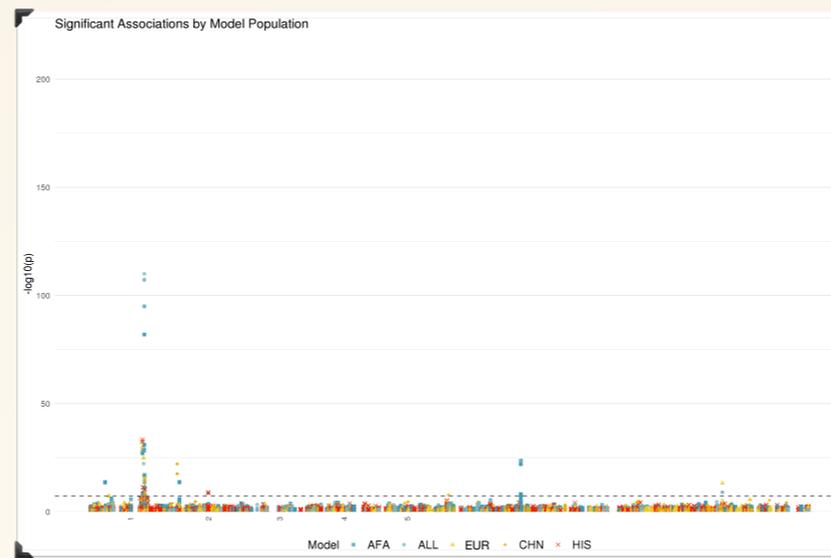
- Body mass index
- Chronic kidney disease
- Cigarettes per day (smoking)
- Coffee consumption
- C-reactive protein levels
- Diabetes (type II)
- Diastolic blood pressure
- End-stage renal failure
- Fasting glucose levels
- Fasting insulin levels
- Glomerular protein levels
- Height
- Hemoglobin levels
- HDL cholesterol levels
- Hypertension
- LDL cholesterol levels
- Mean corpuscular hemoglobin
- PR interval
- Platelet count
- QRS interval
- QT interval
- Systolic blood pressure
- Total cholesterol
- Triglyceride levels
- Waist-hip ratio
- Waist-hip ratio (female)
- Waist-hip ratio (male)
- White blood cell count

- TOPMed models: made with relatively diverse dataset from the TOPMed project
- PWAS is a new method compared to more common TWAS (transcriptome); we are still refining these protein models

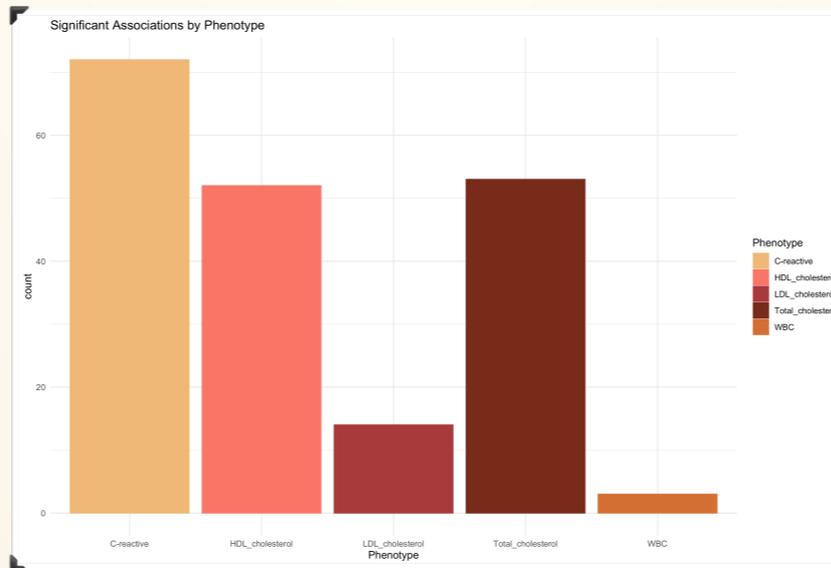
- AFA: African American, n=183
- CHN: Chinese, n=77
- EUR: European, n=414
- HIS: Hispanic, n=301
- ALL: all groups, n=975

- Coloc: software tool used to determine the colocalization of genes in a GWAS, provides insight to which of the significant S-PrediXcan results may be causal
- Replication datasets: taken from published GWAS summary statistics from the UK Biobank, other studies publicly available in the GWAS Catalog

## Results



- 194 Bonferroni significant, colocalized, and replicated protein-trait pairs.
- In non-European PAGE data: more significant results when using the AFA (dark blue) and HIS (red) training models than the EUR (yellow) models, significance threshold shown as the dotted line



- Significant protein-trait associations found for 5 phenotypes:
  - C-reactive protein levels
  - HDL cholesterol levels
  - LDL cholesterol levels
  - Total cholesterol
  - White blood cell count

## Discussion

- 194 total associations across all training models
- 27 unique protein-trait pairs

Gene	Protein	Phenotype
CRP	CRP	C-reactive
APOE	Apo E	HDL cholesterol LDL cholesterol Total cholesterol C-reactive
	Apo E2	HDL cholesterol LDL cholesterol Total cholesterol C-reactive
	Apo E3	HDL cholesterol LDL cholesterol Total cholesterol C-reactive
	Apo E4	HDL cholesterol LDL cholesterol Total cholesterol C-reactive Triglycerides
HP	Mixed-type haptoglobin	LDL cholesterol Total cholesterol
CD36	CD36 antigen	C-reactive HDL cholesterol Platelet count
CSF3	G-CSF	WBC count
IL6R	IL-6 sRa	C-reactive
IL1RN	IL-1Ra	C-reactive
FRZB	sFRP-3	Height

- Published literature supports these associations and provides evidence to the validity of our proteome models. Only one pair, CD36 antigen (CD36 gene) and C-reactive protein level, is a novel finding among published GWAS. We plan to continue refining our training models and conducting more PAS in the future.
- Finding more significant associations in non-European populations with non-European models supports previous work that shows prediction improves with population-matched data. This further emphasizes the need for more diverse GWAS in the future.

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