Cross-population genetic analysis of the circulating proteome implicates novel proteins in Type 2 Diabetes

Abstract

Background:

Previous studies have identified circulating proteins associated with Type 2 Diabetes (T2D) risk, primarily in European populations. However, the extent to which protein associations are shared or differ across populations remains unclear. To address this gap, we conducted a comprehensive proteome-wide association study (PWAS) integrating human blood proteomes with genome-wide association data across populations.

Methods:

We analyzed genome and plasma proteome data from the Multi-Ethnic Study of Atherosclerosis (MESA), including 902 African, 407 Asian, 1,839 European, and 829 Hispanic/Latino participants. Protein prediction models were trained using both *cis*- and *trans*- acting SNPs, and models with prediction performance $R^2 \geq 0.01$ were retained for downstream analyses. These models were applied to large-scale T2D GWAS summary statistics comprising 410,018 cases and 2,072,406 controls from multiple populations. Population-specific PWAS analyses were performed separately within each population, followed by cross-population meta-analysis to identify additional associated proteins. For proteins significantly associated with T2D, potential drug-target relationships were explored using the DrugBank database to assess opportunities for drug repurposing.

Results:

We established 1,918, 1,280, 2,392, and 1,610 protein prediction models with $R^2 \geq 0.01$ for African, Asian, European, and Hispanic/Latino populations, respectively. Population-specific PWAS identified three, 42, 237, and 13 proteins significantly associated with T2D risk in African, Asian, European, and Hispanic/Latino populations, respectively (Bonferroni-corrected $p < 0.05$). Cross-population meta-analysis identified 344 proteins significantly associated with T2D risk, including 85 proteins that were not detected in any single population-specific analysis. Drug repurposing analysis further identified 421 drugs targeting 68 T2D-associated proteins, including drugs targeting the insulin receptor (INSR) and insulin-like growth factor 1 receptor (IGF1R), both well-established regulators of glucose metabolism.

Conclusion:

This multi-population PWAS provides a comprehensive characterization of circulating proteins associated with T2D risk and reveals both shared and population-specific protein signals. These findings improve our understanding of the molecular mechanisms underlying T2D and highlight potential targets for therapeutic development and drug repurposing.