White paper

Empower Genomics with Proteomics

Integration of genomics and proteomics data heralds a new era of discovery, revealing novel drug targets and new insight into disease pathways

The promise of the Human Genome Project

The Human Genome Project promised new drug targets leading to more effective medicines. The results of this are evident as recent research indicates that two-thirds of US FDA-approved drugs (33 out of 50 in 2021) have the "integration of multiple layers of genetic and functional genomics data" along with "clinical knowledge about the molecular and phenotypic characteristics of the disease".[1]

Mechanisms of action need to be further elucidated along with a deeper understanding of disease pathophysiology to speed drug development. In addition, identification of novel disease biomarkers will enable new investigations into drug safety and efficacy, improved patient stratification, and the development of new molecular diagnostics.

Amid a rich history of Genome-Wide Association Studies (GWAS) and a wealth of genetic information, new approaches to investigate proteomics at population scale will empower researchers to identify proteins and pathways likely to be causal in disease, supporting a systematic approach to identify potential new drug targets.[2] As an intermediate phenotype, proteins can help amplify power in genetic studies to link genetics more confidently to disease phenotypes while simultaneously revealing mechanistic insights into disease.

Population health advances using Olink® Explore technology

The UK Biobank began in 2006 as a long-term, large-scale biomedical research resource and database collecting in-depth genetic and health information from half a million UK participants. In 2020 the UK Biobank announced a collaboration with 13 pharmaceutical partners to sponsor the examination of tens of thousands of samples using Olink® Explore 1536 and called this collaboration the UK Biobank Pharma Proteomics Project Consortium (UKB-PPP).

In a pre-print titled "Genetic regulation of the human plasma proteome in 54,306 UK Biobank participants"[3], the UKB-PPP Consortium report over 8,000 novel proteogenomic associations (protein quantitative loci or pQTLs) between genetic variants and circulating protein level, as well as over 2,000 previously reported ones.

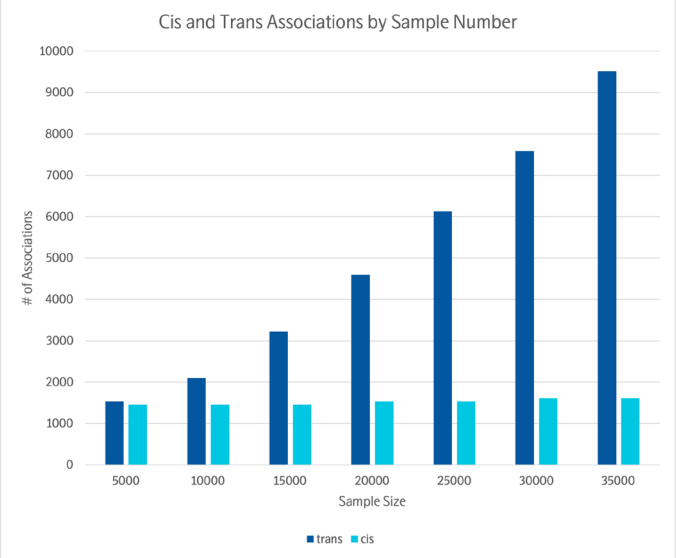

Figure 1. Number of primary *cis*- and *trans*- protein Quantitative Trait Loci (pQTL) associations as a function of sample size. Adapted from reference 3, Figure 2e.

For the majority of proteins measured, *cis*-pQTLs were identified. Such *cis* associations are between a variant in a gene and the protein encoded by that gene. Considered a surrogate measure of specificity, *cis*-pQTLs provide strong evidence that the right protein is being measured. *Cis*-pQTLs were identified for 85% of the proteins evaluated.

In an analysis modeling the trend of significant *cis*- and *trans*-pQTL discoveries as a function of increasing sample size, no evidence of the number of *trans*-pQTLs plateauing could be observed in 35,000 participants. In other words, there is continued added discovery value as sample numbers increase (Figure 1)[3]. Such discoveries offer opportunities to identify new pathways implicated in disease.

The UKB-PPP Consortium's work will accelerate the development of more effective therapeutics, as well as help elucidate biological mechanisms that underlie disease. Confidence in these expectations comes via results from a powerful precursor to the recently reported UKB-PPP Consortium findings: The SCALLOP (Systematic and Combined AnaLysis of Olink Proteins) Consortium.

See what proteomics can deliver to empower your genomics

The SCALLOP Consortium includes 35 investigators from 28 institutions representing 45 cohort studies and 70,000 patients[4] all with genetic and proteomic data and clinical phenotypes. Their seminal work reveals 451 primary genetic associations, 25 causal proteins representing novel drug targets and suggests 18 drug repurposing opportunities.[2] These 25 links to causal proteins bridge the gap between genetic associations and tangible disease pathology.

This milestone paper from SCALLOP provides confidence in a systematic approach to therapeutic target discovery by including proteomics. The UKB-PPP Consortium is using a similar framework, scaling to ~3000 proteins and heralding a new era of biological discovery.

To learn more about how Olink can empower your genomics, contact us today at info@olink.com or through our website at www.olink.com/multiomics

1. Ochoa D and Dunham I et al. Human genetics evidence supports two-thirds of the 2021 FDA-approved drugs. Nat Rev Drug Discov. 2022 21(8):551. doi:10.1038/d41573-022-00120-3
2. Folkersen L and Malarstig A et al. Genomic and drug target evaluation of 90 cardiovascular proteins in 30,931 individuals. Nature Metab 2020 2(10):1135-1148. doi:10.1038/s42255-020-00287-2
3. Sun BB and Whelan CD et al Genetic regulation of the human plasma proteome in 54,306 UK Biobank participants. bioRxiv 18 June 2022 doi:10.1101/2022.06.17.496443
4. http://www.scallop-consortium.com/

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