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An atlas of genetic scores to predict multi-omic traits

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Y.X. and M.I. conceived and designed the study; Y.X., S.C.R. performed the genetic score training and internal validation analyses; Y.X., Y.L., P.R.H.J.T., M.P., U.A.T., S.M.-W., Å.J., P.S., S.D. performed the external validation analyses; S.C.R., A.P.N., E.P., J.E.P., C.O.-W., B.P. performed the data quality control and GWAS in INTERVAL; Y.X., L.L. performed the methods benchmarking analyses; Y.X., S.A.L. performed the PheWAS; Y.X. performed the pathway coverage, correlation and PCA analyses; Y.X., S.C.R. performed the cross-platform validation analyses; S.C.R. performed the genetic score polygenicity analysis; C.F., M.I. interpreted the biological insights; Y.X. developed and maintained the online portal; M.I., A.S.B., J.F.W., C.L., X.S., J.D., R.E.G., D.S.P., E.E.D., R.M.D., E.S.T., E.D.A., N.S., L.B., J.A.L. acquired the resources and datasets; M.I., A.S.B., J.F.W., C.L., X.S., J.D., A.M., R.E.G., C.Y., D.S.P., E.E.D., H.P., N.P. supervised the work; Y.X. and M.I. wrote the original manuscript. All authors reviewed and approved the final paper.

Competing interests

During the drafting of the manuscript, P.R.H.J.T. became a part-time employee of BioAge Labs, Inc., P.S. became a full-time employee of GSK, and D.S.P. became a full-time employee of AstraZeneca. L.B. is an employee of BioMarin. J.D. serves on scientific advisory boards for AstraZeneca, Novartis, and UK Biobank, and has received multiple grants from academic, charitable and industry sources outside of the submitted work. A.M. is an employee of Pfizer. A.S.B. reports institutional grants from AstraZeneca, Bayer, Biogen, BioMarin, Bioverativ, Novartis, Regeneron and Sanofi.

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Abstract

The use of omic modalities to dissect the molecular underpinnings of common diseases and traits has become pervasive. Yet, multi-omic traits can be genetically predicted, enabling highly cost-effective and powerful analyses for studies which do not have multi-omics[1]. Here, we utilised a large cohort (INTERVAL[2]; N=50,000 participants) with extensive multi-omic data for plasma proteomics (SomaScan, N=3,175; Olink, N=4,822), plasma metabolomics (Metabolon HD4, N=8,153), serum metabolomics (Nightingale, N=37,359), and whole blood Illumina RNA sequencing (N=4,136). We used machine learning to train genetic scores for 17,227 molecular traits, including 10,521 which reached Bonferroni-adjusted significance. We evaluated genetic score performances in external validation across European, Asian and African American ancestries. We demonstrated the utility of these multi-omic genetic scores by quantifying the genetic control of biological pathways and by generating a synthetic multi-omic dataset of UK Biobank[3] to identify disease associations using a phenome-wide scan. We highlight a series of biological insights regarding genetic mechanisms in metabolism and canonical pathway associations with disease, e.g. JAK-STAT signalling and coronary atherosclerosis. Finally, we developed a portal (OmicsPred.org) to facilitate public access to all genetic scores and validation results as well as to serve as a platform for future extensions and enhancements of multi-omic genetic scores.

Introduction

Multi-omic analysis has become a powerful approach to predict disease and dissect its underlying biology. However, the collection of transcriptomic, proteomic, metabolomic and other modalities is an extremely expensive and time-consuming process. Because of these barriers, large-scale population cohorts typically generate multi-omic data for only a subset of participants (or not at all), which consequently reduces statistical power and creates inequities for studies without ample resources, particularly in underrepresented demographics.

Genetic prediction of complex human traits can have both analytic validity and potential clinical utility[4-7]. Genetic prediction has been extended to omics data, e.g. whole blood[8] and multi-tissue transcriptomics[9] as well as plasma proteomics[10]. Genetically-predicted traits can elucidate the molecular aetiology of common diseases, incorporating both directionality (the germline genome is fixed over the life course) and the power of large-scale genotyped biobanks to overcome prediction noise[11,12].

Genetic scores which predict, expand and thereby democratize multi-omics data are of intense interest. Genetic prediction in this area has historically focused on gene expression, drawing on heterogeneous sources for training data with limited sample sizes. With many cohorts now performing multi-omics at scale, there is a unique opportunity to greatly expand and enhance these genetic scores. Given robust external validation, the reliability of multi-

omic genetic scores can be quantified and extended to analyses assessing transferability across ancestries, thus facilitating equitable tools for molecular investigation in diverse populations. This approach both facilitates integrative cross-cohort, multi-omic analyses and enables efficient generation of synthetic multi-omic data for studies with only genetic data.

Here, we utilise the INTERVAL study[2], a cohort of UK blood donors with extensive multi-omic profiling, to train genetic prediction models. We externally validated these genetic scores in seven external studies, comprising European, East Asian, South Asian and African American ancestries. We then demonstrate the use of genetically-predicted molecular data, including coverage of biological pathways and the identification of multi-omic predictors of diseases and traits in the UK Biobank. Finally, we construct an open resource (OmicsPred.org) which makes all genetic scores, validations and biomarker analyses freely available to the wider community.

Results

Development of genetic scores

We developed genetic scores for blood RNA transcripts, proteins, and metabolites (Extended Data Fig. 1). We utilised INTERVAL which collected participant serum or plasma on which assays from five omics platforms were performed: SomaScan v3 (SomaLogic Inc., Boulder, Colorado, US), an aptamer-based multiplex protein assay; Olink Target (Olink Proteomics Inc., Uppsala, Sweden), an antibody-based proximity extension assay for proteins; Metabolon HD4 (Metabolon Inc., Durham, US), an untargeted mass spectrometry metabolomics platform; Nightingale (Nightingale Health Plc., Helsinki, Finland), a proton nuclear magnetic resonance (NMR) spectroscopy platform; and whole blood RNA sequencing via the Illumina NovaSeq 6000 (Illumina Inc., San Diego, California, US) (Methods). INTERVAL participants were genotyped on the Affymetrix Biobank Axiom array and imputed using a combined 1000 Genomes Phase 3-UK10K reference panel (Methods). After quality control, 10,572,788 genetic variants were available.

To train genetic scores, we utilised Bayesian ridge regression (BR) as it has been shown to be a powerful and robust approach for genetic prediction[7] which is also computationally scalable to the number of traits analysed here (Methods), thus controlling carbon footprint[13]. We confirmed generalisability across multiple platforms, assessing the impact of different variant filtering strategies (Methods; Supplementary Fig. 1-4, Extended Data Fig. 2). Overall, we found the best performing approach was BR with genome-wide variant selection using p-value $< 5\times10^{-8}$ (Supplementary Fig. 1-4, Extended Data Fig. 2).

We developed genetic scores for 17,227 biomolecular traits from the five platforms, including 726 metabolites (Metabolon HD4), 141 metabolic traits (Nightingale), 308 proteins measured by Olink, 2,384 proteins measured by SomaScan, and 13,668 genes from Illumina RNAseq (Ensembl gene-level counts) (Methods). Across all platforms, we found wide variation in the predictive value (R^2 between genetically predicted and directly measured biomolecular trait) and the number of variants in the genetic scores in internal validation (Extended Data Fig. 3, Supplementary Fig. 5).

We found 10,522 biomolecular traits could be genetically predicted at Bonferroni-adjusted significance (correcting for all genetic scores tested), including those for SomaScan (1,052 traits), Olink (206), Metabolon (379), Nightingale (137) and RNAseq (8,748). Of these, 5,816 and 409 genetic scores had $R^2 > 0.1$ and $R^2 > 0.5$, respectively (Fig. 1 and Supplementary Tables 1-5)

Genetic scores comprised one to 1,862 genetic variants, with 58% including variants from a single LD block, 40% spanning 2-5 LD blocks and 2% spanning 5 or more LD blocks[14]. As expected for gene and protein scores, the contribution from genetic variants in *cis* exceeded that in *trans*. For 89% of these omics traits, *cis* signals (within 1Mb of the transcription start site) contributed most to the genetic score R^2 with the remaining dominated by *trans* signals. We also compared the gain in R^2 of a genetic score to the top single variant (the one with greatest weight) for omic traits in internal validation and found that genetic scores had a median R^2 that was 3.1-fold higher than the top variant. As expected, R^2 gain (1.7-fold) was smaller for scores with 5 variants or less.

Validation in European ancestries

We performed external validation of SomaScan proteins in the FENLAND study[15]; Olink proteins in the Northern Swedish Population Health Study (NSPHS)[16] and the Orkney Complex Disease Study (ORCADES)[17]; Metabolon metabolites in ORCADES; Nightingale metabolic traits in UK Biobank (UKB)[3], Viking Health Study Shetland (VIKING)[18] and ORCADES studies (Extended Data Fig. 1 and Extended Data Table 1). For Metabolon and RNAseq, we performed further validation in withheld sets of INTERVAL (Methods). Overall, we found performance of most genetic scores were consistent between internal and external validation in European ancestries (Fig. 2, Extended Data Fig. 4 and Supplementary Fig. 6-10). As expected, we found that genetic scores with high variant missingness rates had attenuated power (Extended Data Fig. 5).

SomaScan quantified 3,622 plasma proteins in INTERVAL, of which 2,384 proteins had at least one significant genetic variant that could be used for genetic score development (Methods; Extended Data Fig. 3). Internal validation found SomaScan genetic scores had median $R^2 = 0.04$ (IQR = 0.08). Most SomaScan genetic scores (89%; N=2,129) could be tested for external validation in the FENLAND study[15]. Overall, there was high consistency between internal and external R performance (Fig. 2). We metricised validation performance using the slope (λ) of the line of best fit between internal and external R^2. For FENLAND, λ was 0.99. Of the 2,129 externally tested SomaScan genetic scores, we found 45 proteins (2%) with a majority of their variance explained (R^2 0.50) by the genetic score, including several with R^2 0.70 involved in innate and adaptive immune responses (CLEC12A, SIGLEC9, FCGR2A, FCGR2B and LILRB5). 369 SomaScan proteins (17%) could be genetically predicted with $R^2 > 0.10$ in external validation.

Olink proteomics in INTERVAL quantified levels of 368 plasma proteins from four panels (Inflammation, Cardiovascular 2, Cardiovascular 3, Neurology), of which 308 unique proteins qualified for genetic score development (Methods). Internal validation found that Olink genetic scores had median $R^2 = 0.06$ (IQR = 0.12). We were able to test 302 and 301 genetic scores in external European ancestry cohorts, NSPHS ($\lambda = 1.03$) and ORCADES (λ

= 0.70) respectively (Methods; Fig. 2). In both external validation cohorts, we found four proteins (FCGR2B, IL6R, MDGA1, SIRPA) with a majority of their variance explained (R^2 > 0.50) by the genetic score (Fig. 2). As compared to SomaScan, a larger proportion of Olink proteins in NSPHS (N=117; 39%) and ORCADES (N=87; 29%) could be genetically predicted with R^2 > 0.10. Overall, we found consistency between validations in NSPHS and ORCADES (Supplementary Fig. 11).

Metabolon HD4 quantifies >900 plasma metabolites and was used here in two phases of the INTERVAL study (Methods). Phase 1 (N=8,153) was used for development and internal validation of Metabolon genetic scores and phase 2 (N=8,114) was used for external validation (no individuals overlapping between phases). We conducted further external validation in ORCADES. Internal validation found that Metabolon genetic scores had median R^2 = 0.02 (IQR = 0.05). A total of 726 Metabolon metabolites had significant genetic variants with which to construct genetic scores in INTERVAL, of which 527 and 455 metabolites (399 overlapping) could be externally validated in the phase 2 set (λ = 0.84) and ORCADES (λ = 0.73), respectively (Fig. 2). We again found broad consistency between the two external validation sets (Supplementary Fig. 11). There were no Metabolon genetic scores with R^2 > 0.50 in either the phase 2 set or ORCADES; however, 6 metabolites had R^2 > 0.3 in both the phase 2 set and ORCADES (4 metabolites overlapping). Of metabolites that could be externally validated, 10% and 13% (N=50 and N=59) achieved R^2 > 0.10 in the phase 2 set and ORCADES, respectively. The top performing genetic scores included ethylmalonate (phase 2 set R^2 = 0.43; ORCADES R^2 = 0.33), N-acetylcitrulline (both phase 2 set and ORCADES R^2 = 0.38) and androsterone sulfate (phase 2 set R^2 = 0.35; ORCADES R^2 = 0.17).

Nightingale NMR was used to quantify 230 serum metabolic biomarkers from 45,928 INTERVAL participants. Our analyses focused on directly measured (non-derived) metabolic biomarkers, and genetic scores for 141 Nightingale biomarkers were developed using INTERVAL (Methods). Internal validation found Nightingale genetic scores had median R^2 = 0.07 (IQR = 0.03). Genetic scores were externally validated in UKB, ORCADES and VIKING with λ values of 0.62, 0.70 and 0.49, respectively (Fig. 2). Overall, genetic scores for Nightingale explained somewhat less variation in directly measured traits compared to other platforms (Fig. 2, Extended Data Fig. 4). Across UKB, ORCADES and VIKING, 27 Nightingale metabolic biomarkers had an R^2 > 0.10 in at least one external validation cohort, with no biomarkers having R^2 > 0.30. However, Nightingale genetic scores performed consistently across cohorts, with the same mean R^2 for all 141 Nightingale biomarkers of 0.06 across the three external cohorts. The most predictive genetic scores were related to low-density lipoprotein (LDL), e.g. concentrations of cholesteryl esters in small LDL, cholesterol in small LDL, cholesteryl esters in medium LDL, cholesterol in medium LDL and LDL cholesterol (Supplementary Table 2).

Whole blood RNAseq from 4,778 individuals in INTERVAL was performed using Illumina NovaSeq (Methods). While 4,136 individuals were used to develop and test genetic scores, 598 individuals were kept as a withheld set for validation. INTERVAL RNAseq data allowed for the construction of genetic scores using both *cis* and *trans* eQTLs for 13,668 genes, of which 12,958 (95%) could be assessed in the withheld validation set (Fig. 2). Internal

validation found that RNAseq genetic scores had median $R^2 = 0.06$ (IQR = 0.13). Overall, we found strong correlation of R^2 between the internal and withheld validation sets ($\lambda = 0.84$). There were 141 genes with $R^2 > 0.50$ in the withheld validation set, and 798 genes with $R^2 > 0.30$. The most predictive genes were those involved in proteolysis (*RNPEP*; $R^2 = 0.71$), solute cotransport (*SLC12A7*; $R^2 = 0.72$), RNA helicase activity (*DDX11*; $R^2 = 0.71$) and spliceosome function (*U2AF1*; $R^2 = 0.72$).

Transferability of genetic scores

To assess the performance of the genetic scores developed in the predominantly-European INTERVAL cohort in non-European ancestries, we utilised the Singapore Multi-Ethnic Cohort (MEC)[19] and the Jackson Heart Study (JHS)[20]. MEC data comprised individuals of Chinese, Indian and Malay populations with matched genotypes, plasma Nightingale NMR and plasma SomaScan, and the JHS comprised African Americans with matched genotypes and plasma SomaScan (Extended Data Table 1; Methods).

Overall, we found that genetic scores developed in INTERVAL could predict Nightingale and SomaScan trait levels in Asian and African American ancestries, but as expected their performances were significantly reduced when compared to European ancestries (Fig. 3 and Extended Data Fig. 6). For Nightingale, genetic score performance in external validation generally declined from European ancestries (λ=0.62 in UKB) to MEC Chinese (λ=0.41) to MEC Indian (λ=0.35) to MEC Malay (λ=0.15) ancestries (Fig. 2, 3a and Supplementary Fig. 12). However, of the 138 genetic scores statistically significant (nominal p-value < 0.05) in the UKB validation, nearly all were significantly predictive in Chinese (133), Indian (132) and Malay (134) ancestries (Supplementary Table 2). Genetic scores for LDL subclasses displayed some of the most variable cross-ancestry R^2 (Fig. 3b). The most consistently transferrable Nightingale genetic scores were levels of triglycerides, either in total or the triglycerides in LDL, large LDL or medium HDL, and the degree of phosphatidylcholines (Fig. 3b)

Transferability of SomaScan genetic scores was substantially greater than Nightingale (Fig. 3c). The λ for SomaScan in European ancestries (FENLAND) was 0.99 as compared to 0.75, 0.68, 0.66 and 0.51 in MEC Indian, MEC Malay, MEC Chinese and JHS African American ancestries, respectively (Fig. 2, 3c and Supplementary Fig. 13). There were 1,309 genetic scores statistically significant in FENLAND external validation, which decreased to 935, 893, 806 and 451 in MEC Indian, MEC Malay, MEC Chinese and JHS African American ancestries, respectively (Supplementary Table 4). The SomaScan genetic scores that attenuated most in non-European ancestries were those for CD177 (a cell-surface protein on neutrophils and Treg's) and LEPR (leptin receptor) (Fig. 3d). The most transferable SomaScan genetic scores included SIGLEC9 (which mediates sialic-acid binding to cells), SIRPA (a cell surface receptor for CD47 involved in signal transduction) and ACP1 (an acid and protein tyrosine phosphatase), with all internal and external validation $R^2 > 0.50$ (Fig. 3d). Given MEC's longitudinal sampling, we further assessed the longitudinal stability of Nightingale and SomaScan genetic scores across ancestries, finding strong consistency of genetic score performance over a mean of 6.3 years (Methods and Extended Data Fig. 7).

Genetic control of biological pathways

Multi-omic genetic scores may be used to probe the relevance of a biological pathway to a particular trait or disease. To assess coverage of biological pathways by the proteomic genetic scores we present here, we applied genetic scores for SomaScan and Olink to assess the extent to which pathways are genetically controlled (Methods). Here, we considered all genetic scores with $R^2 > 0.01$ in internal validation (2,205 unique proteins) and jointly mapped the SomaScan and Olink scores onto data curated from Reactome[21] (Fig. 4a, Extended Data Fig. 8).

We found wide variation amongst the 27 super-pathways with some super-pathways under relatively little genetic control (e.g. chromatic organisation, or transport of small molecules) and others under substantially greater genetic control (e.g. digestion and absorption, or extracellular matrix organisation) (Fig. 4a). Approximately 18% of proteins in the digestion and absorption super-pathway had internal validation $R^2 > 0.10$, and ~4% with $R^2 > 0.30$. For the lowest-level pathway annotation (N=1,717) of the 27 super-pathways, we found that a majority (N=1,169, 68%) were covered by at least one SomaScan or Olink genetic score with an internal validation $R^2 > 0.01$ (Extended Data Fig. 8). For both the digestion and absorption and the extracellular matrix organisation super-pathways, 25% and 42%, respectively, of lowest-level pathway annotations were covered by at least one SomaScan or Olink genetic score with internal $R^2 > 0.30$.

Phenome-wide association analysis

We next generated genetically-predicted Metabolon, Nightingale, Olink, SomaScan and whole blood RNAseq data for the UK Biobank (Methods). Using these predicted multi-omics data of UKB, we performed a phenome-wide association study using PheCodes[22] (ICD-9 and ICD-10 based diagnosis codes collapsed into hierarchical clinical disease groups; Methods). For simplicity and to maximize the number of qualified PheCodes, we focused the analysis on UKB individuals of white British ancestry. Multiple testing was controlled using Benjamini-Hochberg FDR of 5% (Methods).

At an FDR 5%, we identified 18,404 associations between genetic scores for the multi-omic traits and 18 categories of PheCodes (Fig. 4b). These associations comprised 1,668 for Metabolon HD4, 2,854 for Nightingale NMR, 740 for Olink, 5,501 for SomaScan and 7,641 for RNAseq (Supplementary Tables 6-7). Circulatory system diseases, endocrine/metabolic and digestive diseases yielded the largest number of associations across platforms (Fig. 4b).

PheWAS detected many known blood biomarkers as well as intriguing associations. For example, total cholesterol was significantly associated with myocardial infarction (HR = 1.13 per s.d., FDR-corrected p-value = 1×10^{-61}). Interleukin-6 (IL-6) pathways have been shown to have a causal association with coronary artery disease[23], and notably, IL-6 receptor genetic scores in SomaScan and Olink had $R^2 > 0.50$ in both internal and external validation, showing high genetic predictability. Genetically predicted levels of IL-6 receptor in both Olink and SomaScan were significantly associated with myocardial infarction (HR = 0.97 per s.d., FDR-corrected p-value = 2×10^{-4}; HR = 0.97 per s.d., FDR-corrected p-value = 4×10^{-4}, respectively). Microseminoprotein-beta has been identified as a biomarker

for prostate cancer[24] and PheWAS findings support this association (HR = 0.87 per s.d., FDR-corrected p-value = 3×10^{-49}). Genetically predicted Sex Hormone-Binding Globulin (SHBG) protein was associated with type 2 diabetes (HR = 0.98 per s.d., FDR-corrected p-value = 0.03), consistent with previous observational and genetic analyses[25]. Similarly, we found associations for insulin signaling pathway related proteins, e.g. insulin receptor (INSR) and insulin-like growth factor 1 receptor (IGF1R), with type 2 diabetes[26]; ABO[27] with type 2 diabetes; IL-6 with asthma[28]; and *HLA-DQA1/DQB1* with celiac disease[29] (Supplementary Table 6).

Our results validate those of a recent study identifying putative causal plasma protein mediators between polygenic risk and incident cardiometabolic disease[4], including six novel putatively causal associations for coronary artery disease (Supplementary Table 6). Amongst the strongest signals, we found intriguing associations including chronic pericarditis (N=266 cases) with genetically-predicted gene expression of phospholipase *NAPEPLD* (HR = 0.88 per s.d., FDR-corrected p-value < 1×10^{-307}) and rhesus isoimmunization in pregnancy (N=302 cases) with genetically-predicted protein levels of ICAM4 (HR = 0.19 per s.d., FDR-corrected p-value = 3×10^{-93}). ICAM4 is critical to the Landsteiner-Weiner blood system, which is genetically independent of the rhesus factor (Rh) blood group system. Despite the *ICAM4* locus showing no significant association with rhesus isoimmunization in pregnancy (PheWeb[30]), our ICAM4 results demonstrate that genetic prediction of plasma proteins can identify biologically plausible candidate associations.

Biological insights

Here, we highlight a series of five findings which inform putative genetic mechanisms and pathophysiology with multi-omic genetic scores. The first three of which investigate metabolic mechanisms of relatively simple genetic scores for Metabolon traits, and the latter two comprise the integration of genetic scores across multiple omics to uncover pathway insights into disease biology.

The genetic score for histidine (Metabolon) consisted of three variants, two of which (rs61937878, rs117991621) are in the coding region of *HAL*, which encodes the enzymatic catalyst for the first reaction in histidine catabolism. We found that rs61937878 is also the sole variant in the genetic score for gamma-glutamylhistidine. Gamma-glutamylhistidine can be formed from the condensation of histidine and glutamate, thus we hypothesise that this genetic variant in *HAL* changes levels of gamma-glutamylhistidine by modulating histidine availability.

The 2-methylbutyrylcamitine (Metabolon) genetic score contained five variants, including rs11753995 which is located within *SLC22A1*, encoding a transmembrane transporter of 2-methylbutyrylcarnitine and other acyl-carnitines[31]. Notably, two variants (rs200800380 and rs274555) in this genetic score are located in *SLC22A4* and *SLC22A5*, respectively, which are involved in carnitine transport[32]. The 2-methylbutyrylcarnitine genetic score also harbours an intronic variant (rs4128783) which maps to the gene encoding Acyl-CoA Dehydrogenase Short/Branched Chain (ACADSB). ACADSB catalyses the dehydrogenation of 2-methylbutyryl-CoA. Because 2-methylbutyrylcarnitine is produced by transferring the acyl chain from 2-methylbutyryl-CoA to carnitine, these genetic variants (rs200800380,

rs274555 and rs4128783) may influence levels of 2-methylbutyrylcarnitine by modulating the availability of substrates.

The genetic score for DSGEGDFXAEGGGVR (Metabolon) contained a single variant (rs567455090) intronic to *SLC9A1*. Notably, SLC9A1 is a transmembrane exchanger of Na^+/H^+ which regulates the pH and volume of platelets and plays a significant role in their activation[33]. Activated platelets secrete α-granules of thrombin precursor (prothombin) and fibrinogen. DSGEGDFXAEGGGVR is a peptide derived from the cleavage of fibrinogen by thrombin[34]; thus, rs567455090 may modulate the function and activation of platelets which, in turn, change levels of DSGEGDFXAEGGGVR.

Our PheWAS in UK Biobank identified a series of gene transcripts and proteins in the JAK-STAT signalling pathway as associated with coronary artery disease risk (Fig. 5a-b). JAK-STAT regulates cellular proliferation, differentiation, and apoptosis and also plays a role in modulating inflammation. SomaScan levels of AKT2 and CTF1 and transcript levels of *STAT1* were associated with increased risk of CAD, consistent with the anti-atherogenic effects of targeting these genes in murine hypocholesterolemia models[35-37]. Transcript levels of *PIM1* and *CISH1*, which inhibit the JAK-STAT pathway[38,39], were associated with decreased CAD risk. We further found that levels of IL-6 (Olink) and the IL-6R (Olink and SomaScan) were associated with CAD. Consistent with our findings, circulating IL-6 is a well-established biomarker of CAD and IL-6/IL-6R signalling has been shown to have a putative causal effect on CAD[23]. Our PheWAS supports the investigation of inhibitors of JAK-STAT, which are clinically approved for chronic inflammatory disorders, as repositioning candidates against CAD[40].

We also identified transcripts and proteins involved in Wnt signalling (Fig. 5c-e) as associated with hypothyroidism. Notably, there is a well-established crosstalk between Wnt and thyroid hormone signalling: thyroid hormone nuclear receptors can modulate the expression, stability and localisation of proteins of the Wnt pathway whereas the latter modulates thyroid hormone activity by regulating expression of deiodinases[41], enzymes that regulate thyroid hormones. Furthermore, Wnt signalling is active in thyroid cells[42] and is thought to contribute to thyroid homeostasis[43]. In this regard, pharmacological activation of Wnt has been shown to impair thyroid development in zebrafish[44] and a risk allele for congenital hypothyroidism has been identified within enhancer regions of two Wnt pathway genes[45]. We also found the genetic score for USP25 (SomaScan) was associated with decreased risk of hypothyroidism. USP25 is a deubiquitinating enzyme that can activate Wnt by stabilising TNKS1[46]. USP25 also modulates inflammatory responses[47], contributes to metabolic adaptation to hypoxia[48] and inhibits degradation of abnormal proteins[49]. Notably, we found USP25 was also associated with a wide range of diseases, including psoriasis, type 1 diabetes, sicca syndrome, bronchiectasis, polymyalgia rheumatica, nasal polyps, and systemic sclerosis, making USP25 an intriguing biomarker and potential therapeutic target.

The OmicsPred Portal

We developed an online portal (OmicsPred.org) to facilitate open dissemination of the genetic scores, detailed validation results and visualisations. OmicsPred also serves as an online updatable resource, which allows future expansion and deepening of the omics

platforms, multi-ancestry transferability, newly developed and more powerful genetic scores, as well as results from its applications (Extended Data Fig. 9).

The portal presents genetic scores of multi-omic traits by platform, in which users can access summary statistics of the training and validation cohorts as well as download the corresponding model files for genetic scores (i.e. variants and weights). Users can visualise validation results by selected performance metrics (e.g. R^2 or Spearman's rho) and cohort(s), together with detailed trait and validation information. Users can easily search the portal to find multi-omic traits of interest, either by name or related descriptions. OmicsPred also hosts descriptions and summary results from applications of the genetic scores (e.g. the PheWAS above). OmicsPred also serves as a central resource to which users can submit their multi-omic genetic scores so they can be openly distributed to the community.

Discussion

Here, we developed genetic scores for >17,000 multi-omic traits across five platforms covering proteomics, metabolomics and transcriptomics. The relative predictive values and robustness of the genetic scores were assessed in external validations of European, Asian and African American ancestries; longitudinal stabilities of the genetic score performances were established across ancestries; and the utility of the multi-omic genetic scores was demonstrated by elucidating the relative genetic control of biological pathways and by identifying disease associations from a phenome-wide scan of predicted multi-omic data in UK Biobank. Finally, we developed an open resource OmicsPred (OmicsPred.org) to publicly disseminate and continuously enhance the value of multi-omic genetic scores.

While the utility of predicted transcriptomic data for cohorts with genome-wide genotype data has been demonstrated[1], our work substantially extends these foundations using a large multi-omic cohort, quantifying both intra- and inter-ancestry reliability of proteomic and metabolomic genetic scores across multiple platforms. We generated a predicted multi-omic dataset for UK Biobank and showed that PheWAS can uncover many known and novel omic associations with disease. In turn, this raises the question of what is a meaningful predictive value for a genetic score - for which, given each user's own particular application, there is no simple answer. Given that the increase in sample size required to detect an association for a noisy explanatory variable can be estimated by n/R (where n is the sample size required if no measurement error exists and R is the reliability coefficient)[11], even genetic scores of apparently low predictive value may be powerful enough to detect true associations at the sample sizes of current and forthcoming biobanks. This suggests that large biobanks could reliably and efficiently test trait-disease associations using genetically-predicted multi-omic data, before committing to (frequently expensive) data generation.

Our study has limitations. While blood is a key tissue of broad utility, it is likely a correlate and not the main site of causal biomolecular functions. Genetic score validity was generally consistent across cohorts; however, performance was affected by technical factors (e.g. serum versus plasma, batch variations, fasting versus non-fasting samples and genetic variant missingness), participant demographics, genetic factors (e.g. allele frequency and linkage disequilibrium differences) and environmental factors (e.g. dietary

differences). Genetic scores may also pick up differences in molecular traits shared by multiple platforms (e.g. Olink and SomaScan). Despite genetic scores for most shared proteins being consistently predictive across platforms, large differences can be due to technical factors (e.g. binding affinity) (Methods) as assessed in a recent study[15]. The attenuated performance of polygenic scores across ancestries is well-known[50] and our analysis also found this in multi-omics data. Multi-omics for non-European ancestries will become more common, and we see a key role for OmicsPred in facilitating robust genetic scores which enable multi-omic prediction in diverse populations. Given genetic prediction and its methodology is a rapidly evolving field, we further acknowledge that there are many highly sophisticated machine learning approaches, which may improve genetic score performance and/or transferability. We selected Bayesian ridge because it has been shown to perform well relative to other genetic score approaches in both a previous study[7] and a benchmark carried out here. Additionally, Bayesian ridge has been shown to scale well to large numbers of traits, thus improving computational efficiency and consistency with green computing[7,13]. Optimal variant selection thresholds may also vary across traits. Finally, while OmicsPred provides an important initial step towards better understanding of the distributions of clinically or therapeutically important biomarkers under high genetic control, more research is needed to understand to what extent genetic scores for multi-omic traits may one day have clinical utility.

Future avenues for research include the expansion of OmicsPred to additional platforms and/or cohorts, multi-ancestry training for improved prediction, and causal inference. In summary, we have developed, validated and applied multi-omic genetic scores for >17,000 traits and made them publicly accessible via the new OmicsPred resource (OmicsPred.org), facilitating the generation and application of multi-omics data at scale for the wider community.

Methods

INTERVAL cohort and data quality control

The INTERVAL study[2] is a randomised trial of ~50,000 healthy blood donors, who were recruited at 25 centres of England's National Health Service Blood and Transplant (NHSBT) and aged 18 years or older at recruitment. This trial aimed to study the safety of varying frequency of blood donation, and all the participants completed an online questionnaire when joining the study about their demographic and lifestyle, such as age, sex, weight, height, alcohol intake, smoking habits, and diet, etc. This trial is registered with ISRCTN, number ISRCTN24760606. All participants have given informed consent and this study was approved by the National Research Ethics Service (11/EE/0538).

In total, 48,813 INTERVAL samples were genotyped using the Affymetrix UK Biobank Axiom array in ten batches, which assays approximately 830,000 variants. The variants were phased using SHAPEIT3 and imputed on a combined 1000 Genomes Phase 3-UK10K reference panel. Affymetrix implemented standard QC procedures during the genotype calling pipeline, excluding samples with poor signal intensity (dish QC < 0.82) and samples with low call rate (< 97%) based on ~20,000 high quality probesets. Variants were excluded if they had low call rate (< 95%), had more than three clusters (indicative of off-target

measurement), had cluster statistics (Fisher's linear discriminant, heterozygous cluster strength, homozygote ratio offset) indicative of poor quality genotyping or were complicated multi-allelic variants that couldn't easily be called. Then within-batch sample and variant QC was performed, where non-best probesets were excluded to leave a single probeset per variant. As visual inspection of cluster plots had identified that some variants, particularly rare variants, had minor allele homozygotes incorrectly called due to the presence of an extreme intensity outlier, we failed variants from a batch if: 1) the variant had fewer than ten called minor allele homozygotes; 2) the cluster plot contained at least one sample with an intensity at least twice as far from the origin as the next most extreme sample; 3) the outlying sample (s) had an extreme polar angle (< 15 or > 75 degree) in the direction of the minor allele. We excluded duplicate samples and samples that were clearly not of European ancestry using a set of high-quality autosomal variants, defined as those with: MAF > 0.05, HWE p-value > $1x10^6$, and $r^2 \leq 0.2$ between pairs of variants. Duplicate samples were defined as those with $\widehat{\pi} \geq 0.9$ using the PLINK v1.9 Method-of-Moments identity-by-descent approach[51] and non-Europeans were defined as those with scores on genetic PC1 or genetic PC2 < 0 following a PCA including INTERVAL samples with 1000 Genomes major ancestry populations[52]. More details on the genotyping and sample quality control for INTERVAL data can be found in the previous study[53]. After quality control steps, it finally results in 10,572,788 variants for 43,059 samples. The number of valid samples in each platform for genetic score construction (Extended Data Table 1) excluded samples that did not pass the QC.

Using the aptamer-based SomaScan assay (version 3), this study profiled plasma proteins of 3,562 participants in two batches (n=2,731 and n=831), of which 3,175 samples remained for analysis after quality control. The detailed steps for measurements and quality controls of the protein levels using the SomaScan array in INTERVAL have been previously described[4,54]. In summary, the relative concentration of 3,622 proteins (or protein complexes) targeted by 4,034 modified aptamers (*SOMAmer reagents*, referred to as SOMAmers) on the array were measured from 150-μl aliquots of plasma at SomaLogic Inc. (Boulder Colorado, US). Quality control was performed at the sample and SOMAmer levels by Somalogic, which uses the control aptamers and calibrator samples to correct for systematic variability in hybridization, within-run and between-run technical variability. For this study, we did not exclude protein aptamers with greater than 20% coefficient of variation in either batch, but excluded these aptamers targeting non-human proteins. We also excluded aptamers that, since the original quantification in INTERVAL, had been (1) deprecated by SomaLogic; (2) found to be measuring the fusion construct rather than the target protein; or (3) measuring a common contaminant[4], which finally filtered the data to 3,793 high quality aptamers targeting 3,442 proteins. Within each batch, the relative protein abundances were natural log-transformed, and then adjusted for age, sex, the first three genetic principal components and duration between blood draw and sample processing (binary, 1 day vs >1 day). The protein residuals from this linear regression were finally rank-inverse normalized and used as phenotype values for their GWAS, which has been previously reported in detail[54]. These normalized phenotype values were further adjusted for batch effect and the first 10 genetic principal components, which were used as the phenotype values for the genetic score model training and internal validation (Supplementary Table 8).

Using Olink proximity extension assays[55], the INTERNAL study measured plasma protein abundance of ~5,000 samples on four Olink panels: *Inflammation-1* (INF-1), *Cardiovascular II* (CVD-2), *Cardiovascular III* (CVD-3), and *Neurology* (NEUR) panel, each of which includes 92 proteins. For the INF-1, CVD-2 and CVD-3 panels, samples were assayed in two equal batches and their protein levels were pre-processed and quality controlled by Olink using NPX Manager software. Protein levels were then regressed on age, sex, sample measurement plate, time from blood draw to sample processing (number of days), season (categorical: spring, summer, autumn, winter), and inverse rank normal transformed. Details of quality control and GWAS for proteins on these three panels were given in the previous work[56]. Due to timing and funding differences, the NEUR panel was treated separately from other 3 panels for QC purposes. In detail, samples were assayed in one large batch, and trait levels were also processed by the NPX software and final measurements were presented as NPX values on a $\log_2$ scale (i.e. a one unit increase represents a doubling of protein level). We removed 187 measurements flagged by Olink as potentially having technical issues and 147 samples of potentially non-European origin as determined by principal component analyses, which left 4,811 measurements proceeding to standard QC assessments. We also checked for missing measurements and measurements below the limit of detection. No missing measurements were found. 8 out of 92 proteins had values below the limit of detection (LOD), of which 4 (HAGH, BDNF, GDNF, CSF3) had more than 5% of measurements below the LOD so were not taken forward for further analyses. No participant had more than 4% of protein measurements below LOD, and we did not observe over-representation of particular proteins below LOD for specific participants. Protein measurements were then adjusted for age, sex, season when blood sample drawn (spring, summer, fall and winter) and the first 10 genetic PCs, residuals of which were further inverse normal rank transformed for their association analyses. We ran association tests using SNPTEST (v.2.5.2), with method “expected”, filtering out variants with a minor allele count (MAC) < 10 for analyses. It was noted that there are a small number of shared proteins across the four Olink panels (detailed numbers of proteins and participants per panel after QC were given in Supplementary Table 9). To avoid duplication in genetic score construction, these shared proteins were merged by averaging their protein levels on each sample across panels, and taken as a unique protein. All the genetic variants identified in GWASs for the same protein across multiple panels were combined (if different) for its genetic score development. The normalized proteins levels of 308 unique proteins were adjusted for the first ten genetic principal components (if not adjusted previously), which were used as phenotype values for genetic score model construction and testing in INTERVAL.

The DiscoveryHD4® platform (Metabolon, Inc., Durham, USA) was used to measure plasma metabolites of INTERVAL participants. Four sub-cohorts of 4,316 4,637, 3,333 and 4,802 participants were created through random sampling from the INTERVAL study and metabolites were measured within the four sub-cohorts (or batches) separately at two time phases of the study (two batches at each phase). Samples of the first two batches were used as training data for GWAS and genetic score development of metabolite traits in the platform, and samples of the other two batches were held out for external validation purpose. The two subsets of INTERVAL data were put through the same quality control

process as described below before performing training or validation. No significant technical variability was found between batches and hence batches within a subset (i.e. phase 1 or 2) were merged prior to the QC and genetic analysis including batch as a covariate to adjust for any residual batch effects. In the first step, samples with missing values for each of the ion-counts for a specific metabolite fragment ('OrigScale') were identified. These sample specific metabolite values were set to missing within the scaled and imputed data ('ScaledImpData'), which contains for each metabolite the values within the OrigScale median normalised for run day (median set to 1 for run-day batch). Metabolites were then excluded if measured in only one batch or in less than 100 samples. Metabolite values were then winsorized to 5 standard deviation from the mean where the values exceeded mean +/−5 × standard deviation of the metabolite. Each metabolite was then log (natural) transformed prior to calculating the residuals adjusted for age, sex, Metabolon batch, INTERVAL recruitment centre, plate number, appointment month, the lag time between the blood donation appointment and sample processing, and the first 5 genetic principal components. Prior to the genetic analysis, these residuals were standardised to a mean of 0 and standard deviation of 1. GWASs were then performed for each trait using the standardised trait values on samples of the first two batches, details of which were described in the previous study[57]. Finally, the standardised metabolites levels of the two INTERVAL subsets (batches 1+2 and batches 3+4) were further adjusted for the first 10 genetic principal components, and then used for genetic scores training and external validation respectively.

The Nightingale Health NMR platform was used to assay baseline serum samples of 45,928 INTERVAL participants and quantified 230 analytes in total, which are largely lipoprotein subfractions and ratios, lipids and low molecular weight metabolites. This study only focused on the 141 directly measured analytes and excluded those derived from other analytes. Apart from the missing values for low abundance analytes, the dataset also included zero values for some analytes, which were recoded as missing in our analysis. In addition, those analyte values of participants that had abnormally high/low values of more than 10 SD from the analyte mean across all participants were set as missing too. We further excluded participants with >30% analyte missingness and duplicate samples. Participants that failed genetic QC (see above) or did not have relevant phenotype data available were also removed, which resulted in 37,359 participants remaining in the analysis. Values of each analyte were log (natural) transformed and adjusted for age, sex, recruitment centre, processing duration, month of donation, appointment time, missing appointment time (Yes or No) and the first 10 genetic principal components. The residuals were then inverse normal rank transformed, which were finally used to perform GWAS of these traits and their genetic score development. Details of quality control and GWAS for these traits can be found in the previous study[58].

RNA sequencing was performed on the NovaSeq 6000 system (S4 flow cell, Xp workflow; Illumina) with 75 bp paired-end sequencing reads (reverse stranded) in INTERVAL, which were aligned to the GRCh38 human reference genome (Ensembl GTF annotation v99) using STAR (v2.7.3.a)[59] and obtained the gene count matrix using featureCounts (v2.0.0)[60]. This in total resulted in raw gene-level count data of 60,676 genes (ENSEMBL gene IDs) across 4,778 individuals with 2.03–95.55 million uniquely mapped reads (median: ~24 million). Poor-quality samples with RNA integrity number (RIN) < 4 or read depth < 10

million uniquely mapped reads were removed. Sample swaps and cross-contamination were assessed using match bam to VCF (MBV) method from QTLtools v1.3.1[61], which identified and corrected 10 pairs of mislabelled samples; samples with no clear indication of their matching genotype data were also removed. Genes were retained based on > 0.5 counts per million (CPM) expression threshold in ≥1% of the samples. The filtered count values were converted to trimmed mean of M-values (TMM)-normalized transcript per million mapped reads (FPKM) values[62]. Next, the normalised $\log_2$-FPKM values for each gene were ranked-based inverse normal transformed across samples. We further excluded globin genes, rRNA genes, and pseudogenes. After filtering, a total of 4,732 samples and 19,835 genes were retained for further eQTL analysis. Prior to eQTL mapping, the probabilistic estimation of expression residuals (PEER) method[63] was used to find and correct for latent batch effects and other unknown confounders in the gene expression data. To estimate PEER factors independent of the effects of known variables, a set of 22 covariates of interest was included in the analysis. These were age, sex, BMI, and blood cell traits (N=19), including: (1) Basophil percentage (of white cell count); (2) Eosinophil percentage(of white cell count); (3) Lymphocyte percentage (of white blood cell count; (4) Monocyte percentage (of white blood cell count); (5) Neutrophil percentage (of white blood cell count); (6) White blood cell (leukocyte) count (reported); (7) Immature reticulocyte fraction; (8) Haematocrit (volume percentage of blood occupied by red cells); (9) Reticulocyte percentage (of red cell and reticulocyte count); (10) Haemoglobin concentration; (11) Mean corpuscular haemoglobin; (12) Mean corpuscular haemoglobin concentration; (13) Mean corpuscular (red cell) volume; (14) Red blood cell (erythrocyte) count (reported); (15) Red cell distribution width; (16) Mean platelet volume; (17) Plateletcrit; (18) Platelet distribution width; (19) Platelet count. The eQTL mapping was performed on genome-wide variants using TensorQTL v1.0.6[64] adjusting for age, sex, BMI, the above-mentioned blood cells traits (N=19), the top 10 genetic principal components, RIN, sequencing batch, RNA concentration, season (based on month of blood draw), and PEER factors (N=20). The normalised gene-level values were also adjusted for the same set of covariates used in the eQTL mapping for their genetic score training and validation. Note that we held out the last two batches of samples for external validation purpose and the first four were used for eQTL mapping and genetic score training/intemal validation.

Correlation and PCA analysis

This analysis included all the traits qualified for genetic score development at each platform and all the training samples in INTERVAL. The same quality control steps and covariate adjustments as genetic score development were applied before analysis. The adjusted trait levels were used to calculate Pearson's correlation r (using scipy v1.5.4 in Python v3.6.8) between traits (Supplementary Fig. 14-18) and perform principal component analysis (PCA) in each platform (Supplementary Fig. 19-23), in which the probabilistic PCA method was used to impute missing trait values and perform the PCA analysis at each platform (using pcaMethods v1.86.0 in R v4.1.3)[65]. We then considered traits in each platform as vertices of an undirected graph and vertices were connected via edges if traits were correlated with $r > 0.9$. Thus, subgraphs in this graph were used to identify groups of highly correlated traits in each of the platforms. In total, we identified 2,225, 299, 700, 29, 13,663 (in total

16,916 groups out of 17,227 traits) highly correlated groups of traits in SomaScan, Olink, Metabolon, Nightingale and RNAseq, respectively (Supplementary Table 10).

External validation cohorts

The FENLAND study profiled the plasma proteins of 12,084 participants using the aptamer-based SomaScan assay (version 4), in which 8994 participants were genotyped using the same the Affymetrix UK Biobank Axiom array as INTERVAL[15]. The later subset of Fenland participants was used for the genetic score model validation in our study. As FENLAND and INTERVAL applied two different versions of the SomaScan array (versions 3 and 4), we matched aptamers (or SOMAmers) between the two studies by using their unique SomaScan IDs, which resulted in 2129 matched results. The detailed QC steps for protein measurements, genotype imputation and QC for genotype data in the FENLAND study were described in the previous study[66]. The Fenland study was approved by the National Health Service (NHS) Health Research Authority Research Ethics Committee (NRES Committee – East of England Cambridge Central, ref. 04/Q0108/19), and all participants provided written informed consent. Both the Orkney Complex Disease Study (ORCADES)[17] and Northern Sweden Population Health Study (NSPHS)[16] have measured plasma protein levels of their participants on the four Olink panels that were used in INTERVAL, and whole genome sequenced or genotyped participants (Supplementary Table 11). Thus, participants of the two studies were used to validate genetic score models of Olink proteins considered in our study, where gene names of proteins were used to match proteins between studies. For those proteins that appeared in two or more Olink panels, their validation measurements were averaged across panels for the protein. Detailed imputation and QC steps for protein abundance measurements and genetic data in the two studies were described in the previous studies[67,68]. Protein levels in ORCADES were adjusted for age, sex, plate, plate row, and plate column, sampling year and season, top 10 genetic principal components and kinship using a linear additive model. Similarly, protein levels in NSPHS were adjusted for age, age^2, sex, plate number, plate row, plate column, the first 10 genetic principal components. The model residuals after adjustment in both cohorts were inverse rank normalised before used for validation analyses. The ORCADES study was approved by the South East Scotland Research Ethics Committee, NHS Lothian (reference: 12/SS/0151) and the NSPHS study was approved by the local ethics committee at the University of Uppsala (Regionala Etikprövningsnämnden, Uppsala, Dnr. 2005:325 with approval of extended project period on 2016-03-09). All participants gave their written informed consent in both studies.

In ORCADES, the same platform Metabolon HD4 as INTERVAL was used to measure 1,143 blood metabolites of 1,046 participants in June 2018. Metabolite measurements were normalised by Metabolon in terms of raw area counts and rescaled to set the median equal to 1. There were 221,102 metabolite values below the limit of detection (18.5%), which were set to zero after the following quality control steps. In the quality control, we firstly removed 521 metabolite values which exceeded 10 standard deviations from their respective means (0.04%). At most, a single participant carried no more than 30 such outliers (2.6% of all metabolites), and all individuals were therefore included in the analysis. Next, we identified 94 metabolites of which fewer than 100 participants exceeded the

limit of detection (8.2%). These poorly measured metabolites were excluded, leaving 1,049 metabolites measured in 1,046 individuals for analysis. Metabolite levels were adjusted for age, sex, BMI, genotyping array, season of venepuncture, year of venepuncture, sample volume available, sample volume extracted, plate, row, column and top 20 genetic principal components, where genotyping array indicates whether the individual was genotyped using the Illumina Human Hap 300v2, Illumina Omni Express, or Illumina Omni 1 arrays; sample volume available is the volume of the blood sample delivered to Metabolon; sample volume extracted is the volume of the blood sample used to measure the metabolite abundance; and plate/column/row refer to the plate box number and sample well position (row and column), and model residuals were then inverse rank normalized before used for the validation analysis. A total of 1,007 participants had complete covariates. We used COMP identifier in the platform to match metabolites between INTERVAL and ORCADES, which resulted in 455 overlapped metabolites.

The UK Biobank, ORCADES and the VIKING health study[18] were used as external cohorts to validate genetic scores of Nightingale traits, and traits identifiers provided in the platform were used to successfully match all 141 traits between these studies and INTERVAL. Quality control for these traits in UK Biobank has been described previously in details[69], and levels of these traits were adjusted for sex age, BMI, use of lipid lowering medication, top 10 genetic PCs and technical variance following the protocol of the previous study[69] and only genetically defined European participants[3] were included in the validation analyses.

In ORCADES, 2,055 participants had 249 blood metabolites measured in December 2020 using the same Nightingale NMR platform as INTERVAL. In total, 2070 samples were measured, with 15 participants having multiple measurements; for these participants, the mean value was used. We removed 22 participants who did not have any valid metabolite measurements. For the remaining 2,033 participants, the vast majority had zero missing metabolite values (1,938; 95%), and a small subset had up to 4% missing metabolite values (95; 5%). Conversely, the highest sample missing rate per metabolite was 87 participants (4%). Each metabolite was adjusted by the following covariates in a linear model: age, sex, BMI, season of venepuncture, year of venepuncture, genotyping array and top 20 genetic principal components, where genotyping array indicates whether the individual was genotyped using Illumina Human Hap 300v2, Illumina Omni Express, or Illumina Omni 1 arrays. Model residuals were then inverse rank normalised and used for the validation analysis. A total of 1,884 individuals had complete covariates.

In the VIKING study, 2,104 participants (no duplicates) had 249 blood metabolites measured in December 2020 using the Nightingale NMR platform. We removed 37 participants who did not have any valid metabolite measurements. For the remaining 2,067 participants, the vast majority had zero missing metabolite values (1,911; 92%), and a small subset had up to 4% missing metabolite values (156; 8%). Conversely, the highest sample missing rate per metabolite was 150 participants (7%). Each metabolite was adjusted by the following covariates in a linear model: age, sex, BMI, season of venepuncture, year of venepuncture and the top 20 genetic principal components. Model residuals were then inverse rank normalised and used for the validation analysis. A total of 2,046 individuals had complete covariates. Detailed descriptions on the genetic data and its quality control in

VIKING were provided in the previous study[18]. The study was approved by Research Ethics Committees in Orkney, Aberdeen (North of Scotland REC), and South East Scotland REC, NHS Lothian (reference: 12/SS/0151). All participants gave written informed consent.

The Multi-Ethnic Cohort (MEC) recruited three major Asian ethnic groups represented in Singapore: Chinese, Malays and Indians, between 2004 and 2010 to better understand how genes and lifestyle influence health and diseases differently in persons of different ethnicities[19]. Between 2011 and 2016, the participants were further invited for a follow-up. Analyses on the MEC study were approved by the National University Institutional Review Board (NUS-IRB: LN-18-059 and NUS-IRB-2021-812) and Singapore Population Health Studies Scientific Committee. Whole genome-sequencing was performed on 2,902 MEC participants as Phase I of the Singapore National Precision Medicine Programme (https://npm.a-star.edu.sg/)[70]. Samples were whole-genome sequenced to an average of 15X coverage. Read alignment was performed with BWA-MEM v0.7.17 and variant discovery and genotyping were performed with GATK v4.0.6.0. Site-level filtering includes only retaining VQSR-PASS and non-STAR allele variants. At the sample level, samples with call rate < 95%, BAM cross-contamination rate > 2%, or BAM error rate > 1.5%; at the genotype call level, genotypes with DP < 5 or GQ < 20 or AB > 0.8 (heterozygotes calls), were set to NULL. Finally, samples with abnormal ploidy were excluded. To determine the genetic ancestry of samples, we first performed the principal component analysis on the variant panel of verifyBamID2[71] (1000G, phase 3), and the obtained top 15 genetic PCs and their associated explained variance were used to perform k-means clustering (k=3). An ancestry label (Chinese, Malay, or Indian) was then assigned to each sample based on the major self-reported ethnicity of each cluster. Both SomaScan (version 4) and Nightingale NMR platforms were used to assay baseline and revisit blood samples of participants in MEC. For quality control of Nightingale data, participants with >10% missing metabolic biomarker values were excluded from subsequent analyses. For participants with biomarker values lower than detection level, we replaced values of 0 with a value equivalent to 0.9 multiplied by the non-zero minimum value of that measurement. For quality control of SomaScan data, protein levels were first normalized to remove hybridization variation within a run. This was followed by median normalization across calibrator control samples to remove other assay biases within the run. Overall scaling and calibration were then performed on a per-plate basis to remove overall intensity differences between runs with calibrator controls. Finally, median normalization to a reference was performed on the individual samples with QC controls. During these standardization steps, multiple scaling factors were generated for each sample/aptamer at each step. The final number of samples in each ethnic groups used in our validation were given in Extended Data Table 1. For both SomaScan and Nightingale traits, natural log-transformation was applied before adjusting for age, sex, T2D status, and BMI (Nightingale traits only) and first 10 genetic principal components. Residuals from the regression were inverse-normalised for correlation analyses with genetic scores trained in INTERVAL.

The Jackson Heart Study (JHS) is a community-based longitudinal cohort study begun in 2000 of 5,306 self-identified Black individuals from the Jackson, Mississippi metropolitan statistical area[20,72]. The participants included in our validation of genetic scores for SomaScan proteins are samples collected at Visit 1 between 2000 and 2004 from 1,852

individuals with whole genome sequencing and proteomic profiling (SomaScan) performed, quality controls of which were detailed in the previous studies[20,73,74]. SomaScan IDs were used to match shared proteins between JHS and INTERVAL, which identified 820 proteins in total. Protein levels were adjusted for age, sex and the first 10 principal components of genetic ancestry in JHS, before they were used for evaluating the performance of genetic scores. This study was approved by the JHS Publications and Presentations Subcommittee and the TOPMed Multi-Omics Working group.

In summary, we performed quality controls in each external cohort to ensure the quality of the omic data used for validation and adjusted trait levels for covariates to minimize potential validation bias across cohorts, which include age, sex, genetic PCs, and other cohort-, platform-specific environmental and technical factors (Supplementary Table 11). Note that using Nightingale traits in ORCADES as examples, we found that the control for family structure (e.g. adjustment for kinship) had very minor impact on the validation results (Supplementary Fig. 24), thus we did not consider the control for this factor as essential in the external validation.

Polygenic scoring method

A genetic score is most commonly constructed as a weighted sum of genetic variants carried by an individual, where the genetic variants are selected and their weights quantified via univariate analysis in a corresponding genome-wide association study[75,76]:

$$\widehat{PGS}_i = \sum_{j \in S} \beta_j \times x_{ij} \quad (1)$$

where S is the set of variants, referring to single nucleotide polymorphisms (SNPs) in this study, that are identified in the variant selection step described below; β_j is the effect size of the SNP j that is obtained through the univariate statistical association tests in the GWAS; x_{ij} is the genotype dosage of SNP j of the individual i. As the variant set S is derived through a LD thinning and p-value thresholding process, this method is often named as the P+T. However, P+T relies on hard cut-off thresholds to remove LD correlations among variants and select associated variants. It is often challenging to balance between keeping predictive variants and removing redundant and uninformative variants that can limit the prediction precision. Also, due to the inherent linear assumption of the univariate analysis in P+T, this method leaves no modelling considerations for joint effects between variants. To alleviate these limitations, various machine learning based methods, such as Bayesian ridge (BR), elastic net (EN)[77] and LDpred[78], have been utilized to construct genetic scores for a wide range of traits and diseases[7]. In particular, BR and EN have been shown to outperform other methods when developing scores for predicting biomolecular traits, such as blood cell traits and gene expression[7,9], which are similar to the type of traits considered in this study. We adopted the BR method for the genetic score construction of all the biomolecular traits as BR is more efficient to run in practice (see details below).

Bayesian ridge is a multivariate linear model which assumes that the genetic variants have linear additive effects on the genetic score of the trait[7,79]. In addition, BR also assumes that

the genetic score of a trait follows a Gaussian distribution, and the prior for effect sizes of variants is also given by a spherical Gaussian:

$$p(\widehat{PGS} \mid \boldsymbol{x}, \boldsymbol{\beta}, \alpha) \sim N\left(\widehat{PGS} \mid \sum_{j \in S} x_j \beta_j, \alpha^{-1}\right) \quad (3)$$

$$p(\boldsymbol{\beta} \mid \lambda) \sim N(\boldsymbol{\beta} \mid 0, \lambda^{-1}) \quad (4)$$

where S is the set of input variants, α and λ are coefficients of the model and subject to two Gamma distribution: Gamma(α_1, α_2) and Gamma(λ_1, λ_2). These two prior Gamma distributions can be set via a validation step.

Genetic score training and evaluation

The explained variance (R^2) and Spearman's rank correlation coefficient (Rho) were used to measure the performance of constructed genetic scores in the INTERVAL training samples and external cohorts (or INTERVAL withheld subset), where R^2 scores were calculated using the squared Pearson correlation coefficient (r). Python (v3.6.8) package scipy v1.5.4 was used to derive Rho and r scores, where statistical significance was calculated using two-sided t-test for r and using two-sided Mann-Whitney U test for Rho. We adopted a similar strategy for sample partition when training and evaluating genetic scores within the training samples as previous studies[7,9] that utilised learning-based methods to construct genetic scores for molecular traits. The training samples of a trait were randomly and equally partitioned to five subsets, from which any four subsets are used as true-training data to learn a genetic score model of the trait, and test the model's performance on the remaining 20% of samples (Extended Data Fig. 1). Given a genetic scoring method and a trait, we obtained five different genetic score models of the trait and the mean of their performance measurements in the corresponding testing samples in INTERVAL was reported (internal validation). Note that, due to the high similarities between the five genetic score models trained for most traits, only one model was randomly selected from the five and evaluated in the external cohorts (or INTERVAL withheld set for Metabolon).

When training genetic score models using BR method, we need to select two appropriate prior gamma distributions, i.e. α_1, α_2, λ_1 and λ_2. To do so, a grid search across a set of optional hyperparameters are often performed, however, this searching process is resource and timeintensive, which makes it challenging to run for tens of thousands of multi-omic traits. To address this problem, we randomly selected subsets of SomaScan, Olink and Metabolon traits (20 each), on which we trained and internally validated genetic scores on any α_1, α_2, λ_1 and λ_2 taken from $\{0, 10^{-10}, 10^{-5}, 10^{-3}, 10^{-1}, 10, 10^3\ 10^5, 10^{10}\}$. The results suggested that using non-informative priors[80] (α_1, α_2, λ_1 and $\lambda_2 \in \{0, 10^{-10}, 10^{-5}, 10^{-3}\}$) performed as good as that of using the best-performing hyperparameters selected through extensive search (Supplementary Fig. 25-28). We further externally validated the performance of genetic scores developed using non-informative priors (α_1, α_2, λ_1 and $\lambda_2 = 10^{-5}$) and the best-performing priors selected in internal validation for each of the 20 Metabolon traits on INTERVAL withheld set, which showed they have nearly identical R^2

performance (Supplementary Fig. 28b). Therefore, we adopted the non-informative priors (α_1, α_2, λ_1 and $\lambda_2 = 10^{-5}$) in BR for genetic score development of all other traits. We further note that our approach also minimises the risk of collider bias, for example by using BR to re-estimate the weights for all genetic variants passing univariate genome-wide significance, then performing external validation using only minimal covariates (sex, age and genetic PCs).

Variant selection and method comparison

Selecting a proper set of variants and feeding into a polygenic scoring method are a key step for effective genetic score construction. To do so and further confirm the superiority of BR method, we looked at the performance of BR and P+T on a variety of variant selection schemes for the traits in three platforms (SomaScan, Olink and Metabolon), where Python (v3.6.8) packages scikit-learn v0.21.2, pandas v1.1.5 and numpy v1.19.5 were used to implement BR for genetic score training.

To ensure the generalizability of genetic score models when applied to other cohorts, a variant filtering step was first performed for all the traits considered, which applied a MAF threshold of 0.5% and excluded all multi-allelic variants as well as ambiguous variants (i.e. A/T, G/C) in INTERVAL. To remove LD dependencies among variants, a follow-up LD thinning step was carried out at an r^2 threshold of 0.8 on all the variants for both BR and P+T methods using *indep-pairwise* in Plink v2.0[51]. The remaining variants were then filtered at given p-value thresholds (from their GWAS summary statistics conducted on the INTERVAL training data) for a trait in different platforms as inputs of BR and P+T. To identify an appropriate variant selection scheme for the use of all the biomolecular traits, we attempted the following four p-value thresholding schemes for protein traits in Olink and SomaScan platforms: (1) p-value $< 5 \times 10^{-8}$ on all the variants; (2) p-value $<5 \times 10^{-8}$ on variants in the *cis* region only (within 1MB of the corresponding gene's transcription start site); (3) all the *cis* variants only; (4) all the *cis* variants and p-value $< 1 \times 10^{-3}$ on the *trans* variants; and the two different p-value thresholds on the genome-wide variants for metabolite traits in the Metabolon platform (as they do not distinguish *cis* and *trans* regions): (1) p-value $< 5 \times 10^{-8}$; (2) p-value $< 1 \times 10^{-3}$.

Then, we compared the performance of BR and P+T on these variant sets in the internal validation (Supplementary Fig. 1-3). Regarding the proteomic traits (SomaScan and Olink), the two variant selection schemes: (1) p-value $< 5\times10^{-8}$ on genome-wide variants and (2) all the *cis* variants and p-value $< 1\times10^{-3}$ on the *trans* variants, were shown to be the best performing schemes with either of the methods; BR method largely outperformed P+T across the two variant selection schemes. Meanwhile, it was noted that the two selection schemes led to greatly different performance, with the latter scheme achieving an unrealistic mean R^2 of ~0.74 across all the proteins (only ~0.09 for the former scheme). Similarly, for the metabolomic traits (Metabolon), the applied two variant selection schemes significantly differ in their performance in internal validation, and BR was also shown to be a better performing method.

To further identify the optimal variant selection scheme for BR, we also looked at the performance of genetic score models trained with the two identified (for proteins) or all

the two applied (for metabolites) schemes using BR method for Olink traits and Metabolon traits (Fig. 2 and Supplementary Fig. 4) in external cohorts (NSPHS and ORCADES) or withheld INTERVAL data. Despite the second scheme (all the *cis* variants and p-value < 1×10^{-3} on the *trans* variants for proteins, or p-value < 1×10^{-3} on genome-wide variants for metabolites) showed outstanding performance in internal validation, its performance saw a dramatic decline in external validation for almost every trait validated (Supplementary Fig. 4). It indicates this variant selection scheme caused an overfitting problem in genetic score training, which is consistent with previous findings when using overly lenient p-value thresholds for variant selection[7].

The performance of BR (variant set with p-value threshold of 5×10^{-3}) was further benchmarked alongside P+T (p-value thresholds of 5×10^{-3} and 1×10^{-3}) and LDpred2[81] for a random subset of 20 Metabolon traits in the INTERVAL withheld set. We used the LDpred2-auto model to train genetic scores, where R (v3.6.1) package bigsnpr v1.10.8 was used to implement LDpred2-auto, and summary statistics from GWAS in the training samples and the recommended Hapmap3 variant set were used as model inputs. All the INTERVAL samples, excluding those withheld for independent validation, were used to obtain the variant-variant correlation matrix for LDpred2. Our results showed that BR outperformed P+T. While LDpred2 showed similar R^2 as BR for most traits, some were substantially attenuated in the withheld set (Extended Data Fig. 2). Additionally, our benchmark results showed BR, P+T and LDpred2-auto have an average running time of 3.1 seconds (2 CPU cores), 2.9 seconds (2 CPU cores) and 51 minutes (20 CPU cores) per trait respectively on the Cambridge Service for Data-Driven Discovery platform (www.hpc.cam.ac.uk), showing that BR performed well in both performance and scalability.

These results suggested that the BR method with the variant selection scheme of p-value < 5×10^{-8} on genome-wide variants was the optional method (of those tested) for genetic score development of these biomolecular traits, thus we applied this approach to all other traits for their genetic score development in this study. We noted that the optimal variant set had been selected using a much larger p-value threshold in the previous study[7], which could be due to there is an order of magnitude difference in training sample size and greater polygenicity of the traits as compared to the current study.

Longitudinal stability of genetic scores

Within MEC, 1,739 individuals were measured at both baseline and revisit with mean length of follow-up 6.31 years (SD 1.45 years). This allowed longitudinal assessment of the stability of genetic scores for SomaScan (N = 403 Chinese, 356 Indian and 353 Malay) and Nightingale (N = 721 Chinese, 376 Indian and 363 Malay) platforms. For SomaScan traits, we found strong consistency between the predictive capacity of genetic scores between baseline and revisit samples (Pearson r = 0.99 for Chinese, 0.98 for Indian and 0.98 for Malay populations), and little difference in longitudinal stability between ancestries (Extended Data Fig. 7d-f). For Nightingale traits, despite variation in the predictive capacity of genetic scores between baseline and revisit samples, the longitudinal stability was still largely consistent between Indian and Malay ancestries (Pearson r = 0.60 for Chinese, 0.84 for Indian and 0.85 for Malay populations; Extended Data Fig. 7a-c).

Genetic score cross-platform performance

SomaScan and Olink used two different technologies for protein level measurement. The two platforms measured many proteins in common, among which there are 169 unique proteins whose genetic scores we have validated. To check the impact of technologies on genetic prediction, we looked at how the genetic scores trained on one platform can predict protein levels from the other platform on the INTERVAL training samples (Supplementary Fig. 29). We confirmed that performance of these overlapped genetic scores trained in the other platform was generally consistent with that of the scores trained in their original platform. However, we did observe, in some cases, the genetic scores trained in the two platforms can lead to very different predictions, for which we found that they are mainly due to the differences in what the two platforms are actually quantifying. For example, among the 169 proteins, there are 11 proteins in SomaScan that had a $R^2 > 0.3$ in internal validation, in which 10 proteins also achieved a $R^2 > 0.3$ but the remaining protein (CHI3L1) received a poor $R^2 < 0.1$ when predicting with Olink genetic scores. We found that the remaining protein received the lowest Pearson's *r* score among the 11 proteins between their actual protein levels measured in the two platforms. In INTERVAL, there were ~700 participants (depending on the protein) who were assayed by both SomaScan and Olink, which allowed us to calculate the correlations between the actual protein levels measured by the two platforms for the same protein. These results suggested, despite great consistency, genetic scores of the same protein trained in the two platforms can represent distinct aspects of protein biology of prediction and integration of diverse proteomic techniques may enable to develop better genetic scores for these proteins[82]. Similarly, we have also investigated the predictive performance of our Nightingale genetic scores on the biochemistry assay data in UK Biobank for overlapping biomarkers. We found the performances of these INTERVAL-trained genetic scores were largely robust with respect to measurement technology (Supplementary Fig. 30).

Pathway coverage analysis of proteins

In this analysis, SomaScan and Olink proteins were combined based on their Uniprot ID, where duplicate proteins were removed if identified. We only kept proteins with $R^2 > 0.01$ in internal validation, resulting in a total of 2,205 unique proteins for the analysis. We used pathway data of Homo sapiens curated at Reactome[21] and conducted analyses to uncover the coverage of these proteins in the pathways. In detail, this analysis looked at the percentages of these proteins in annotated physical entities of each super-pathway, and the percentages of the lowest-level pathways these proteins covered among all the lowest-level pathways of each super-pathway. Where at least one protein in this study were included in entities of a lowest-level pathway, we considered this pathway is covered by proteins of this study.

Phenome-wide association analysis in UKB

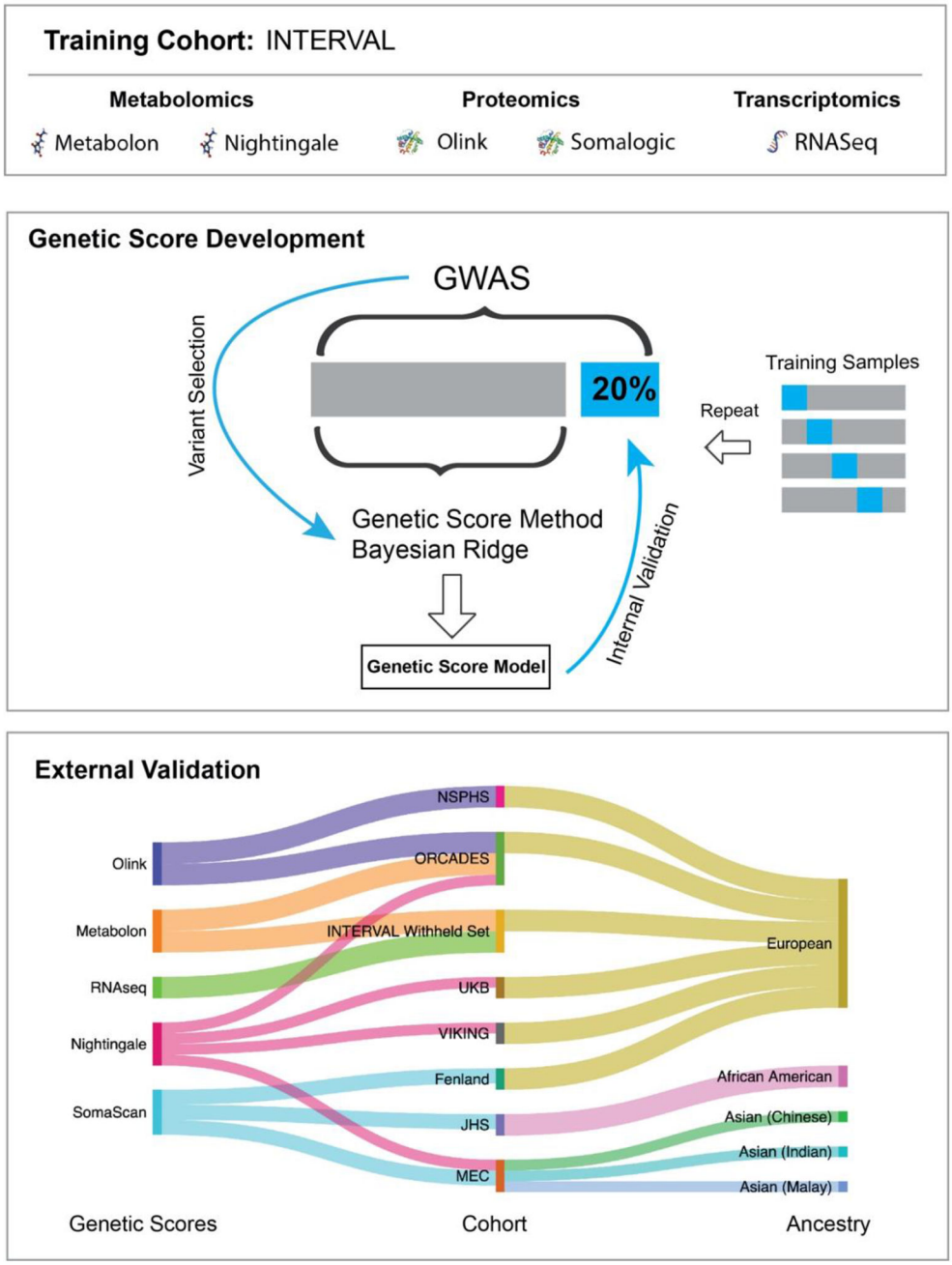
We included biomolecular traits with $R^2 > 0.01$ in internal validation in this analysis (11,576 traits in total) and considered only participants of European ancestry in UKB (the White British subset). We used the version 3 of imputed and quality controlled genotype data for UKB, which were detailed in the previous study[3]. Using version 1.2 of the PheWAS Catalog[22], we extracted the curated phenotype definitions of all phecodes. Each phecode is

provided as a set of WHO International Classification of Diseases (ICD) diagnosis codes in versions 9 (ICD-9) and 10 (ICD-10) of the ontology to define individuals with the phenotype of interest, and a set of related phecodes that should be excluded from the control cohort of unaffected individuals. To define cases for each phecode, we searched for the presence of any of the constituent ICD-9/10 codes in linked health records (including in-patient Hospital Episode Statistics data, cases of invasive cancer defined in the cancer registry, and primary and secondary cause of death information from the death registry), and converted the earliest coded date to the age of phenotype onset. Individuals without any codes for the phenotype of interest were recorded as controls, and censored according to the maximum follow-up of the health linkage data (January 31, 2020) or the date of death whichever came first. To define the cohort for testing molecular genetic score associations with the age-of-onset of each phenotype, we used the set of events and censored individuals described above and removed any individuals with related phenotypes (based on definitions from the PheWAS Catalog), restricting analyses to be sex-specific (e.g. ovarian and prostate cancer) where requires. To ensure a well-powered study we restricted the PheWAS analysis to phenotypes with at least 200 cases in the 409,703 European ancestry individuals whose reported sex match the genetically inferred sex from the UKB quality controlled genotype data[3], resulting in a set of 1,123 phecodes included in the final analysis. The association of the genetic score for biomolecular traits with the onset of each phenotype was assessed by using a Cox proportional hazards model with age-as-timescale, stratified by sex and adjusted for genotyping array and 10 PCs of genetic ancestry. The association between genetic scores and each phecode is reported in terms of its effect size (Hazard ratio) and corresponding significance (p-value), and significant results were defined as Benjamini/Hochberg FDR-corrected p-value < 0.05 for all the tested traits (two-sided Wald test). Statistical analyses were performed in Python (v3.6.8) and the Cox model was implemented using the lifelines v0.26.0 package[83].

Carbon impact and offsetting

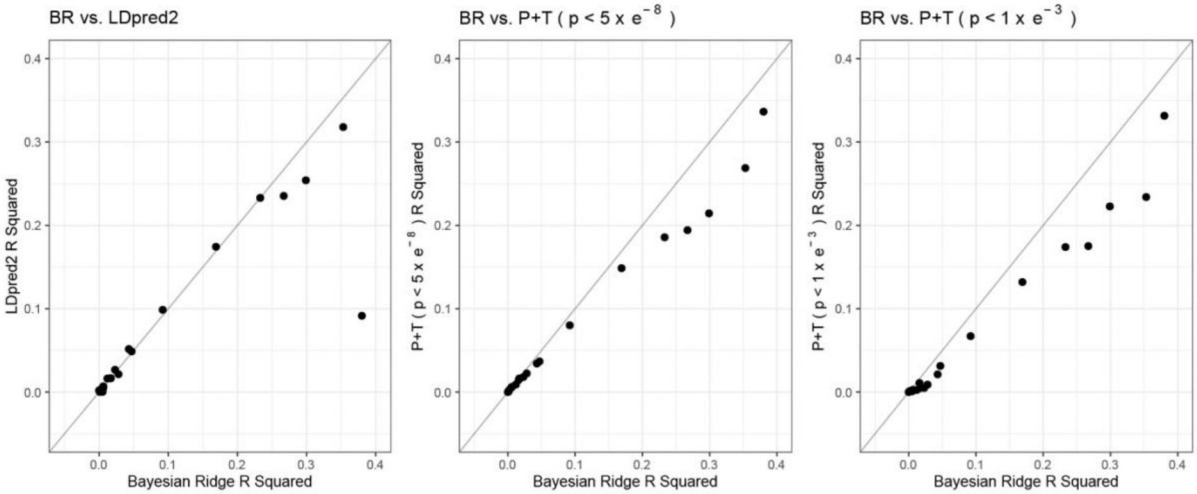
We used GreenAlgorithms v.1.0[84] to estimate that the main computational work in this study had a carbon impact of at least 1,004 kg of CO_2 emissions (CO_2e), corresponding to 94 tree-years. As a commitment to the reduction of carbon emissions associated with computation in research, we consequently funded planting of 45 trees through a local Australian charity, which across their lifetime will sequester a combined estimated ~12,000 kg of CO_2e, or 12 times the amount of CO_2e generated by this study.

Extended Data



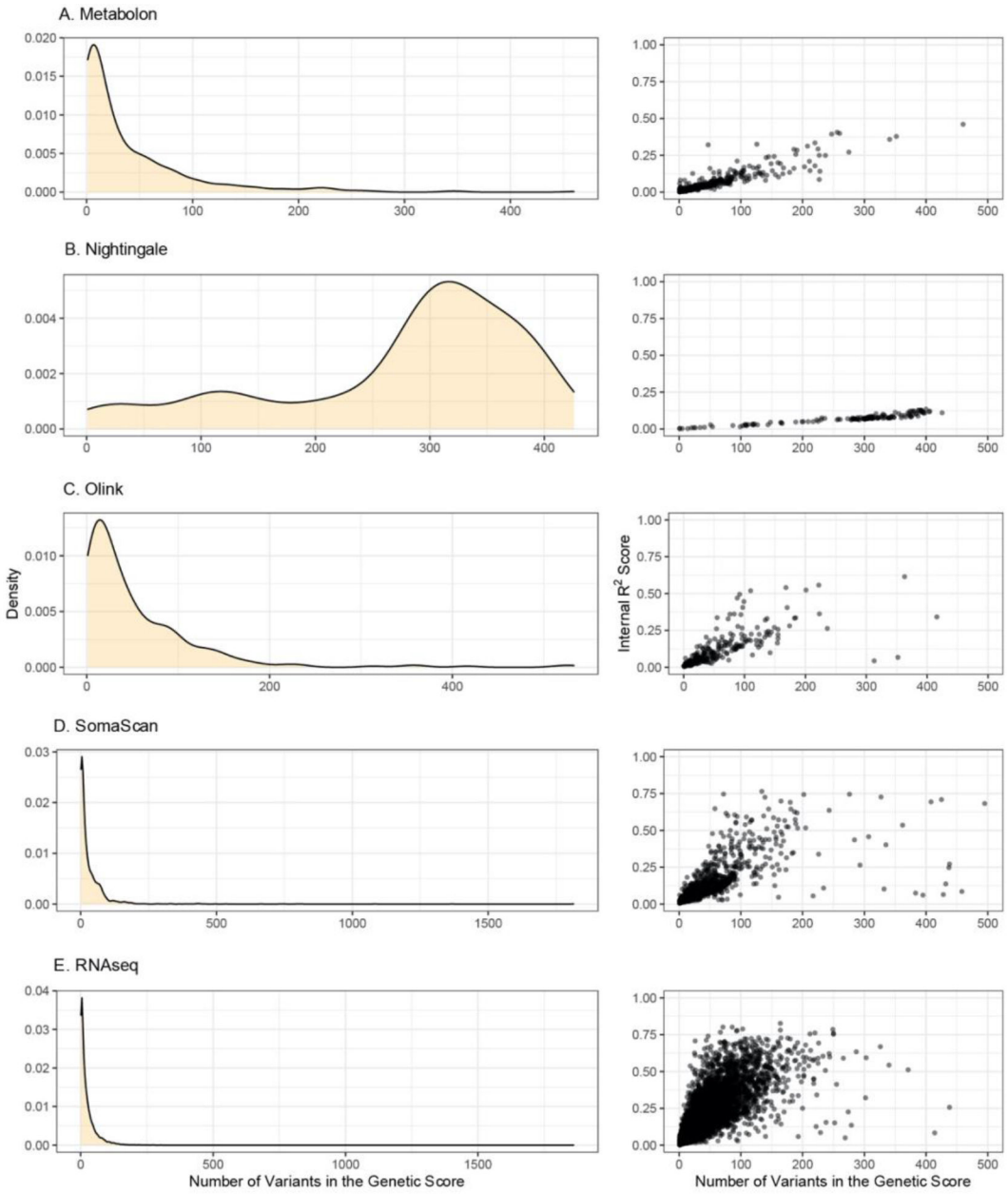
Extended Data Figure 1: Schematic framework for the development and validation of multi-omic genetic scores.

This figure presents the overall study design for the development of genetic scores for multi-omic traits across five platforms (Nightingale, Metabolon, Olink, SomaScan and RNAseq) using INTERVAL data as well as their validation in seven external cohorts of multiple ancestries (European, Asian-Chinese, Asian-Malay, Asian-Indian and African American).



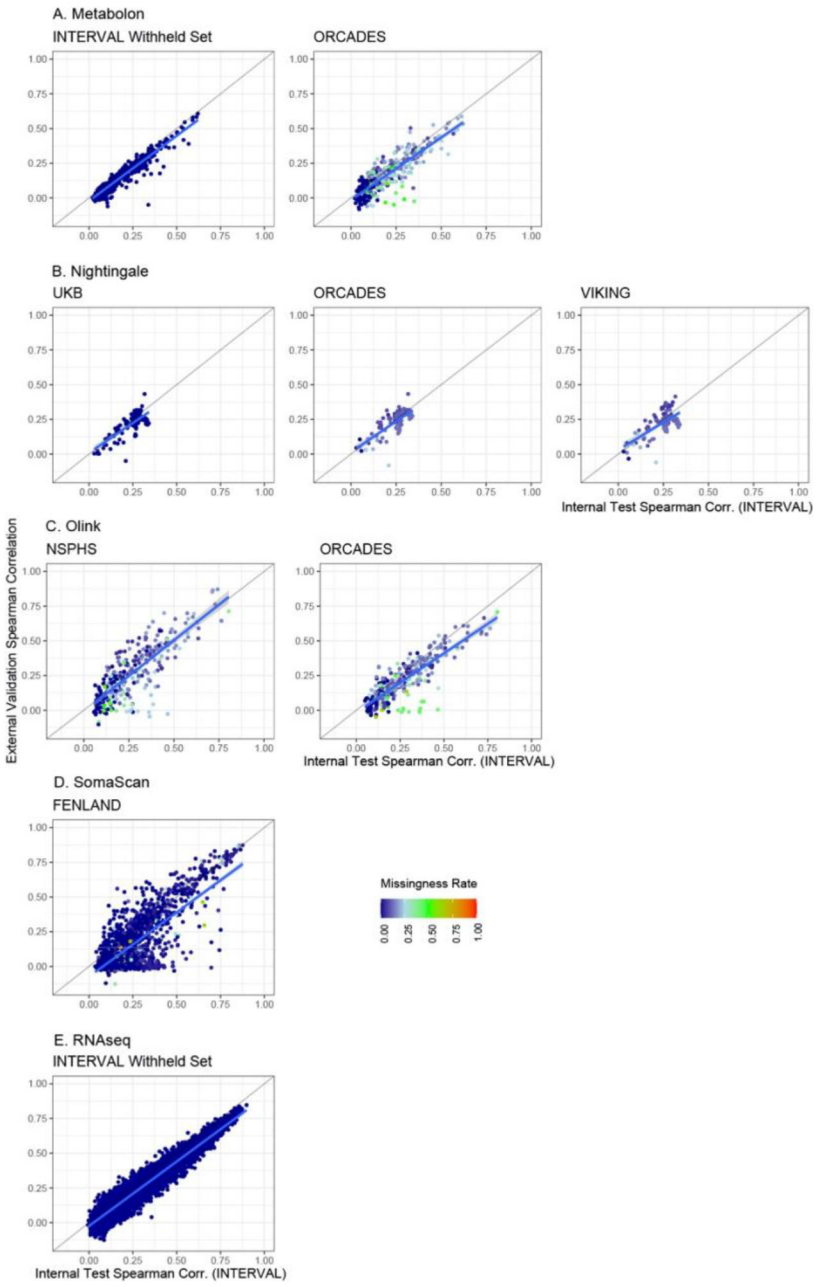
Extended Data Figure 2: R^2 performance comparison between Bayesian ridge, LDpred2, P+T for Metabolon traits in external validation (INTERVAL withheld set).

This figure compares the R^2 performance between BR (on the set of genome-wide variants with p-value < 5×10^{-8}; x-axis) and LDpred2 (Hapmap3 variant set), and between BR and P+T (variant sets of two p-value thresholds: 5×10^{-8} and 1×10^{-3}) for 20 randomly selected Metabolon traits in external validation (INTERVAL withheld set; Methods). P-values in the GWAS for omic traits were derived by t-test in linear regression and all tests were two-sided.



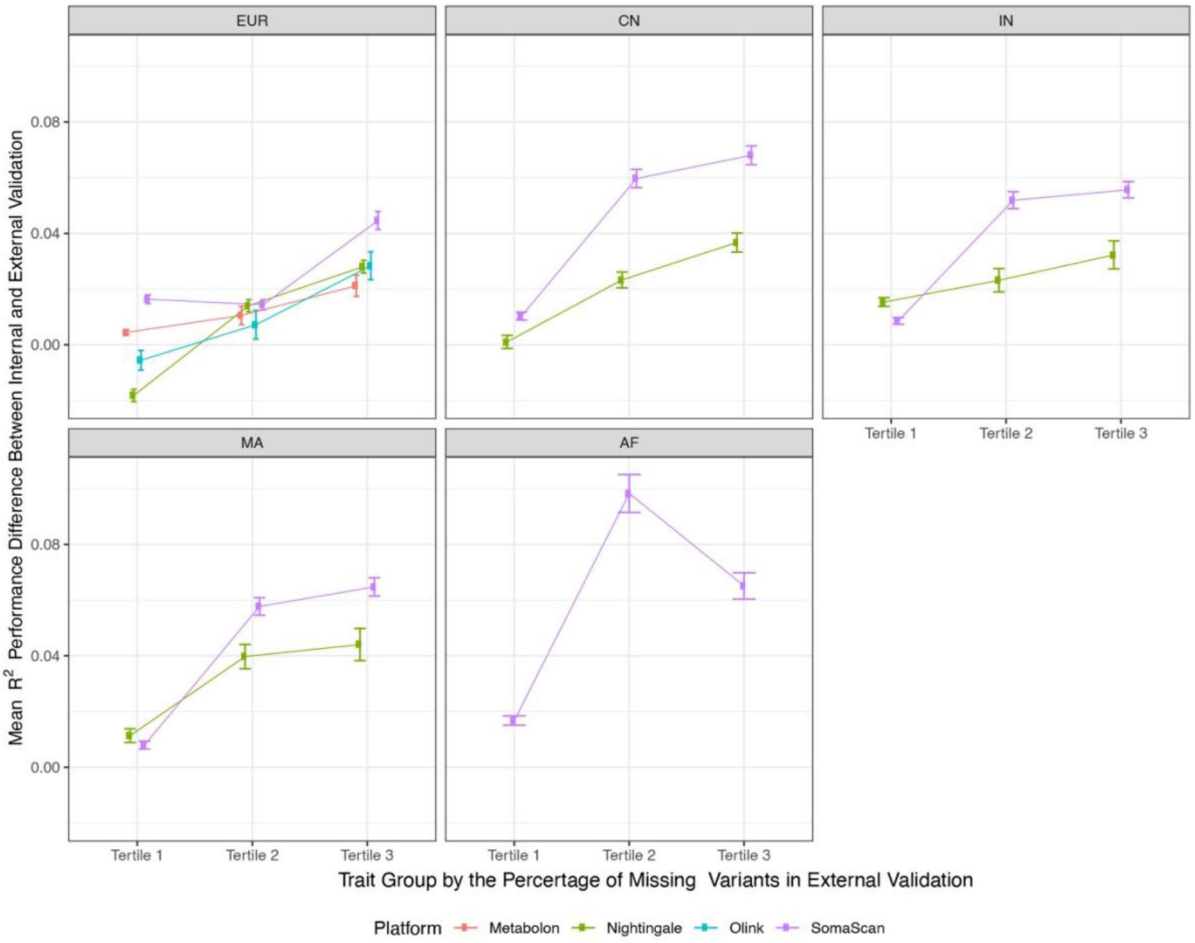
Extended Data Figure 3: Distribution of the number of variants in the genetic scores and the correlations between performance (R^2) of genetic scores and the number of variants comprising the score.

The density plots show the distribution of the number of variants comprising the genetic scores at each platform. The scatter plots show the change of R^2 score in the internal validation by the number of variants in the genetic score model.



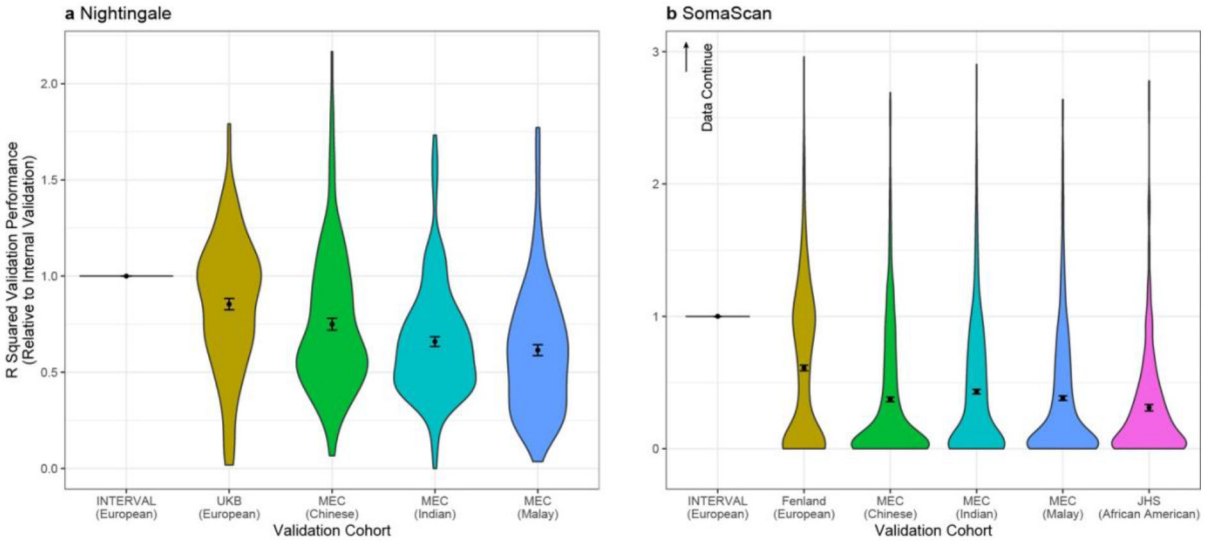
Extended Data Figure 4: Validation of genetic scores in external European cohorts.

The scatter plots compare the spearman correlation scores between internal validation and external validation with a European cohort on each platform, in which points are coloured by the variant missingness rate in the external cohort and the blue line shows the linear models fitting the data points. This analysis included all the developed genetic scores in this study.



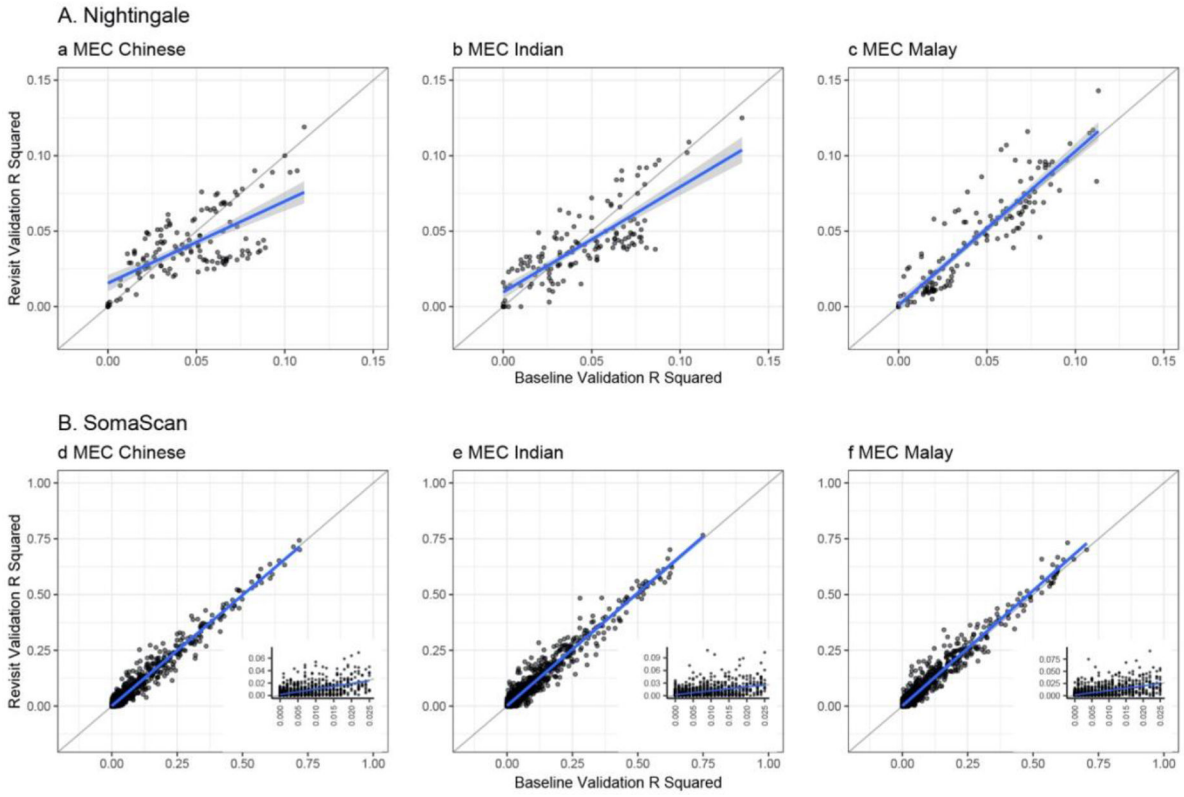
Extended Data Figure 5: Validation performance change of genetic scores by their variant missing rates in external cohorts of different ancestries.

External validation results in European cohorts were merged in each platform to increase the statistical power in this analysis, which include NSPHS and ORCADES validations for Olink, and ORCADES and VIKINGS validations for Nightingale. Note that INTERVAL withheld subset validations and UKB validation for Nightingale traits were excluded in this analysis due to there is no or nearly no variant missingness in these external cohorts. Validation results in each platform were ranked by their variant missing rate of genetic score models in the external cohort and grouped into tertiles, where variant missing rate is the number of variants missing in the validation cohort / the total number of variants in the genetic score. This figure presents the mean and standard error (SE) of R^2 performance change of genetic scores between internal and external validation across tertiles of validation results. The analysis included validation results of 2,129 SomaScan, 603 Olink, 455 Metabolon and 423 Nightingale traits (traits can be overlapped for the same platform across multiple validation cohorts) for European (EUR); 2,047 SomaScan and 139 Nightingale traits for Chinese (CN), Indian (IN) and Malay (MA); 820 SomaScan traits for African American (AF).



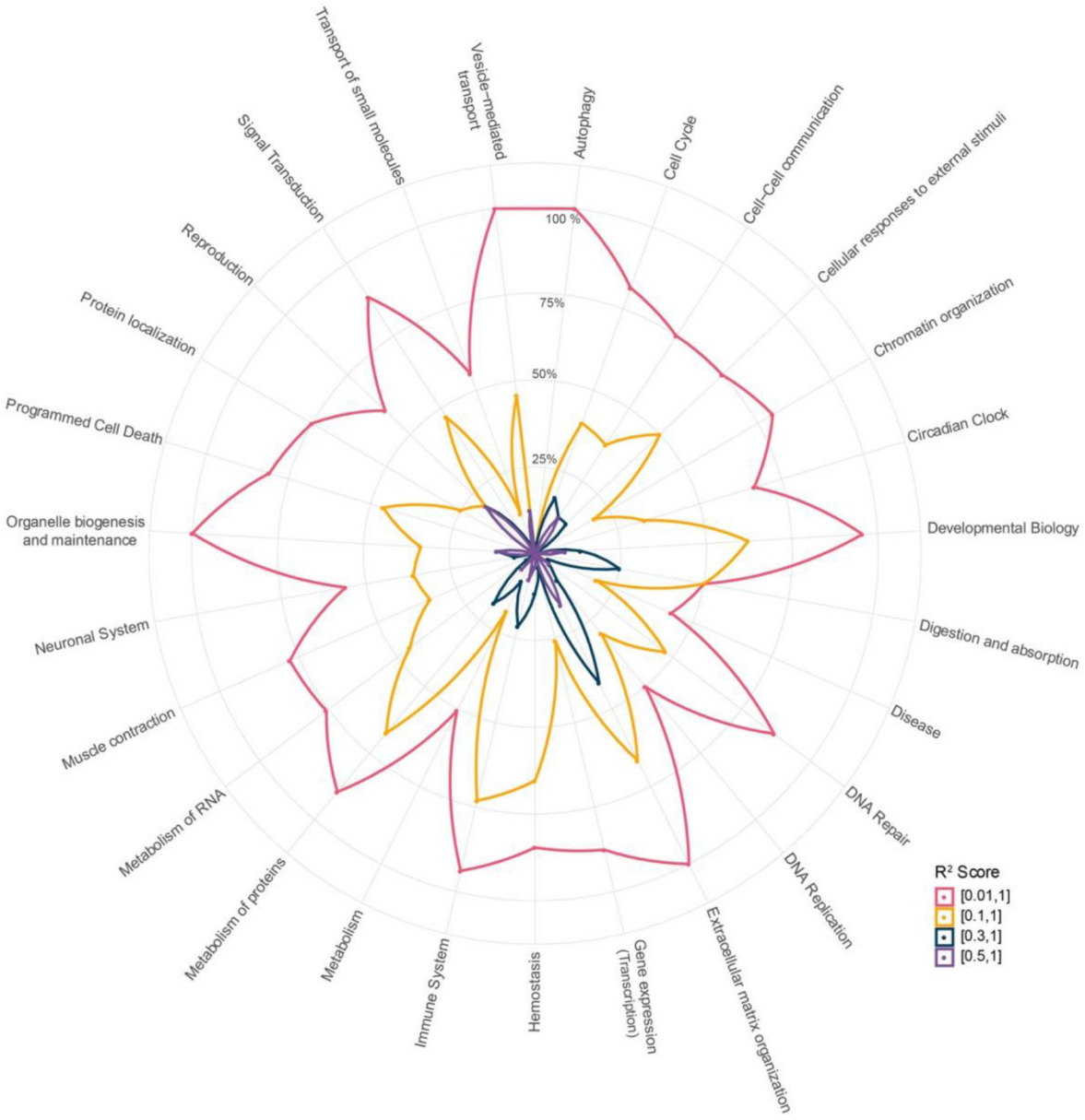
Extended Data Figure 6: Performance (R^2) of genetic scores for Nightingale (a) and SomaScan (b) in external cohorts of various ancestries relative to R^2 in internal validation (INTERVAL).

Transferability was only tested if the genetic score had a significant (two-sided t-test; Bonferroni corrected p-value < 0.05 for all the 17,227 omic traits tested) association with the directly measured molecular trait in internal validation (n = 1631, 7471, 964, 635 and 827 for Metabolon, Nightingale, Olink, SomaScan and RNAseq traits respectively). This resulted in 137, 136 Nightingale metabolic traits for UKB (n = 98,245 participants) and MEC (Chinese, n = 1,067; Indian, n = 654; Malay, n = 634) respectively and 949, 1052, 378 SomaScan proteins for FENLAND (n = 8,832), MEC (Chinese, n = 645; Indian, n = 564; Malay, n = 563) and JHS (n = 1,852). Violin plots show distributions of the ratio of R^2 values. Black points show mean values and error bars are standard errors.



Extended Data Figure 7: Performance (R^2) of genetic scores between longitudinal samples and across ancestries in the MEC cohort.

Paired samples include a baseline and a revisit sample from each individual run on SomaScan and Nightingale for MEC Chinese (N=403 and 721 individuals), MEC Indian (N= 356 and 376) and MEC Malay (N=353 and 363). Blue lines denote linear models fitted to each set of data points and the shaded areas represent 95% confidence intervals where applicable. There is no Nightingale genetic scores with a $R^2 > 0.15$ in both internal and MEC validation, so (**a, b, c**) only show R^2 in the range of [0, 0.15] for clarity. The sub-box plots at the right bottom of (**d**, **e**, **f**) show the validation results of these traits with baseline validation performance (R^2) between 0 and 0.025 in each ancestry.



Extended Data Figure 8: Coverage analysis for blood proteins in the lowest-level pathways.
This analysis looked at all the lowest-level pathways of super-pathways curated at Reactome. Where at least one protein genetic score are included in the entities of a lowest-level pathway, we consider this pathway is covered by proteins of this study. This figure shows the percentage of the lowest-level pathways a group of proteins (by R^2 in internal validation) covered among all the lowest-level pathways of each super-pathway.

Extended Data Figure 9: Key features of OmicsPred portal for accessing genetic scores of multi-omic traits.

a, Organization of genetic scores on the portal. **b,** Example of how biomolecular traits and their genetic score-related information can be explored. **c,** Example of how summary statistics of training and validation cohorts are presented. **d,** Example of how validation results and genetic score models can be downloaded. **e,** Example of how validation results and trait-related information can be visualized.

Extended Data Table 1:

Demographic statistics of training and validation samples for genetic score construction of blood biomolecular traits by platform.

The table shows the mean ± standard deviation of age and BMI for participants in each cohort or cohort subset.

Platform	Cohort	Ancestry	#Traits	#Samples	%Men	Age (years)	BMI (kg/m^2)
Training and Internal Validation							
Metabolon	INTERVAL	European	726	8,153	51.0%	43.9 ± 14.1	26.4 ± 4.6
Nightingale			141	37,359	51.0%	43.7 ± 14.1	26.4 ± 4.6
Olink			308	4,822	59.3%	59.0 ± 6.7	26.5 ± 4.1
SomaScan			2,384	3,175	50.8%	43.6 ± 14.2	26.3 ± 4.7
Illumina RNAseq			13,668	4,136	56.4%	54.6 ± 11.6	26.6 ± 4.4
External Validation							
Metabolon	INTERVAL withheld subset	European	527	8,114	49.4%	47.9 ± 13.8	26.5 ± 4.6
	ORCADES		455	1,007	43.9%	54.0 ± 15.3	27.7 ± 4.9
Nightingale	UKB	European	141	98,245	45.8%	56.5 ± 8.1	27.4 ± 4.8
	ORCADES		141	1,884	40.0%	53.9 ± 15.0	27.8 ± 5.0
	VIKING		141	2,046	39.9%	49.8 ± 15.2	27.4 ± 4.9
	MEC	Chinese	139	1,067	47.2%	52.1 ± 9.9	23.5 ± 3.8
		Indian	139	654	43.7%	44.5 ± 11.6	26.4 ± 5.1
		Malay	139	634	42.9%	44.9 ± 11.1	26.9 ± 5.1
Olink	NSPHS	European	302	872	47.6%	49.6 ± 20.2	26.7 ± 4.8
	ORCADES		301	1,052	44.1%	53.8 ± 15.7	27.7 ± 4.9
SomaScan	FENLAND	European	2,129	8,832	47.1%	48.8 ± 7.4	26.9 ± 4.8
	MEC	Chinese	2,047	645	46.0%	51.9 ± 10.9	23.5 ± 3.9
		Indian	2,047	564	45.0%	44.0 ± 12.0	26.3 ± 5.3
		Malay	2,047	563	43.9%	44.4 ± 11.3	26.9 ± 5.2
	JHS	African American	820	1,852	39.0%	55.7 ± 12.8	31.6 ± 7.3
Illumina RNAseq	INTERVAL withheld subset	European	12,958	598	49.5%	45.0 ± 13.1	26.8 ± 4.8

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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Research (NIHR), the NIHR BioResource (http://bioresource.nihr.ac.uk) and the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014) [*]. The academic coordinating centre for INTERVAL was supported by core funding from the: NIHR Blood and Transplant Research Unit (BTRU) in Donor Health and Genomics (NIHR BTRU-2014-10024), NIHR BTRU in Donor Health and Behaviour (NIHR203337), UK Medical Research Council (MR/L003120/1), British Heart Foundation (SP/09/002; RG/13/13/30194; RG/18/13/33946) and NIHR Cambridge BRC (BRC-1215-20014; NIHR203312) [*]. A complete list of the investigators and contributors to the INTERVAL trial is provided in reference [**]. The academic coordinating centre would like to thank blood donor centre staff and blood donors for participating in the INTERVAL trial. 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Data availability

All the genetic score models trained in this study and GWAS summary statics used to develop genetic scores are publicly accessible through the OmicsPred portal (www.omicspred.org; accession codes OPGS000001-OPGS017227). INTERVAL study data from this paper are available to bona fide researchers from helpdesk@intervalstudy.org.uk and information, including the data access policy, are available at http://www.donorhealth-btru.nihr.ac.uk/project/bioresource.

Code availability

The original codes used to train the genetic scores with INTERVAL data, internally validate these scores, and benchmark the performance of different genetic score construction methods are available at https://github.com/xuyu-cam/atlas_genetic_scores_omic_traits.

References

1. Barbeira AN et al. Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. Nat. Commun 9, 1–20 (2018). [PubMed: 29317637]
2. Moore C et al. The INTERVAL trial to determine whether intervals between blood donations can be safely and acceptably decreased to optimise blood supply: study protocol for a randomised controlled trial. Trials 15, 363 (2014). [PubMed: 25230735]

3. Bycroft C et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 562, 203–209 (2018). [PubMed: 30305743]
4. Ritchie SC et al. Integrative analysis of the plasma proteome and polygenic risk of cardiometabolic diseases. Nat. Metab 3, 1476–1483 (2021). [PubMed: 34750571]
5. Lambert SA et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. Nature Genetics vol. 53 420–425 (2021). [PubMed: 33692568]
6. Adeyemo A et al. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. Nat. Med 27, 1876–1884 (2021). [PubMed: 34782789]
7. Xu Y et al. Machine learning optimized polygenic scores for blood cell traits identify sex-specific trajectories and genetic correlations with disease. Cell Genomics 2, 100086 (2022). [PubMed: 35072137]
8. Gusev A et al. Integrative approaches for large-scale transcriptome-wide association studies. Nat. Genet 48, 245–252 (2016). [PubMed: 26854917]
9. Gamazon ER et al. A gene-based association method for mapping traits using reference transcriptome data. Nat. Genet 47, 1091–1098 (2015). [PubMed: 26258848]
10. Mosley JD et al. Probing the Virtual Proteome to Identify Novel Disease Biomarkers. Circulation 138, 2469–2481 (2018). [PubMed: 30571344]
11. Hutcheon JA, Chiolero A & Hanley JA Random measurement error and regression dilution bias. BMJ 340, 1402–1406 (2010).
12. Pividori M, Schoettler N, Nicolae DL, Ober C & Im HK Shared and distinct genetic risk factors for childhood-onset and adult-onset asthma: genome-wide and transcriptome-wide studies. Lancet Respir. Med 7, 509–522 (2019). [PubMed: 31036433]
13. Lannelongue L, Grealey J, Bateman A & Inouye M Ten simple rules to make your computing more environmentally sustainable. PLOS Comput. Biol 17, e1009324 (2021). [PubMed: 34543272]
14. Berisa T & Pickrell JK Approximately independent linkage disequilibrium blocks in human populations. Bioinformatics 32, 283–285 (2016). [PubMed: 26395773]
15. Pietzner M et al. Mapping the proteo-genomic convergence of human diseases. Science 374, (2021).
16. Igl W, Johansson A & Gyllensten U The Northern Swedish Population Health Study (NSPHS) - a paradigmatic study in a rural population combining community health and basic research. Rural Remote Health 10, 1363 (2010). [PubMed: 20568910]
17. McQuillan R et al. Runs of Homozygosity in European Populations. Am. J. Hum. Genet 83, 359 (2008). [PubMed: 18760389]
18. Kerr SM et al. An actionable KCNH2 Long QT Syndrome variant detected by sequence and haplotype analysis in a population research cohort. Sci. Rep 9, 1–11 (2019). [PubMed: 30626917]
19. Tan KHX et al. Cohort Profile: The Singapore Multi-Ethnic Cohort (MEC) study. Int. J. Epidemiol 47, 699–699j (2018). [PubMed: 29452397]
20. Katz DH et al. Whole Genome Sequence Analysis of the Plasma Proteome in Black Adults Provides Novel Insights into Cardiovascular Disease. Circulation 145, 357–370 (2021). [PubMed: 34814699]
21. Fabregat A et al. The Reactome Pathway Knowledgebase. Nucleic Acids Res. 46, D649–D655 (2018). [PubMed: 29145629]
22. Patrick et al. Mapping ICD-10 and ICD-10-CM Codes to Phecodes: Workflow Development and Initial Evaluation. JMIR Med Inf. 7, e14325 (2019).
23. Sarwar N et al. Interleukin-6 receptor pathways in coronary heart disease: A collaborative meta-analysis of 82 studies. Lancet 379, 1205–1213 (2012). [PubMed: 22421339]
24. Haiman CA et al. Levels of Beta-Microseminoprotein in Blood and Risk of Prostate Cancer in Multiple Populations. J. Natl. Cancer Inst 105, 237–243 (2013). [PubMed: 23213189]
25. Ding EL et al. Sex Hormone–Binding Globulin and Risk of Type 2 Diabetes in Women and Men. N. Engl. J. Med 361, 1152–1163 (2009). [PubMed: 19657112]
26. Saini V Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. World J. Diabetes 1, 68 (2010). [PubMed: 21537430]

27. Qi L et al. Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. Hum. Mol. Genet 19, 1856–1862 (2010). [PubMed: 20147318]
28. Peters MC et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. Lancet Respir. Med 4, 574–584 (2016). [PubMed: 27283230]
29. Banaganapalli B et al. Exploring celiac disease candidate pathways by global gene expression profiling and gene network cluster analysis. Sci. Rep 10, 1–13 (2020). [PubMed: 31913322]
30. Gagliano Taliun SA et al. Exploring and visualizing large-scale genetic associations by using PheWeb. Nat. Genet 52, 550–552 (2020). [PubMed: 32504056]
31. Kim HI et al. Fine Mapping and Functional Analysis Reveal a Role of SLC22A1 in Acylcarnitine Transport. Am. J. Hum. Genet 101, 489 (2017). [PubMed: 28942964]
32. Tamai I Pharmacological and pathophysiological roles of carnitine/organic cation transporters (OCTNs: SLC22A4, SLC22A5 and Slc22a21). Biopharm. Drug Dispos 34, 29–44 (2013). [PubMed: 22952014]
33. Chang HB, Gao X, Nepomuceno R, Hu S & Sun D Na+/H+ exchanger in the regulation of platelet activation and paradoxical effects of cariporide. Exp. Neurol 272, 11–16 (2015). [PubMed: 25595121]
34. de Vries PS et al. Whole-genome sequencing study of serum peptide levels: the Atherosclerosis Risk in Communities study. Hum. Mol. Genet 26, 3442–3450 (2017). [PubMed: 28854705]
35. Babaev VR et al. Loss of 2 Akt (Protein Kinase B) Isoforms in Hematopoietic Cells Diminished Monocyte and Macrophage Survival and Reduces Atherosclerosis in Ldl Receptor-Null Mice. Arterioscler. Thromb. Vasc. Biol 39, 156–169 (2019). [PubMed: 30567482]
36. Miteva K et al. Cardiotrophin-1 Deficiency Abrogates Atherosclerosis Progression. Sci. Reports 2020 101 10, 1–14 (2020).
37. Agrawal S et al. Signal transducer and activator of transcription 1 is required for optimal foam cell formation and atherosclerotic lesion development. Circulation 115, 2939–2947 (2007). [PubMed: 17533179]
38. Peltola KJ et al. Pim-1 kinase inhibits STAT5-dependent transcription via its interactions with SOCS1 and SOCS3. Blood 103, 3744–3750 (2004). [PubMed: 14764533]
39. Khor CC et al. CISH and Susceptibility to Infectious Diseases. N. Engl. J. Med 362, 2092–2101 (2010). [PubMed: 20484391]
40. Baldini C, Moriconi FR, Galimberti S, Libby P & De Caterina R The JAK-STAT pathway: an emerging target for cardiovascular disease in rheumatoid arthritis and myeloproliferative neoplasms. Eur. Heart J 42, 4389–4400 (2021). [PubMed: 34343257]
41. Skah S, Uchuya-Castillo J, Sirakov M & Plateroti M The thyroid hormone nuclear receptors and the Wnt/β-catenin pathway: An intriguing liaison. Dev. Biol 422, 71–82 (2017). [PubMed: 28069375]
42. Chen G et al. Regulation of GSK-3 beta in the proliferation and apoptosis of human thyrocytes investigated using a GSK-3 beta-targeting RNAi adenovirus expression vector: involvement the Wnt/beta-catenin pathway. Mol. Biol. Rep 37, 2773–2779 (2009). [PubMed: 19757160]
43. Ely KA, Bischoff LA & Weiss VL Wnt Signaling in Thyroid Homeostasis and Carcinogenesis. Genes (Basel). 9, 204 (2018). [PubMed: 29642644]
44. Haerlingen B et al. Small-Molecule Screening in Zebrafish Embryos Identifies Signaling Pathways Regulating Early Thyroid Development. Thyroid 29, 1683–1703 (2019). [PubMed: 31507237]
45. Narumi S et al. GWAS of thyroid dysgenesis identifies a risk locus at 2q33.3 linked to regulation of Wnt signaling. Hum. Mol. Genet 00, 1–8 (2022).
46. Xu D et al. USP25 regulates Wnt signaling by controlling the stability of tankyrases. Genes Dev. 31, 1024–1035 (2017). [PubMed: 28619731]
47. Lin D et al. Induction of USP25 by viral infection promotes innate antiviral responses by mediating the stabilization of TRAF3 and TRAF6. Proc. Natl. Acad. Sci. U. S. A 112, 11324–11329 (2015). [PubMed: 26305951]
48. Nelson JK et al. USP25 promotes pathological HIF-1-driven metabolic reprogramming and is a potential therapeutic target in pancreatic cancer. Nat. Commun 13, 1–18 (2022). [PubMed: 34983933]

49. Blount JR, Burr AA, Denuc A, Marfany G & Todi SV Ubiquitin-Specific Protease 25 Functions in Endoplasmic Reticulum-Associated Degradation. PLoS One 7, e36542 (2012). [PubMed: 22590560]
50. Martin AR et al. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat. Genet 51, 584–591 (2019). [PubMed: 30926966]
51. Chang CC et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 4, 7 (2015). [PubMed: 25722852]
52. Auton A et al. A global reference for human genetic variation. Nature 526, 68 (2015). [PubMed: 26432245]
53. Astle WJ et al. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell 167, 1415--1429.e19 (2016). [PubMed: 27863252]
54. Sun BB et al. Genomic atlas of the human plasma proteome. Nature 558, 73–79 (2018). [PubMed: 29875488]
55. Lundberg M, Eriksson A, Tran B, Assarsson E & Fredriksson S Homogeneous antibody-based proximity extension assays provide sensitive and specific detection of low-abundant proteins in human blood. Nucleic Acids Res. 39(15), (2011).
56. Folkersen L et al. Genomic and drug target evaluation of 90 cardiovascular proteins in 30,931 individuals. Nat. Metab 2, 1135–1148 (2020). [PubMed: 33067605]
57. Surendran P et al. Rare and common genetic determinants of metabolic individuality and their effects on human health. Nat. Med 12, 1–12 (2022).
58. Karjalainen MK et al. Genome-wide characterization of circulating metabolic biomarkers reveals substantial pleiotropy and novel disease pathways. medRxiv (2022) doi:10.1101/2022.10.20.22281089.
59. Dobin A et al. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 29, 15–21 (2013). [PubMed: 23104886]
60. Liao Y, Smyth GK & Shi W featureCounts: an efficient general purpose program for assigning sequence reads to genomic features. Bioinformatics 30, 923–930 (2014). [PubMed: 24227677]
61. Fort A et al. MBV: a method to solve sample mislabeling and detect technical bias in large combined genotype and sequencing assay datasets. Bioinformatics 33, 1895–1897 (2017). [PubMed: 28186259]
62. Robinson MD & Oshlack A A scaling normalization method for differential expression analysis of RNA-seq data. Genome Biol. 11, 1–9 (2010).
63. Stegle O, Parts L, Piipari M, Winn J & Durbin R Using probabilistic estimation of expression residuals (PEER) to obtain increased power and interpretability of gene expression analyses. Nat. Protoc 7, 500–507 (2012). [PubMed: 22343431]
64. Taylor-Weiner A et al. Scaling computational genomics to millions of individuals with GPUs. Genome Biol. 20, 1–5 (2019). [PubMed: 30606230]
65. Stacklies W, Redestig H, Scholz M, Walther D & Selbig J pcaMethods—a bioconductor package providing PCA methods for incomplete data. Bioinformatics 23, 1164–1167 (2007). [PubMed: 17344241]
66. Pietzner M et al. Genetic architecture of host proteins involved in SARS-CoV-2 infection. Nat. Commun 11, 1–14 (2020). [PubMed: 31911652]
67. Bretherick AD et al. Linking protein to phenotype with Mendelian Randomization detects 38 proteins with causal roles in human diseases and traits. PLoS Genet. 16, (2020).
68. Kierczak M et al. Contribution of rare whole-genome sequencing variants to plasma protein levels and the missing heritability. Nat. Commun 13, 1–12 (2022). [PubMed: 34983933]
69. Ritchie SC et al. Quality control and removal of technical variation of NMR metabolic biomarker data in ~120,000 UK Biobank participants. medRxiv (2021) doi:10.1101/2021.09.24.21264079.
70. Wong E et al. The Singapore National Precision Medicine Strategy. Nat. Genet (2023) doi:10.1038/S41588-022-01274-X.
71. Zhang F et al. Ancestry-agnostic estimation of DNA sample contamination from sequence reads. Genome Res. 30, 185–194 (2020). [PubMed: 31980570]

72. Taylor HAJ et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethn. Dis 15, S6-4–17 (2005).
73. Taliun D et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature 590, 290–299 (2021). [PubMed: 33568819]
74. Ngo D et al. Aptamer-Based Proteomic Profiling Reveals Novel Candidate Biomarkers and Pathways in Cardiovascular Disease. Circulation 134, 270–285 (2016). [PubMed: 27444932]
75. Torkamani A, Wineinger NE & Topol EJ The personal and clinical utility of polygenic risk scores. Nat. Rev. Genet 19, 581–590 (2018). [PubMed: 29789686]
76. Chatterjee N, Shi J & Garcia-Closas M Developing and evaluating polygenic risk prediction models for stratified disease prevention. Nat. Rev. Genet 17, 392–406 (2016). [PubMed: 27140283]
77. Okser S et al. Regularized machine learning in the genetic prediction of complex traits. PLoS Genet. 10, e1004754 (2014). [PubMed: 25393026]
78. Vilhjálmsson BJ et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. Am. J. Hum. Genet 97, 576–592 (2015). [PubMed: 26430803]
79. Bishop CM Pattern recognition and machine learning. (New York, NY : Springer, 2006).
80. Tipping ME Sparse Bayesian learning and the relevance vector machine. J. Mach. Learn. Res 1, 211–244 (2001).
81. Privé F, Arbel J & Vilhjálmsson BJ LDpred2: better, faster, stronger. Bioinformatics 36, 5424–5431 (2021). [PubMed: 33326037]
82. Pietzner M et al. Synergistic insights into human health from aptamer- and antibody-based proteomic profiling. Nat. Commun 12, 1–13 (2021). [PubMed: 33397941]
83. Davidson-Pilon C lifelines: survival analysis in Python. J. Open Source Softw 4, 1317 (2019).
84. Lannelongue L, Grealey J & Inouye M Green Algorithms: Quantifying the Carbon Footprint of Computation. Adv. Sci 8, 2100707 (2021).

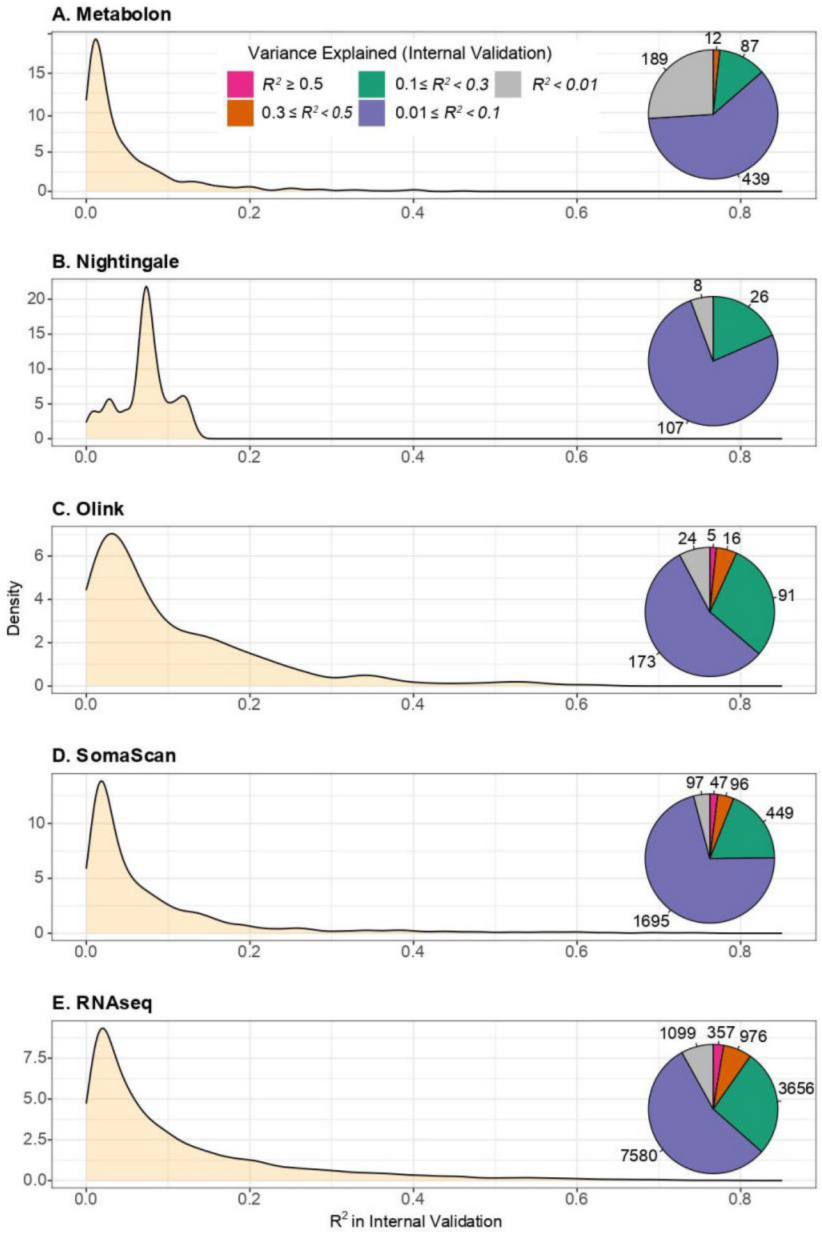

Figure 1: Performance of multi-omic genetic scores in internal validation.

The variance explained in the measured biomolecular trait (R^2) by the genetic score is assessed in the internal validation set of INTERVAL (Methods). Pie charts reflect the number of genetic scores in a particular R^2 range.

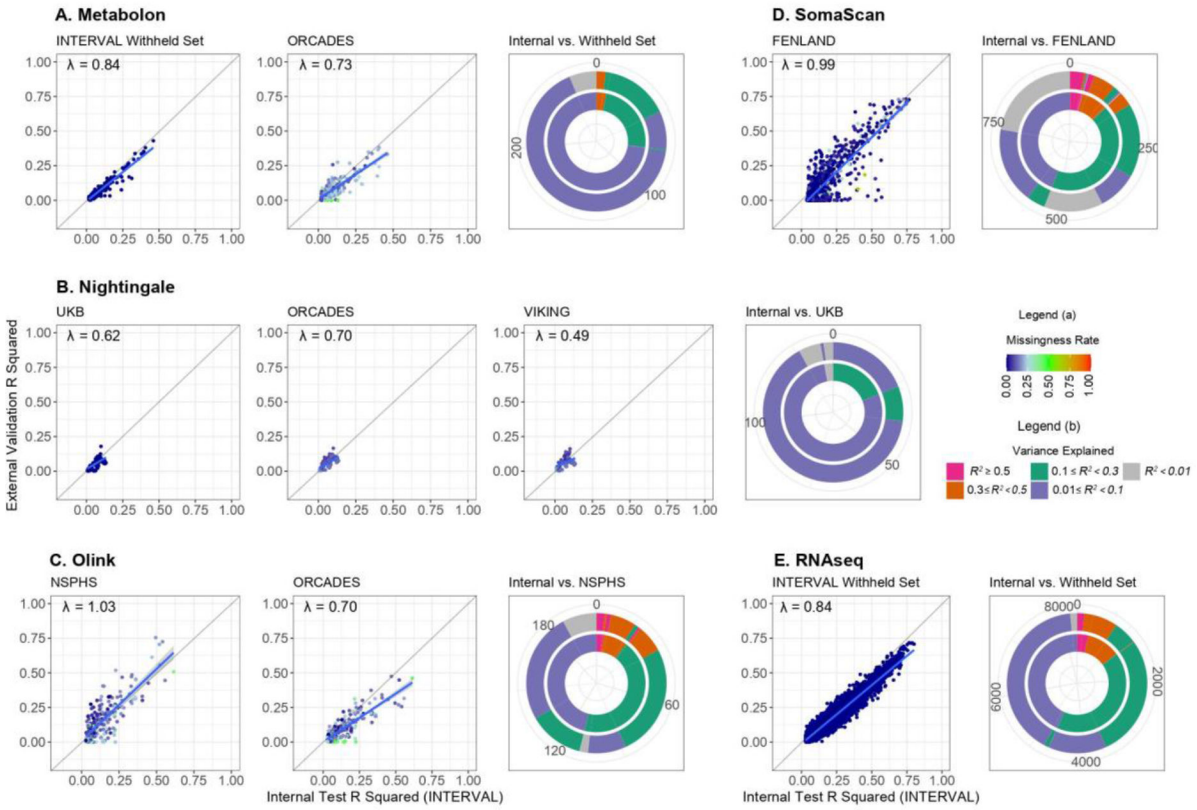

Figure 2: External validation of genetic scores in cohorts of European ancestry.

Comparisons of R^2 in internal validation and external validation for each omic platform, for genetic scores with Bonferroni-adjusted p-value < 0.05 in internal validation (two-sided t-test; correcting for 17,227 omic traits). Data points coloured by variant missingness rate in the external cohort. Blue lines show fitted linear models and λ are model slopes. Concentric circles show number of genetic scores in different ranges of R^2 in internal validation (inner ring) and external validation (outer ring).

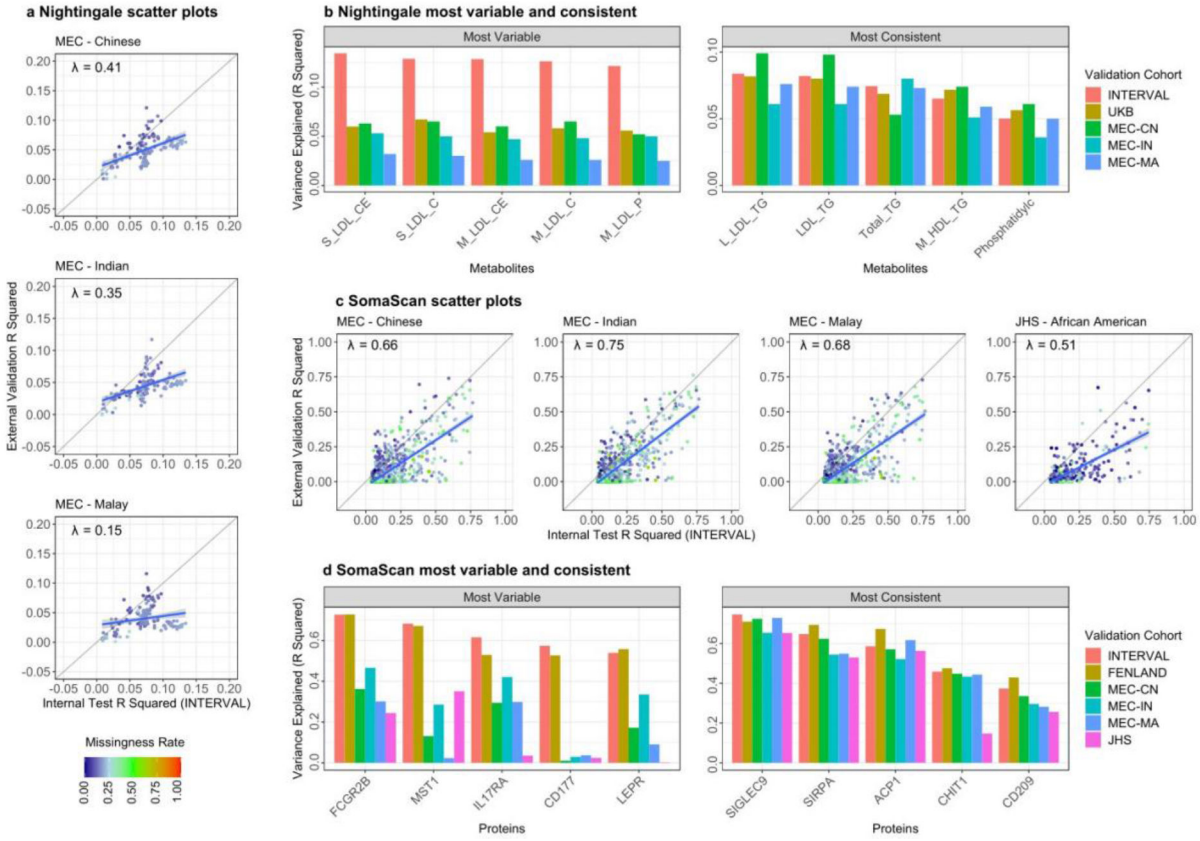

Figure 3: Transferability of genetic scores to Asian and African American ancestries.

a, **c**, Performance comparison between internal validation and external validation in non-European ancestries for (**a**) Nightingale and (**c**) SomaScan genetic scores. Transferability was tested for genetic scores with Bonferroni-adjusted p-value < 0.05 in internal validation (two-sided t-test; correcting for 17,227 omic traits). Data points are coloured by variant missingness rate in the external cohort. **b**, **d**, R^2 of genetic scores for (**b**) Nightingale and (**d**) SomaScan with the five most variable or five most consistent for prediction in multi-ancestry validation, as quantified by mean absolute difference in R^2 for genetic scores with Nightingale $R^2 > 0.05$, SomaScan $R^2 > 0.30$ in internal validation.

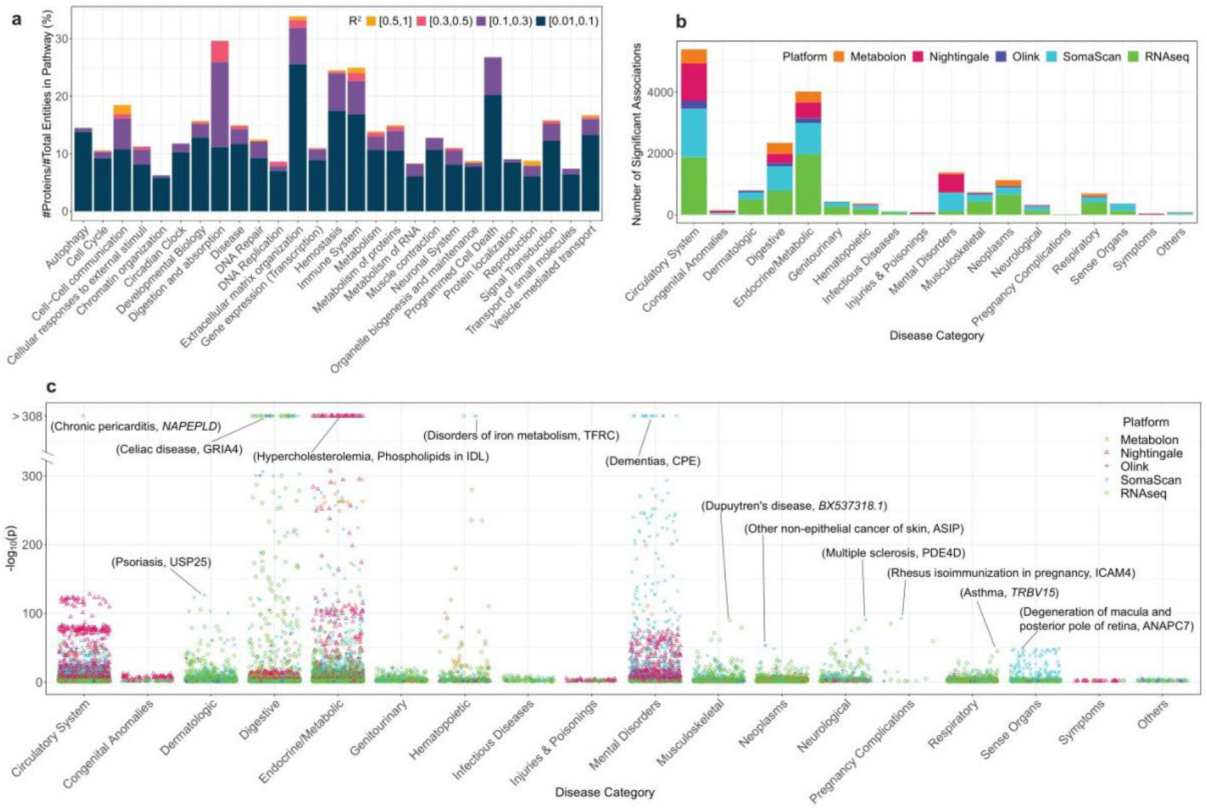

Figure 4: Applications of genetic scores of multi-omic traits.

a, Genetic control of Reactome super-pathways using SomaScan and Olink genetic scores of varying R^2 in internal validation (Methods). **b**, Phenome-wide association study in UK Biobank. Stacked barplots show the number of detected significant associations by PheCode category of disease and omic platform (two-sided Wald test and FDR-corrected p-value < 0.05 for 11,576 tested traits). **c**, Strength of associations by category of disease and omic platform. Association with the lowest p-value for each disease category is labelled.

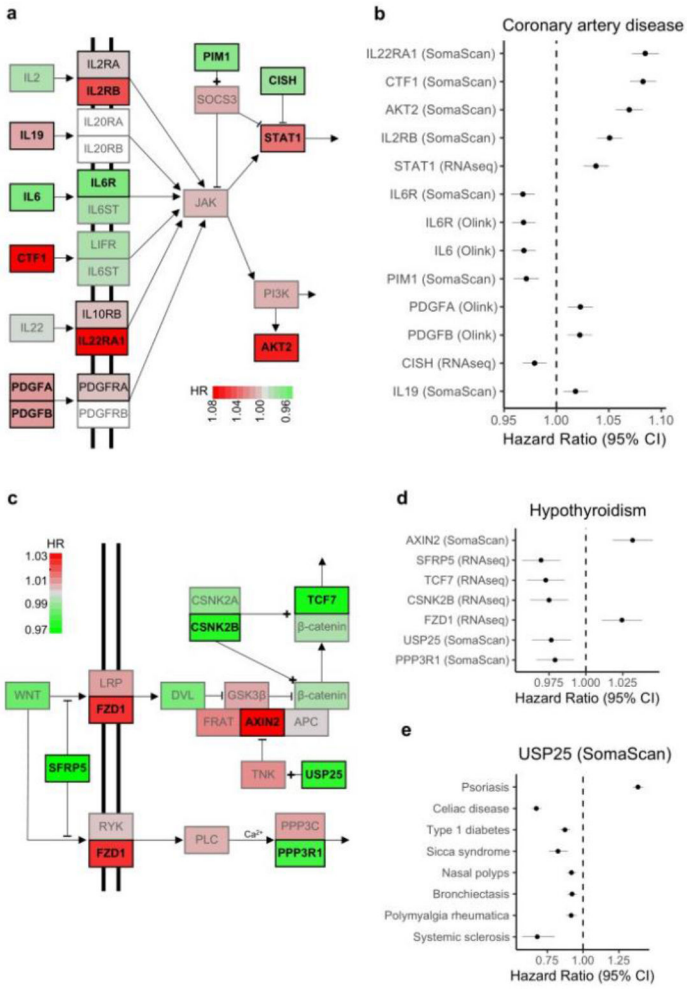

Figure 5: JAK/STAT and Wnt signalling pathways.

a, c, Pathway diagrams for (**a**) JAK/STAT and (**c**) Wnt signalling. Nodes coloured based on hazard ratio (HR) of the genetic score for (**a**) coronary artery disease (CAD) and (**c**) hypothyroidism. Nodes are white if there is not a corresponding genetic score. The most significant HR across omic platforms is used at each node. Nodes are bold if the genetic score had FDR-adjusted p-value < 0.05 (two-sided Wald test and correcting for 11,576 tested traits). **b, d,** Forest plots of FDR-significant HRs for (**b**) CAD (n = 28,854 cases and 390,159 controls) and (**d**) hypothyroidism (n = 21,871 cases and 404,440 controls) for genetic scores in (**b**) JAK/STAT or (**d**) Wnt signalling. **e,** Forest plot of HRs and 95% confidence intervals for the genetic score of USP25 (SomaScan) across multiple diseases.