Projecting genetic associations through gene expression patterns highlights disease etiology and drug mechanisms

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## Abstract

Understanding how dysregulated transcriptional processes result in tissue-specific pathology requires a mechanistic interpretation of expression regulation across different cell types. It has been shown that this insight is key for the development of new therapies. These mechanisms can be identified with transcriptome-wide association studies (TWAS), which have represented an important step forward to test the mediating role of gene expression in GWAS associations. However, due to pervasive eQTL sharing across tissues, TWAS has not been successful in identifying causal tissues, and other methods generally do not take advantage of the large amounts of RNA-seq data publicly available. Here we introduce a polygenic approach that leverages gene modules (genes with similar co-expression patterns) to project both gene-trait associations and pharmacological perturbation data into a common latent representation for a joint analysis. We observed that diseases were significantly associated with gene modules expressed in relevant cell types, such as hypothyroidism with T cells and thyroid, hypertension and lipids with adipose tissue, and coronary artery disease with cardiomyocytes. Our approach was more accurate in predicting known drug-disease pairs and revealed stable trait clusters, including a complex branch involving lipids with cardiovascular, autoimmune, and neuropsychiatric disorders. Furthermore, using a CRISPR-screen, we show that genes involved in lipid regulation exhibit more consistent trait associations through gene modules than individual genes. Our results suggest that a gene module perspective can contextualize genetic associations and prioritize alternative treatment targets when GWAS hits are not druggable.

## Introduction

Human diseases have tissue-specific etiologies and manifestations [[1](#ref-O0e3EhY6),[2](#ref-18jYvPauB),[3](#ref-wNE0EQlN)]. In this context, determining how genes influence these complex phenotypes requires mechanistically understanding expression regulation across different cell types [[4](#ref-9Pr9idng),[5](#ref-1DoyZS7y0),[6](#ref-nhaocxmR)], which in turn should lead to improved treatments [[7](#ref-REXpV7nA),[8](#ref-PgEwSS4Q)]. Previous studies have described regulatory DNA elements, including chromatin-state annotations [[9](#ref-15J98V2qM),[10](#ref-sLkFMFZj)], high-resolution enhancers [[11](#ref-SxuuTQTQ),[12](#ref-xRGqPsT2)], DNase I hypersensitivity maps [[5](#ref-1DoyZS7y0)], and genetic effects on gene expression across different tissues [[4](#ref-9Pr9idng)]. Integrating functional genomics data and GWAS data [[13](#ref-aIyQY5ZT)] has improved the identification of these transcriptional mechanisms that, when dysregulated, commonly result in tissue- and cell lineage-specific pathology.

Given the availability of gene expression data across several tissues [[4](#ref-9Pr9idng),[14](#ref-6SPTvFXq),[15](#ref-Nz3IMEzd),[16](#ref-57TjOMEA)], a popular approach to identify these biological processes is the transcription-wide association study (TWAS), which integrates expression quantitative trait loci (eQTLs) data to provide a mechanistic interpretation for GWAS findings. TWAS relies on testing whether perturbations in gene regulatory mechanisms mediate the association between genetic variants and human diseases [[17](#ref-yEdRP9Xx),[18](#ref-1D63fEEPb),[19](#ref-1FFzCXo1s),[20](#ref-Z8bvDdVq)]. However, TWAS have not reliably detected tissue-specific effects because eQTLs are commonly shared across tissues [[21](#ref-4iMVo07x),[22](#ref-WFslDIWl)]. This sharing makes it challenging to identify the tissue or tissues specifically associated with a phenotype. Alternative existing statistical approaches that connect GWAS findings with gene expression data can infer disease-relevant tissues and cell types [[22](#ref-WFslDIWl),[23](#ref-nga58tSh),[24](#ref-kXUuzq6I),[25](#ref-kUDav9OX),[26](#ref-z8MQTAnJ),[27](#ref-12w2U7X9m)], but they generally rely on small sets of expression data compared with the total number of RNA-seq samples that are increasingly available [[14](#ref-6SPTvFXq),[15](#ref-Nz3IMEzd)]. Moreover, widespread gene pleiotropy and polygenic traits reveal the highly interconnected nature of transcriptional networks [[28](#ref-pZZn28he),[29](#ref-PDWEwciL)], where potentially all genes expressed in disease-relevant cell types have a non-zero effect [[30](#ref-vpIDZCSa),[31](#ref-LXvTZzEA)]. Consequently, this complicates the interpretation of genetic effects and hampers translational efforts.

We propose PhenoPLIER, a polygenic approach that maps both gene-trait associations and drug-transcriptional responses into a common representation for a joint analysis. For this, we integrated more than 4,000 gene-trait associations (using TWAS from PhenomeXcan [[32](#ref-lY5ln3dB)]) and transcriptional profiles of drugs (LINCS L1000 [[33](#ref-F7lIlh2N)]) into a low-dimensional space learned from public gene expression data on tens of thousands of RNA-seq samples (recount2 [[14](#ref-6SPTvFXq),[34](#ref-14rnBunuZ)]). We used a latent representation defined by a computational approach [[35](#ref-Ki2ij7zE)] that learns recurrent gene co-expression patterns with certain sparsity constraints and preferences for those that align with prior knowledge (pathways). This low-dimensional space comprised features representing groups of genes (gene modules) with coordinated expression across different tissues and cell types. When mapping gene-trait associations to this reduced expression space, we observed that diseases were significantly associated with gene modules expressed in relevant cell types, such as hypothyroidism with T cells and thyroid, coronary artery disease with cardiomyocytes, hypertension and lipids with adipose tissue, and heart problems with heart ventricle and muscle cells. We replicated gene module associations with cardiovascular and autoimmune diseases in the Electronic Medical Records and Genomics (eMERGE) network phase III [[36](#ref-wfqjCerX)]. Moreover, we performed a CRISPR-screen to analyze lipid regulation in HepG2 cells and observed more consistent trait associations with modules than we observe with individual genes. Our approach was also robust in finding meaningful gene module-trait associations, even when individual genes involved in lipid metabolism did not reach genome-wide significance in lipid-related traits. Compared to a single-gene approach, our module-based method also better predicted FDA-approved drug-disease links by capturing tissue-specific pathophysiological mechanisms linked with the mechanism of action of drugs (e.g., niacin with cardiovascular traits via a known immune mechanism), suggesting that modules may provide a better means to examine drug-phenotype relationships than individual genes. Finally, exploring the phenotype-module space also revealed stable trait clusters associated with relevant tissues, including a complex branch involving lipids with cardiovascular, autoimmune, and neuropsychiatric disorders.

## Results

### PhenoPLIER: an integration framework based on gene co-expression patterns

Figure 1: Schematic of the PhenoPLIER framework. a) The integration process between gene co-expression patterns from MultiPLIER (top) and TWAS results from PhenomeXcan (bottom). PhenoPLIER projects gene-trait associations to a latent space learned from large gene expression datasets. The process generates matrix \mathbf{\hat{M}}, where each trait is now described by latent variables (LV) or gene modules. b) After the integration process, we found that neutrophil counts and other white blood cells (bottom) were ranked among the top 10 traits for LV603, which was termed a neutrophil signature in the original MultiPLIER study. Genes in LV603 were expressed in relevant cell types (top). PBMC: peripheral blood mononuclear cells; mDCs: myeloid dendritic cells.

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PhenoPLIER combines TWAS results with gene co-expression patterns by projecting gene-trait associations onto a latent gene expression representation (Figure [1](#fig:entire_process)). We used PhenomeXcan [[32](#ref-lY5ln3dB)], a TWAS resource for the UK Biobank [[37](#ref-nmJxPpE5)] and other cohorts that provides results for 4,091 different diseases and traits. We obtained a latent gene expression representation from MultiPLIER [[34](#ref-14rnBunuZ)], an unsupervised learning approach applied to recount2 [[14](#ref-6SPTvFXq)] (a gene expression dataset including RNA-seq data on a huge and heterogeneous number of samples, including rare diseases, cell types on specific differentiation stages, or under different stimuli, among others). Each of the 987 latent variables (LV) represents a gene module, essentially a group of genes with coordinated expression patterns (i.e., expressed together in the same tissues and cell types as a functional unit). Since LVs might represent a functional set of genes regulated by the same transcriptional program [[38](#ref-1FVd2WW6G),[39](#ref-DN7TyZzb)], the projection of TWAS results into this latent space could provide context for their interpretation. PhenoPLIER translates gene-trait associations to an LV-trait score, linking different traits and diseases to LVs representing specific cell types and tissues, even at specific developmental stages or under distinct stimuli. Examining these LVs is possible because the MultiPLIER models link to samples, which may be annotated for experimental conditions (represented by matrix in Figure [1](#fig:entire_process) a) in which genes in an LV are expressed.

In the original MultiPLIER study, the authors found one of the latent variables, LV603, to be significantly associated with a known neutrophil pathway and highly correlated with neutrophil count estimates from gene expression [[40](#ref-18TSqd1tG)]. We analyzed LV603 using PhenoPLIER (Figure [1](#fig:entire_process) b) and found that neutrophil counts and other white blood cell traits were ranked among the top 10 traits for this LV, suggesting a high degree of internal consistency. We adapted the gene-property approach from MAGMA [[41](#ref-19XiXgYmd)] for LVs and found that gene weights in this LV were predictive of gene associations for neutrophil abundance (FDR < 0.01). These initial results strongly suggested that shared patterns exist in the gene expression space (which has no GTEx samples) and the TWAS space (with gene models trained using GTEx v8); the approach linked transcriptional patterns from large and diverse dataset collections, including tissue samples and perturbation experiments, to complex traits.

### LVs link genes that alter lipid accumulation with relevant traits and tissues

We performed a fluorescence-based CRISPR-Cas9 screen for genes associated with lipid accumulation. We found 271 genes associated with lipids accumulation by using a genome-wide lentiviral pooled CRISPR-Cas9 library targeting 19,114 genes in the human genome in the HepG2 cell line. From these, we identified two gene-sets that either caused a decrease (96 genes in total, with eight high-confidence genes: *BLCAP*, *FBXW7*, *INSIG2*, *PCYT2*, *PTEN*, *SOX9*, *TCF7L2*, *UBE2J2*) or an increase of lipids (175 genes in total, with six high-confidence genes: *ACACA*, *DGAT2*, *HILPDA*, *MBTPS1*, *SCAP*, *SRPR*) (Supplementary File 1). Four LVs were significantly enriched for these lipid-altering gene-sets (FDR<0.05) (Supplementary Table [1](#tbl:sup:lipids_crispr:modules_enriched)).

First, for each lipid-altering gene-set, we assessed the genes’ effects on all phenotypes by adding their -values (transformed to -scores) and obtaining a ranked list of traits. The top associated traits for genes in the decreasing-lipids gene-set were highly relevant to lipid levels, such as hypertension, diastolic and systolic blood pressure, and vascular diseases, also including asthma and lung function (Supplementary Table [2](#X6c05f4adce6ca2d299b4d8689935d86a52ade44)). We performed the same operation for our LV-based approach by considering 24 LVs nominally enriched (unadjusted -value < 0.05) with the decreasing-lipids gene-set by using Fast Gene Set Enrichment Analysis (FGSEA) [[42](#ref-Z8WXLD67)]. In this case, we also found lipid-related traits among the top 25, including hypertension, blood pressure, cardiometabolic diseases like atherosclerosis, and celiac disease (Supplementary Table [3](#X01e09723316722ac310dec2c9d9a6200f08a76a)).

Figure 2: Tissues and traits associated with a gene module related to lipid metabolism (LV246).  a) Top cell types/tissues where LV246’s genes are expressed in. Values in the y-axis come from matrix \mathbf{B} in the MultiPLIER models (Figure 1 a). In the x-axis, cell types/tissues are sorted by the maximum value.  b) Gene-trait associations (S-MultiXcan; threshold at -log(p)=10) and colocalization probability (fastENLOC) for the top traits in LV246. The top 40 genes in LV246 are shown, sorted by their module weight, from largest (top gene SCD) to smallest (gene FAR2); DGAT2 and ACACA, in bold, are two of the six high-confidence genes in the increasing-lipids gene set from our HepG2 CRISPR analyses.  SGBS: Simpson Golabi Behmel Syndrome; CH2DB: CH2 groups to double bonds ratio; NMR: nuclear magnetic resonance; HDL: high-density lipoprotein; RCP: locus regional colocalization probability. 

Figure 2: **Tissues and traits associated with a gene module related to lipid metabolism (LV246).** **a)** Top cell types/tissues where LV246’s genes are expressed in. Values in the -axis come from matrix in the MultiPLIER models (Figure [1](#fig:entire_process) a). In the -axis, cell types/tissues are sorted by the maximum value. **b)** Gene-trait associations (S-MultiXcan; threshold at -log()=10) and colocalization probability (fastENLOC) for the top traits in LV246. The top 40 genes in LV246 are shown, sorted by their module weight, from largest (top gene *SCD*) to smallest (gene *FAR2*); *DGAT2* and *ACACA*, in bold, are two of the six high-confidence genes in the increasing-lipids gene set from our HepG2 CRISPR analyses. SGBS: Simpson Golabi Behmel Syndrome; CH2DB: CH2 groups to double bonds ratio; NMR: nuclear magnetic resonance; HDL: high-density lipoprotein; RCP: locus regional colocalization probability.

When we considered the increasing-lipids gene-set, genes and LVs were associated with a more diverse set of traits, such as blood count tests, impedance measures, and bone-densitometry (Supplementary Tables [4](#Xb0389bb0a81dbc8f41eef9b5f749855bc9f8645) and [5](#X147d13159ec8489ad2abb83c49cc804c5ac4bf7)). FGSEA found 27 LVs nominally enriched for the increasing-lipids gene-set which were associated with the same traits, and additionally to lung function, arterial stiffness, intraocular pressure, handgrip strength, rheumatoid arthritis, and celiac disease. Among these, LV246 contained genes mainly co-expressed in adipose tissue (Figure [2](#fig:lv246) a), which plays a key role in coordinating and regulating lipid metabolism. Additionally, using the gene-property analysis, we found that gene weights for this LV were predictive of gene associations for blood lipids and hypercholesterolemia (Supplementary Table [7](#tbl:sup:phenomexcan_assocs:lv246)). Two high-confidence genes from our CRISPR screening, *DGAT2* and *ACACA*, are responsible for encoding enzymes for triglycerides and fatty acid synthesis and were among the highest-weighted genes of LV246. However, as it can be seen in Figure [2](#fig:lv246) b, these two genes were not strongly associated with any of the top traits for this LV and thus would not be revealed by TWAS alone; other members of LV246, such as *SCD*, *LPL*, *FADS2*, *HMGCR*, and *LDLR*, were instead significantly associated and colocalized with lipid-related traits. This suggested that an LV-based perspective can integrate hits across modalities by leveraging information from functionally related genes.

### PhenoPLIER with LVs predicts drug-disease pairs better than single genes

We systematically evaluated whether substituting LVs in place of individual genes more accurately predicted known treatment-disease pairs. For this, we used the transcriptional responses to small molecule perturbations profiled in LINCS L1000 [[33](#ref-F7lIlh2N)], which were further processed and mapped to DrugBank IDs [[43](#ref-6PR8LEXK),[44](#ref-O21tn8vf),[45](#ref-1DJZvtwP1)]. Based on an established drug repurposing strategy that matches reversed transcriptome patterns between genes and drug-induced perturbations [[46](#ref-1ClBKizD7),[47](#ref-mZjkE1xU)], we adopted a previously described framework that uses imputed transcriptomes from TWAS to prioritize drug candidates [[48](#ref-17oeJ0CXy)]. For this, we computed a drug-disease score by anti-correlating the -scores for a disease (from TWAS) and the -scores for a drug (from LINCS) across sets of genes of different size. Therefore, a large score for a drug-disease pair indicated that a higher (lower) predicted expression of disease-associated genes are down (up)-regulated by the drug, thus predicting a potential treatment. Similarly, for the LV-based approach, we estimated how pharmacological perturbations affected the gene module activity by projecting expression profiles of drugs into our latent representation (see Methods). We used a manually-curated gold standard set of drug-disease medical indications [[44](#ref-O21tn8vf),[49](#ref-10KA5jTBQ)] for 322 drugs across 53 diseases to evaluate the prediction performance.

Figure 3: Drug-disease prediction performance for gene-based and module-based approaches.  The receiver operating characteristic (ROC) (left) and the precision-recall curves (right) for a gene-based and our module-based approach.  AUC: area under the curve; AP: average precision. 

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The gene-trait associations and drug-induced expression profiles projected into the latent space represent a compressed version of the entire set of results. Despite this compression, the LV-based method outperformed the gene-based one with an area under the curve of 0.632 and an average precision of 0.858 (Figure [3](#fig:drug_disease:roc_pr)). The prediction results suggest that this low-dimensional space captures biologically meaningful patterns that can link pathophysiological processes with the mechanism of action of drugs.

We examined a specific drug-disease pair to determine whether the LVs driving the prediction were biologically plausible. Nicotinic acid (niacin) is a B vitamin widely used clinically to treat lipid disorders. Niacin exerts its effects on multiple tissues, although not all its mechanisms have been documented [[50](#ref-LVihFr3g),[51](#ref-7OgaYjeL)]. This compound can increase high-density lipoprotein (HDL) by inhibiting an HDL catabolism receptor in the liver. Niacin also inhibits diacylglycerol acyltransferase–2 (DGAT2), which decreases the production of low-density lipoproteins (LDL) by modulating triglyceride synthesis in hepatocytes, or by inhibiting adipocyte triglyceride lipolysis [[50](#ref-LVihFr3g)]. Niacin was one of the drugs in the gold standard indicated for atherosclerosis (AT) and coronary artery disease (CAD). For AT, the LV-based approach predicted niacin as a therapeutic drug with a score of 0.52 (above the mean), whereas the gene-based method assigned a negative score of -0.01 (below the mean). To understand why the LV-based method gave an anticipated prediction different from the gene-based approach, we obtained the LVs that contributed substantially to the score, including those with top positive/negative LV values for the disease and top negative/positive LV values for the drug of interest. Notably, LV246 (analyzed previously) was among the top 20 modules contributing to the prediction of niacin as a therapeutic drug for AT. Gene weights of LV246 were predictive of cardiovascular traits (Supplementary Table [7](#tbl:sup:phenomexcan_assocs:lv246)), and several of its top genes were significantly associated and colocalized with cardiovascular-related traits: *SCD* (10q24.31) was associated with hypercholesterolemia (*P*=1.9e-5) and its GWAS and eQTL signals were fully colocalized (RCP=1.0); *LPL* (8p21.3), which was previously linked to different disorders of lipoprotein metabolism, was significantly associated with hypercholesterolemia (*P*=7.5e-17, RCP=0.26), and family history of heart disease (*P*=1.7e-5, RCP=0.22); other genes associated with hypercholesterolemia in this LV were *FADS2* (11q12.2) (*P*=9.42e-5, RCP=0.623), *HMGCR* (5q13.3) (*P*=1.3e-42, RCP=0.23), and *LDLR* (19p13.2) (*P*=9.9e-136, RCP=0.41).

The analysis of other niacin-AT-contributing LVs revealed additional known mechanisms of action of niacin. For example, *GPR109A/HCAR2* encodes a G protein-coupled high-affinity niacin receptor in adipocytes and immune cells, including monocytes, macrophages, neutrophils and dendritic cells [[52](#ref-izbPw2kc),[53](#ref-wI0IjT3i)]. It was initially thought that the antiatherogenic effects of niacin were solely due to inhibition of lipolysis in adipose tissue. However, it has been shown that nicotinic acid can reduce atherosclerosis progression independently of its antidyslipidemic activity through the activation of *GPR109A* in immune cells [[54](#ref-1Bz0jRHYo)], thus boosting anti-inflammatory processes and reversing cholesterol transport [[55](#ref-1DblG8swn)]. In addition, flushing, a common adverse effect of niacin, is also produced by the activation of GPR109A in Langerhans cells (macrophages of the skin). This alternative mechanism for niacin could have been hypothesized by examining the cell types where the top two modules positively contributing to the niacin-AT prediction are expressed: LV116 and LV931 (Supplementary Figures [9](#fig:sup:lv116) and [10](#fig:sup:lv931)). Among these, we also found LV678 positively contributing to this prediction, which was significantly enriched with the lipids-decreasing genes from our CRISPR screening (Supplementary Table [1](#tbl:sup:lipids_crispr:modules_enriched)). This module was expressed in the heart and muscle cells (Supplementary Figure [8](#fig:sup:lv678)).

The LV-based method was able to integrate different data types to provide an interpretable approach for drug repositioning research based on genetic studies. Additionally, our approach could also be helpful to understand better the mechanism of pharmacological effect of known or experimental drugs. For example, LV66, one of the top LVs affected by niacin (Supplementary Figure [11](#fig:sup:lv66)) was mainly expressed in ovarian granulosa cells. This compound has been very recently considered as a potential therapeutic for ovarian diseases [[56](#ref-kLRErKXz),[57](#ref-TovvsrDr)], as it was found to promote follicle growth and inhibit granulosa cell apoptosis in animal models. Our LV-based approach could be helpful to generate novel hypotheses to evaluate potential mechanisms of action, or even adverse effects, of different drugs.

### LV projections reveal trait clusters with shared transcriptomic properties

Figure 4: Cluster analysis on traits using the latent gene expression representation.  a) The projection of TWAS results on n=3,752 traits into the latent gene expression representation is the input data to the clustering process. A linear (PCA) and non-linear (UMAP) dimensionality reduction techniques were applied to the input data, and the three data versions were processed by five different clustering algorithms. These algorithms derive partitions from the data using different sets of parameters (such as the number of clusters), leading to an ensemble of 4,428 partitions. Then, a distance matrix is derived by counting how many times a pair of traits were grouped in different clusters across the ensemble. Finally, a consensus function is applied to the distance matrix to generate consolidated partitions with different number of clusters (from 2 to \sqrt{n}\approx 60). These final solutions were represented in the clustering tree (Figure 5).  b) The clusters found by the consensus function were used as labels to train a decision tree classifier on the original input data, which detects the LVs that better differentiate groups of traits. 

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The previous results suggested that the compression into increases the signal-to-noise ratio. Thus, we analyzed to find groups of traits that were affected by the same transcriptional processes. Selecting a clustering algorithm implies that a particular assumption about the structure of the data is most appropriate. Instead, we employed a consensus clustering approach where we applied different methods with varying sets of parameters and later combined these into a consolidated solution. Our clustering pipeline generated 15 final consensus clustering solutions with 5 to 29 clusters (Supplementary Figure [28](#fig:sup:consensus_agreement)). Instead of selecting a specific number of clusters, we used a clustering tree [[58](#ref-xhtEAzx6)] (Figure [5](#fig:clustering:tree)) to examine stable groups of traits across multiple resolutions. To interpret the clusters, we trained a decision tree classifier (a highly interpretable machine learning model) on the input data using the clusters found as labels. This quickly revealed the latent variables/gene modules that differentiated the groups of traits.

Figure 5: Clustering tree using multiple resolutions for clusters of traits.  Each row represents a partition/grouping of the traits, and each circle is a cluster from that partition, and the number of clusters go from 5 to 29. Arrows indicate how traits in one cluster move across clusters from different partitions. Most of the clusters are preserved across different resolutions, showing highly stable solutions even with independent runs of the clustering algorithm.  MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MRV: mean reticulocyte volume; MSCV: mean sphered cell volume; RDW: red cell (erythrocyte) distribution width; BMI: body mass index; WC: waist circumference; HC: hip circumference; BMR: basal metabolic rate; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; IBD: inflammatory bowel disease;  Descriptions of traits by cluster IDs (from left to right): 12: also includes lymphocyte count and allergies such as allergic rhinitis or eczema; 4: includes reticulocyte count and percentage, immature reticulocyte fraction, and high light scatter reticulocytes count and percentage; 5: includes erythrocyte count, hemoglobin concentration, and hematocrit percentage; 18: also includes ankle spacing width; 1: includes platelet count, crit, mean volume, and distribution width; 13: diabetes refers to age when the diabetes was first diagnosed; 25: includes vascular problems such as angina, deep vein thrombosis (DVT), intraocular pressure, eye and mouth problems, pulse rate, hand-grip strength, several measurements of physical activity, jobs involving heavy physical work, types of transport used, intake of vitamin/mineral supplements, and various types of body pain and medications for pain relief; 21: also includes attention deficit hyperactivity disorder (ADHD), number of years of schooling completed, bone density, and intracranial volume measurement; 28: includes diabetes, gout, arthrosis, and respiratory diseases (and related medications such as ramipril, allopurinol, and lisinopril), urine assays, female-specific factors (age at menarche, menopause, first/last live birth), and several environmental/behavioral factors such as intake of a range of food/drink items including alcohol, time spent outdoors and watching TV, smoking and sleeping habits, early-life factors (breastfed as a baby, maternal smoking around birth), education attainment, psychological and mental health, and health satisfaction; 11: also includes fasting blood glucose and insulin measurement; 16: lipids include high and low-density lipoprotein cholesterol (HDL and LDL), triglycerides, and average number of methylene groups per a double bond; 14: includes myocardial infarction, coronary atherosclerosis, ischaemic heart disease (wide definition). 9: includes neutrophil count, neutrophil+basophil count, neutrophil+eosinophil count, granulocyte count, leukocyte count, and myeloid cell count. 

Figure 5: **Clustering tree using multiple resolutions for clusters of traits.** Each row represents a partition/grouping of the traits, and each circle is a cluster from that partition, and the number of clusters go from 5 to 29. Arrows indicate how traits in one cluster move across clusters from different partitions. Most of the clusters are preserved across different resolutions, showing highly stable solutions even with independent runs of the clustering algorithm. MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MRV: mean reticulocyte volume; MSCV: mean sphered cell volume; RDW: red cell (erythrocyte) distribution width; BMI: body mass index; WC: waist circumference; HC: hip circumference; BMR: basal metabolic rate; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; IBD: inflammatory bowel disease; *Descriptions of traits by cluster IDs (from left to right):* 12: also includes lymphocyte count and allergies such as allergic rhinitis or eczema; 4: includes reticulocyte count and percentage, immature reticulocyte fraction, and high light scatter reticulocytes count and percentage; 5: includes erythrocyte count, hemoglobin concentration, and hematocrit percentage; 18: also includes ankle spacing width; 1: includes platelet count, crit, mean volume, and distribution width; 13: diabetes refers to age when the diabetes was first diagnosed; 25: includes vascular problems such as angina, deep vein thrombosis (DVT), intraocular pressure, eye and mouth problems, pulse rate, hand-grip strength, several measurements of physical activity, jobs involving heavy physical work, types of transport used, intake of vitamin/mineral supplements, and various types of body pain and medications for pain relief; 21: also includes attention deficit hyperactivity disorder (ADHD), number of years of schooling completed, bone density, and intracranial volume measurement; 28: includes diabetes, gout, arthrosis, and respiratory diseases (and related medications such as ramipril, allopurinol, and lisinopril), urine assays, female-specific factors (age at menarche, menopause, first/last live birth), and several environmental/behavioral factors such as intake of a range of food/drink items including alcohol, time spent outdoors and watching TV, smoking and sleeping habits, early-life factors (breastfed as a baby, maternal smoking around birth), education attainment, psychological and mental health, and health satisfaction; 11: also includes fasting blood glucose and insulin measurement; 16: lipids include high and low-density lipoprotein cholesterol (HDL and LDL), triglycerides, and average number of methylene groups per a double bond; 14: includes myocardial infarction, coronary atherosclerosis, ischaemic heart disease (wide definition). 9: includes neutrophil count, neutrophil+basophil count, neutrophil+eosinophil count, granulocyte count, leukocyte count, and myeloid cell count.

We found that phenotypes grouped into five clear branches (Figure [5](#fig:clustering:tree)). These were 0) a “large” branch that includes most of the traits subdivided only starting at =16 (with asthma, subjective well-being traits, and nutrient intake clusters), 1) heel bone-densitometry measurements, 2) hematological assays on red blood cells, 3) physical measures, including spirometry and body impedance, and anthropometric traits with fat-free and fat mass measures in separate sub-branches, and 4) a “complex” branch including keratometry measurements, assays on white blood cells and platelets, skin and hair color traits, autoimmune disorders (type 1 diabetes, psoriasis, hyper/hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, celiac disease), and cardiovascular diseases (hypertension, coronary artery disease, myocardial infraction, hypercholesterolemia, and other cardiovascular-related traits such hand-grip strength [[59](#ref-aBVh8zt1)], and environmental/behavioral factors such as physical activity and diet) (See Supplementary Files 1-5 for clustering results). Within these branches, results were relatively stable. The same traits were often clustered together across different resolutions, even with the consensus algorithm using random initializations at each level. Arrows between different clusters show traits moving from one group to another across different resolutions. This mainly happens between clusters within the “complex” branch, and between clusters from the “large” branch to the “complex” branch. We would expect that continuing to explore higher dimensionalities would result in further subdivisions of these large groupings. This behavior was expected since complex diseases are usually associated with shared genetic and environmental factors and are thus hard to categorize into a single cluster. We would also expect that exploring solutions with a larger number of clusters would result in further subdivisions of these large groupings.

Figure 6: Cluster-specific and general transcriptional processes.  The plot shows a submatrix of \hat{\mathbf{M}} for the main trait clusters at k=29, considering only LVs (rows) that align well with at least one known pathway.  Values are standardized from -5 (lighter color) to 16 (darker color). 

Figure 6: **Cluster-specific and general transcriptional processes.** The plot shows a submatrix of for the main trait clusters at =29, considering only LVs (rows) that align well with at least one known pathway. Values are standardized from -5 (lighter color) to 16 (darker color).

Next, we analyzed which LVs were driving these clusters of traits. We trained decision tree classifiers on the input data (Figure [4](#fig:clustering:design)) using each cluster at =29 (bottom of Figure [5](#fig:clustering:tree)) as labels (see Methods). This yielded for each cluster the top LVs, where several of them were well-aligned to existing pathways, and others were “novel” and expressed in relevant tissues. We summarized this in Figure [6](#fig:clustering:heatmap), where it can be seen that some LVs were highly specific to certain types of traits, while some were associated with a wide range of different traits and diseases, thus potentially involved in more general biological functions. For example, LVs such as LV928 and LV30 (Supplementary Figures [12](#fig:sup:lv928) and [13](#fig:sup:lv30)), which were well-aligned to early progenitors of the erythrocytes lineage [[60](#ref-Zk82GvJV)], were predominantly expressed in early differentiation stages of erythropoiesis, and strongly associated with different assays on red blood cells (erythrocytes and reticulocytes). On the other side, others, such as LV730, were highly specific and expressed in thrombocytes from different cancer samples (Supplementary Figures [14](#fig:sup:lv730)), and strongly associated with hematological assays on platelets; or LV598, whose genes were expressed in corneal endothelial cells (Supplementary Figures [15](#fig:sup:lv598)) and associated with keratometry measurements (FDR < 0.05; Supplementary Table [12](#tbl:sup:phenomexcan_assocs:lv598)).

The autoimmune diseases sub-branch also had significant LVs associations expressed in relevant cell types. LV155 was strongly expressed in thyroid (Supplementary Figures [16](#fig:sup:lv155)), and significantly associated with hypothyroidism both in PhenomeXcan and eMERGE (FDR < 0.05; Supplementary Tables [13](#tbl:sup:phenomexcan_assocs:lv155) and [14](#tbl:sup:emerge_assocs:lv155)). LV844 was the most strongly associated gene module with autoimmune disorders (FDR < 1e-15; Supplementary Tables [15](#tbl:sup:phenomexcan_assocs:lv844) and [16](#tbl:sup:emerge_assocs:lv844)), and was expressed in a wide range of cell types, including blood, breast organoids, myeloma cells, lung fibroblasts, and different cell types from the brain (Supplementary Figures [17](#fig:sup:lv844)). Other important LVs associated with autoimmunity in both PhenomeXcan and eMERGE were LV57 expressed in T cells (Supplementary Figure [18](#fig:sup:lv57), and Supplementary Tables [17](#tbl:sup:phenomexcan_assocs:lv57) and [18](#tbl:sup:emerge_assocs:lv57)), and LV54 expressed in different soft tissue tumors, breast, lung, pterygia and epithelial cells (Supplementary Figure [19](#fig:sup:lv54), and Supplementary Tables [19](#tbl:sup:phenomexcan_assocs:lv54) and [20](#tbl:sup:emerge_assocs:lv54)).

The cardiovascular sub-branch also exhibited significant associations, such as LV847 (Supplementary Figure [20](#fig:sup:lv847)) with blood pressure traits and hypertension (Supplementary Tables [21](#tbl:sup:phenomexcan_assocs:lv847) and [22](#tbl:sup:emerge_assocs:lv847)), which was expressed in CD19 (B cells) (which are related to preeclampsia [[61](#ref-YyXvsbU9)]), Jurkat cells (T lymphocyte cells), and cervical carcinoma cell lines (the uterus was previously reported to be linked to blood pressure through a potential hormonal pathway [[62](#ref-Om8ZhS06),[63](#ref-meFYGVLK)]). LV136 was aligned with known collagen formation and muscle contraction pathways, and it was associated to coronary artery disease, myocardial infarction and keratometry measurements (Supplementary Tables [23](#tbl:sup:phenomexcan_assocs:lv136) and [24](#tbl:sup:emerge_assocs:lv136)), and expressed in a wide range of cell types, including fibroblasts, mesenchymal stem cells, osteoblasts, pancreatic stellate cells, cardiomyocytes, and adipocytes (Supplementary Figure [21](#fig:sup:lv136)). Lipids were clustered with chronotype and Alzheimer’s disease, and were significantly associated with several modules expressed mainly in brain cell types, including LV93 (Supplementary Figure [22](#fig:sup:lv93), and Supplementary Tables [25](#tbl:sup:phenomexcan_assocs:lv93) and [26](#tbl:sup:emerge_assocs:lv93)), LV206 (Supplementary Figure [23](#fig:sup:lv206), and Supplementary Tables [27](#tbl:sup:phenomexcan_assocs:lv206) and [28](#tbl:sup:emerge_assocs:lv206)), and LV260 (Supplementary Figure [24](#fig:sup:lv260), and Supplementary Tables [29](#tbl:sup:phenomexcan_assocs:lv260) and [30](#tbl:sup:emerge_assocs:lv260)). These modules were associated mainly with cardiovascular traits in eMERGE.

Within the cardiovascular sub-branch, we found neuropsychiatric and neurodevelopmental disorders such as Alzheimer’s disease, schizophrenia, and attention deficit hyperactivity disorder (ADHD). These disorders were previously linked to the cardiovascular system [[64](#ref-10qjLoufR),[65](#ref-j2Sl4DAE),[66](#ref-17LYMnG9n),[67](#ref-13t4TuFeJ)], and share several risk factors, including hypertension, high cholesterol, obesity, smoking, among others [[68](#ref-D83Aqhga),[69](#ref-9BGyO071)]. In our results, however, these diseases were grouped by potentially shared transcriptional processes expressed in specific tissues/cell types. Alzheimer’s disease, for example, was significantly associated with LV21 (FDR < 1e-18) and with LV5 (FDR < 0.01) (Supplementary Tables [31](#tbl:sup:phenomexcan_assocs:lv21) and [33](#tbl:sup:phenomexcan_assocs:lv5)). LV21 was strongly expressed in a variety of soft tissue sarcomas, monocytes/macrophages (including microglia from cortex samples), and aortic valves (Supplementary Figure [25](#fig:sup:lv21)); as discussed previously, macrophages play a key role in the reverse cholesterol transport and thus atherogenesis [[70](#ref-idlBgtFz)]. LV5 was expressed in breast cancer and brain glioma samples, microglia (cortex), liver, and kidney, among other cell types (Supplementary Figure [26](#fig:sup:lv5)). LV21 and LV5 were also strongly associated with lipids: LDL cholesterol (FDR < 0.001) and triglycerides (FDR < 0.05 and FDR < 0.001, respectively). Additionally, LV5 was associated with depression traits from the UK Biobank. ADHD was the only significantly associated trait for LV434 (FDR < 0.01) (Supplementary Table [35](#tbl:sup:phenomexcan_assocs:lv434)), which was expressed in breast cancer and glioma cells, cerebral organoids, and several different cell populations from the brain: fetal neurons (replicating and quiescence), microglia, and astrocytes (Supplementary Figure [27](#fig:sup:lv434)). Schizophrenia was not significantly associated with any gene module tested in our analysis. None of these LVs were aligned to prior pathways, which might represent potentially novel transcriptional processes affecting the cardiovascular and central nervous systems.

## Discussion

We have introduced a novel computational approach that can map TWAS results into a representation learned from gene expression to infer cell type-specific features of complex phenotypes. Our key innovation is that we project association statistics through a representation and that representation is derived not strictly from measures of normal tissue but also cell types under a variety of stimuli and at various developmental stages. We found that this analysis using latent representations prioritized relevant associations, even when single gene-trait effects are not detected with standard methods. Projecting gene-trait and gene-drug associations into this common representation links drug-disease treatment pairs more accurately than the single-gene method we derived this strategy from; and the findings were more interpretable for potential mechanisms of action. Finally, we found that the analysis of associations through latent representations provided reasonable groupings of diseases and traits affected by the same transcriptional processes and highlighted disease-specific modules expressed in highly relevant tissues.

In some cases, the features linked to phenotypes appear to be associated with specific cell types. Associations with such cell type marker genes may reveal cell types that are potentially causal for a phenotype with more precision. We observed modules expressed primarily in one tissue (such as adipose in LV246, thyroid in LV155, or ovary in LV66). Others appeared to be expressed in many contexts. These may capture pathways associated with a set of related complex diseases (for example, LV136 is associated with coronary artery disease and keratometry measurements, and expressed in fibroblasts, osteoblasts, pancreas, liver, and cardiomyocytes). To our knowledge, projection through a representation learned on complementary but distinct datasets is a novel approach to identify cell type and pathway effects on complex phenotypes that is computationally simple to implement.

Our approach rests on the assumption that gene modules with coordinated expression will also manifest coordinated pathological effects. Our implementation in this work integrates two complementary approaches. One, MultiPLIER, which extracts latent variables from large expression datasets. In this case, we use a previously published model derived from the analysis of recount2, which was designed for interpretability. The MultiPLIER LVs could represent real transcriptional processes or technical factors (“batch effects”). Also, the underlying factorization method rests on linear combinations of variables, which could miss important and more complex co-expression patterns, and the training dataset of recount2 has since been surpassed in size and scale by other resources [[15](#ref-Nz3IMEzd),[71](#ref-TPVeG4GP)]. Second, TWAS have several limitations that can lead to false positives [[72](#ref-l6ogswV3),[73](#ref-ndd3tW4g)]. Like GWAS, which generally detects groups of associated variants in LD (linkage disequilibrium), TWAS usually identifies several genes within the same locus [[20](#ref-Z8bvDdVq),[74](#ref-AxVJwanp)]. This is due to sharing of GWAS variants in gene expression models, to correlated expression of nearby genes, or even correlation of their predicted expression due to eQTLs in LD, among others [[72](#ref-l6ogswV3)]. Larger datasets and methods designed to learn representations with this application in mind could further refine the approach and are a promising avenue for future research.

Our findings are concordant with previous studies showing that drugs with genetic support are more likely to succeed through the drug development pipeline [[7](#ref-REXpV7nA),[48](#ref-17oeJ0CXy)]. In this case, projecting association results through latent variables better prioritizes disease-treatment pairs than considering single-gene effects alone. An additional benefit is that the latent variables driving predictions can be examined. We also demonstrate that clustering trees, introduced as a means to examine developmental processes in single-cell data, provide multi-resolution grouping of phenotypes based on latent variable associations. In this portion, we used S-MultiXcan associations, which only provide the association strength between a gene and a trait, but with no direction of effect. This does mean that traits are grouped based on associated genes, but genes could have opposite effects on traits within the same cluster. Second, we employed hard-partitioning algorithms (one trait belongs exclusively to one cluster) where the distance between two traits takes into account all gene modules. Considering groups of related diseases was previously shown to be more powerful to detect shared genetic etiology [[75](#ref-LyJmyoQr),[76](#ref-veADXImD)], and clustering trees provide a way to explore such relationships in the context of latent variables.

Ultimately, the key to performance is the quality of the representations. Here we use a representation derived from a factorization of bulk RNA-seq data. Detailed perturbation datasets and single-cell profiling of tissues, with and without perturbagens, and at various stages of development provide an avenue to generate higher quality and more interpretable representations. The key to interpretability is driven by the annotation of sample metadata. New approaches to infer and annotate with structured metadata are promising and can be directly applied to existing data [[77](#ref-fnDaLjFy)]. Rapid improvements in both areas set the stage for latent variable projections to be widely applied to disentangle the genetic basis of complex human phenotypes.

## Methods

### PhenomeXcan: gene-based associations on 4,091 traits

We used TWAS results from PhenomeXcan [[32](#ref-lY5ln3dB)] on 4,091 traits for 22,515 genes. PhenomeXcan was built using publicly available GWAS summary statistics to compute 1) gene-based associations with the PrediXcan family of methods [[19](#ref-1FFzCXo1s),[20](#ref-Z8bvDdVq),[78](#ref-vLyTudUB)], and 2) a posterior probability of colocalization between GWAS loci and *cis*-eQTL with fastENLOC [[32](#ref-lY5ln3dB),[79](#ref-wyKoQS8N)]. The PrediXcan family of methods first build prediction models using data from the Genotype-Tissue Expression project (GTEx v8) [[4](#ref-9Pr9idng)] for gene expression imputation and then correlate this predicted expression with the phenotype of interest. This family is comprised of S-PrediXcan [[78](#ref-vLyTudUB)] (which computes a gene-tissue-trait association using GWAS as input) and S-MultiXcan [[19](#ref-1FFzCXo1s)] (which computes a gene-trait association by aggregating evidence of associations across all tissues).

We refer to the standardized effect sizes (-scores) of S-PrediXcan across traits and genes in tissue as . For S-MultiXcan we do not have the direction of effect, and we used the -values converted to -scores , where is the probit function. Higher -scores correspond to stronger associations.

### MultiPLIER and Pathway-level information extractor (PLIER)

MultiPLIER [[34](#ref-14rnBunuZ)] extracts patterns of co-expressed genes from recount2 [[14](#ref-6SPTvFXq)], a large gene expression dataset. The approach applies the pathway-level information extractor method (PLIER) [[35](#ref-Ki2ij7zE)], which performs unsupervised learning using prior knowledge (canonical pathways) to reduce technical noise. Via a matrix factorization approach, PLIER deconvolutes the gene expression data into a set of latent variables (LV), where each represents a gene module. This reduced the data dimensionality into 987 latent variables or gene modules.

Given a gene expression dataset with genes and experimental conditions and a prior knowledge matrix for MSigDB pathways [[80](#ref-1CbVoEpNJ)] (so that if gene belongs to pathway ), PLIER finds , , and minimizing

subject to ; are the gene loadings with latent variables, is the latent space for conditions, specifies which of the prior-information pathways in are represented for each LV, and are different regularization parameters used in the training step. is a low-dimensional representation of the gene space where each LV aligns as much as possible to prior knowledge, and it might represent either a known or novel gene module (i.e., a meaningful biological pattern) or noise.

We projected (either from S-PrediXcan across each tissue, or S-MultiXcan) into the low-dimensional gene module space learned by MultiPLIER using:

where in all traits in PhenomeXcan are now described by gene modules.

### CRISPR-Cas9 screening

Add details

### Gene module-trait associations

To compute an association between a gene module and a trait, we used an approach similar to the gene-property analysis in MAGMA [[41](#ref-19XiXgYmd)], which is essentially a competitive test using gene weights from to predict gene -scores from . Thus, the regression model uses genes as data points by fitting , where , are gene -values (for a trait) from S-MultiXcan that we transformed to -scores as mentioned before. Since we are only interested in whether genes with a stronger membership to a module (highest weights) are more associated with the phenotype, we performed a one-sided test on the coefficient with the null hypothesis of against the alternative . Since the error terms could be correlated due to correlation between predicted expression, we used a generalized least squares approach instead of standard linear regression. To calculate , we first estimated the correlation of predicted expression for each gene pair in tissue using equations from [[19](#ref-1FFzCXo1s),[78](#ref-vLyTudUB)]:

$$
\begin{split}
\hat{\Sigma}\_{ij}^{t} & = Cor(\mathbf{t}\_i, \mathbf{t}\_j) \\
& = \frac{ Cov(\mathbf{t}\_i, \mathbf{t}\_j) } { \sqrt{\widehat{\mathrm{var}}(\mathbf{t}\_i) \widehat{\mathrm{var}}(\mathbf{t}\_j)} } \\
& = \frac{ Cov(\sum\_{a \in \mathrm{model}\_i} w\_a^i X\_a, \sum\_{b \in \mathrm{model}\_j} w\_b^j X\_b) } {\sqrt{\widehat{\mathrm{var}}(\mathbf{t}\_i) \widehat{\mathrm{var}}(\mathbf{t}\_j)} } \\
& = \frac{ \sum\_{a \in \mathrm{model}\_i \\ b \in \mathrm{model}\_j} w\_a^i w\_b^j Cov(X\_a, X\_b)} {\sqrt{\widehat{\mathrm{var}}(\mathbf{t}\_i) \widehat{\mathrm{var}}(\mathbf{t}\_j)} } \\
& = \frac{ \sum\_{a \in \mathrm{model}\_i \\ b \in \mathrm{model}\_j} w\_a^i w\_b^j \Gamma\_{ab}} {\sqrt{\widehat{\mathrm{var}}(\mathbf{t}\_i) \widehat{\mathrm{var}}(\mathbf{t}\_j)} },
\end{split}
\qquad (3)$$

where is the genotype covariance matrix using 1000 Genomes Project data [[81](#ref-11PJIeJyi),[82](#ref-1BWx1HXgP)]. The variances for predicted gene expression of gene is estimated as:

$$
\begin{split}
\widehat{\mathrm{var}}(\mathbf{t}\_i) & = (\mathbf{W}^i)^\top \Gamma^i \mathbf{W}^i \\
& = \sum\_{a \in \mathrm{model}\_i \\ b \in \mathrm{model}\_i} w\_a^i w\_b^i \Gamma\_{ab}^i.
\end{split}
\qquad (4)$$

Finally, where =49 is the number of tissues.

### Drug-disease prediction

For the drug-disease prediction, we used a method based on a drug repositioning framework previously used for psychiatry traits [[48](#ref-17oeJ0CXy)] where gene-trait associations are anticorrelated with expression profiles for drugs. For the single-gene approach, we computed a drug-disease score by multiplying each S-PrediXcan set of results in tissue , , with the transcriptional responses profiled in LINCS L1000 [[33](#ref-F7lIlh2N)], (for compounds): , where refers to the number of most significant gene associations in for each trait. As suggested in [[48](#ref-17oeJ0CXy)], could be either all genes or the top 50, 100, 250, and 500; then we average score ranks across all and obtain . Finally, for each drug-disease pair, we took the maximum prediction score across all tissues: .

The same procedure was used for the gene module-based approach, where we projected S-PrediXcan results into our latent representation, leading to ; and also , leading to . Finally, , where in this case could be all LVs or the top 5, 10, 25 and 50 (since have an order of magnitude less LVs than genes).

Since the gold standard of drug-disease medical indications used contained Disease Ontology IDs (DOID) [[83](#ref-1FsruosUW)], we mapped PhenomeXcan traits to the Experimental Factor Ontology [[84](#ref-9okjVu3s)] using [[85](#ref-16RTdMKxI)], and then to DOID.

### Consensus clustering of traits

We performed two preprocessing steps on the S-MultiXcan results before the cluster analysis procedure. First, we combined results in (S-MultiXcan) for traits that mapped to the same Experimental Factor Ontology (EFO) [[84](#ref-9okjVu3s)] term using the Stouffer’s method: , where is a weight based on the GWAS sample size for trait , and is the -score for gene . Second, we standardized all -scores for each trait by their sum to reduce the effect of highly polygenic traits: . Finally, we projected this data matrix using Equation [2](#eq:proj), obtaining with =3752 traits and =987 LVs as the input of our clustering pipeline.

A partitioning of with traits into clusters is represented as a label vector . Consensus clustering approaches consist of two steps: 1) the generation of an ensemble with partitions of the dataset: , and 2) the combination of the ensemble into a consolidated solution defined as:

where is a set of data indices with known cluster labels for partition , is a function that measures the similarity between two partitions, and is a measure of central tendency, such as the mean or median. We used the adjusted Rand index (ARI) [[86](#ref-e4AuoW8N)] for , and the median for . To obtain , we define a consensus function with as the input. We used consensus functions based on the evidence accumulation clustering (EAC) paradigm [[87](#ref-cuROQDFa)], where is first transformed into a distance matrix , where is the number of times traits and were grouped in different clusters across all partitions in . Then, can be any similarity-based clustering algorithm, which is applied on to derive the final partition .

For the ensemble generation step, we used different algorithms to create a highly diverse set of partitions (see Figure [4](#fig:clustering:design)), since diversity is an important property for ensembles [[88](#ref-8js8Q3pF),[89](#ref-rcTMvL18),[90](#ref-t5p3UpxZ)]. We used three data representations: the raw dataset, its projection into the top 50 principal components, and the embedding learned by UMAP [[91](#ref-157h5hA34)] using 50 components. For each of these, we applied five clustering algorithms, covering a wide range of different assumptions on the data structure: -means [[92](#ref-MxGpAiPu)], spectral clustering [[93](#ref-x3CT24TB)], a Gaussian mixture model (GMM), hierarchical clustering, and DBSCAN [[94](#ref-JrL3iQea)]. For -means, spectral clustering and GMM, we specified a range of between 2 and , and for each we generated five partitions using random seeds. For hierarchical clustering, for each we generated four partitions using four common linkage criteria: ward, complete, average and single. For DBSCAN, we combined different ranges for parameters (the maximum distance between two data points to be considered part of the same neighborhood) and *minPts* (the minimum number of data points in a neighborhood for a data point to be considered a core point). Specifically, we used *minPts* values from 2 to 125, and for each data version, we determined a plausible range of values by observing the distribution of the mean distance of the *minPts*-nearest neighbors across all data points. Since some combinations of *minPts* and might not produce a meaningful partition (for instance, when all points are detected as noisy or only one cluster is found), we resampled partitions generated by DBSCAN to ensure an equal representation in the ensemble. This procedure generated a final ensemble of 4428 partitions.

Finally, we used spectral clustering on to derive the final consensus partitions. was first transformed into a similarity matrix by applying an RBF kernel using four different values for that we empirically determined to work best. Thus for each between 2 and 60, we derived four consensus partitions and selected the one that maximized Equation [5](#eq:consensus:obj_func). We further filtered this set of 59 solutions to keep only those with an ensemble agreement larger than the 75th percentile, leaving a total of 15 final consensus partitions shown in Figure [5](#fig:clustering:tree).

### Cluster interpretation

We used a supervised learning approach to interpret clustering results by detecting which gene modules are the most important for clusters of traits. For this, we used the highest resolution partition (=29, although any could be used) to train a decision tree model using each of the clusters as labels and the projected data as the training samples. For each , we built a set of binary labels with the current cluster’s traits as the positive class and the rest of the traits as the negative class. Then, we selected the LV in the root node of the trained model only if its threshold was positive and larger than one standard deviation. Next, we removed this LV from (regardless of being previously selected or not) and trained the model again. We repeated this procedure 20 times to extract the top 20 LVs that better discriminate traits in a cluster from the rest.

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## Supplementary material

### Gene modules enriched for lipids gene-sets

Table 1: Gene modules (LVs) enriched for lipids gene-sets found with CRISPR screening.

|  |  |  |  |
| --- | --- | --- | --- |
| Gene module | Lipids gene-set | p-value | FDR |
| LV678 | decrease | 2.61e-07 | 2.57e-04 |
| LV707 | increase | 1.74e-07 | 2.57e-04 |
| LV905 | increase | 4.29e-05 | 2.82e-02 |
| LV915 | increase | 6.37e-05 | 3.14e-02 |

### Top traits across lipids-associated genes and modules

Table 2: Top 25 traits associated with genes from the lipids-decreasing gene-set found with CRISPR screening.

|  |  |  |
| --- | --- | --- |
| Order | Trait | Category |
| 1 | Vascular/heart problems diagnosed by doctor: High blood pressure | Diseases (cardiovascular) |
| 2 | Diastolic blood pressure, automated reading | Blood pressure |
| 3 | Non-cancer illness code, self-reported: hypertension | Diseases (cardiovascular) |
| 4 | Suggestive for eosinophilic asthma | Diseases (FinnGen) |
| 5 | Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Blood pressure medication | Medication |
| 6 | Forced expiratory volume in 1-second (FEV1), predicted | Spirometry |
| 7 | Vascular/heart problems diagnosed by doctor: None of the above | Diseases (cardiovascular) |
| 8 | Treatment/medication code: levothyroxine sodium | Medications |
| 9 | Haematocrit percentage | Blood count |
| 10 | Treatment/medication code: lisinopril | Medications |
| 11 | Haemoglobin concentration | Blood count |
| 12 | Job coding: counter clerk, bank clerk, cashier, post office clerk | Employment history |
| 13 | Acute alcohol intoxication | Diseases (FinnGen) |
| 14 | Systolic blood pressure, automated reading | Blood pressure |
| 15 | Platelet count | Blood count |
| 16 | Red Blood Cell Count | Blood |
| 17 | Peak expiratory flow (PEF) | Spirometry |
| 18 | Sitting height | Body size measures |
| 19 | Treatment/medication code: bendroflumethiazide | Medications |
| 20 | Age started wearing glasses or contact lenses | Eyesight |
| 21 | Comparative height size at age 10 | Early life factors |
| 22 | Workplace very cold: Often | Employment history |
| 23 | Salt added to food | Diet |
| 24 | Difficulty concentrating during worst period of anxiety | Anxiety |
| 25 | Treatment/medication code: metformin | Medications |

Table 3: Top 25 traits associated with gene modules (LVs) enriched for the lipids-decreasing gene-set found with CRISPR screening.

|  |  |  |
| --- | --- | --- |
| Order | Trait | Category |
| 1 | Non-cancer illness code, self-reported: malabsorption/coeliac disease | Diseases (gastrointestinal/abdominal) |
| 2 | Diastolic blood pressure, automated reading | Blood pressure |
| 3 | Immature reticulocyte fraction | Blood count |
| 4 | Treatment/medication code: ferrous salt product | Medications |
| 5 | Vascular/heart problems diagnosed by doctor: None of the above | Diseases (cardiovascular) |
| 6 | Platelet distribution width | Blood count |
| 7 | Unstable angina pectoris | Diseases (FinnGen) |
| 8 | Vascular/heart problems diagnosed by doctor: High blood pressure | Diseases (cardiovascular) |
| 9 | Nucleated red blood cell count | Blood count |
| 10 | Diagnoses - main ICD10: K90 Intestinal malabsorption | Diseases (ICD10 main) |
| 11 | Coeliac disease | Diseases (FinnGen) |
| 12 | Non-cancer illness code, self-reported: hypertension | Diseases (cardiovascular) |
| 13 | Nucleated red blood cell percentage | Blood count |
| 14 | Relative age of first facial hair | Male-specific factors |
| 15 | Treatment/medication code: thiamine preparation | Medications |
| 16 | Diagnoses - main ICD10: I70 Atherosclerosis | Diseases (ICD10 main) |
| 17 | White Blood Cell Count | Blood |
| 18 | Treatment/medication code: gtn 400micrograms spray | Medications |
| 19 | Treatment/medication code: singulair 10mg tablet | Medications |
| 20 | Difficulty not smoking for 1 day | Smoking |
| 21 | Mean reticulocyte volume | Blood count |
| 22 | Other malignant neoplasms of skin | Diseases (FinnGen) |
| 23 | Length of working week for main job | Employment |
| 24 | Pulse rate, automated reading | Blood pressure |
| 25 | Milk type used: Skimmed | Diet |

Table 4: Top 25 traits associated with genes from the lipids-increasing gene-set found with CRISPR screening.

|  |  |  |
| --- | --- | --- |
| Order | Trait | Category |
| 1 | Lymphocyte percentage | Blood count |
| 2 | Neutrophill percentage | Blood count |
| 3 | Neutrophill count | Blood count |
| 4 | Red blood cell (erythrocyte) count | Blood count |
| 5 | Lymphocyte Count | Blood |
| 6 | Trunk predicted mass | Impedance measures |
| 7 | Trunk fat-free mass | Impedance measures |
| 8 | Mean corpuscular volume | Blood count |
| 9 | Mean sphered cell volume | Blood count |
| 10 | White blood cell (leukocyte) count | Blood count |
| 11 | Skin colour | Sun exposure |
| 12 | Arm fat-free mass (left) | Impedance measures |
| 13 | Impedance of arm (left) | Impedance measures |
| 14 | Mean reticulocyte volume | Blood count |
| 15 | Whole body water mass | Impedance measures |
| 16 | Impedance of arm (right) | Impedance measures |
| 17 | Mean corpuscular haemoglobin | Blood count |
| 18 | Whole body fat-free mass | Impedance measures |
| 19 | Arm predicted mass (left) | Impedance measures |
| 20 | Arm predicted mass (right) | Impedance measures |
| 21 | Arm fat-free mass (right) | Impedance measures |
| 22 | Hair colour (natural, before greying): Red | Sun exposure |
| 23 | Ease of skin tanning | Sun exposure |
| 24 | High light scatter reticulocyte count | Blood count |
| 25 | White Blood Cell Count | Blood |

Table 5: Top 25 traits associated with gene modules (LVs) enriched for the lipids-increasing gene-set found with CRISPR screening.

|  |  |  |
| --- | --- | --- |
| Order | Trait | Category |
| 1 | Ankle spacing width | Bone-densitometry of heel |
| 2 | Ankle spacing width (left) | Bone-densitometry of heel |
| 3 | Ankle spacing width (right) | Bone-densitometry of heel |
| 4 | Job SOC coding: Advertising and public relations managers | Employment history |
| 5 | Hair colour (natural, before greying): Red | Sun exposure |
| 6 | Sitting height | Body size measures |
| 7 | Platelet distribution width | Blood count |
| 8 | Non-cancer illness code, self-reported: malabsorption/coeliac disease | Diseases (gastrointestinal/abdominal) |
| 9 | Job coding: advertising or public relations manager, media/publicity manager, campaign/fundraising manager | Employment history |
| 10 | Forced expiratory volume in 1-second (FEV1), predicted | Spirometry |
| 11 | Heel Broadband ultrasound attenuation, direct entry | Bone-densitometry of heel |
| 12 | Intra-ocular pressure, Goldmann-correlated (right) | Intraocular pressure |
| 13 | Hearing test done: No, I am unable to do this | Hearing test |
| 14 | Rheumatoid Arthritis | Diseases (ICD10 main) |
| 15 | Red blood cell (erythrocyte) distribution width | Blood count |
| 16 | Job coding: childminder, au pair, children’s nanny | Employment history |
| 17 | Heel bone mineral density (BMD) | Bone-densitometry of heel |
| 18 | Heel quantitative ultrasound index (QUI), direct entry | Bone-densitometry of heel |
| 19 | Heel bone mineral density (BMD) T-score, automated | Bone-densitometry of heel |
| 20 | Job SOC coding: Hand craft occupations n.e.c. | Employment history |
| 21 | Reason for glasses/contact lenses: For just reading/near work as you are getting older (called ‘presbyopia’) | Eyesight |
| 22 | Intra-ocular pressure, Goldmann-correlated (left) | Intraocular pressure |
| 23 | Pulse wave peak to peak time | Arterial stiffness |
| 24 | Hand grip strength (left) | Hand grip strength |
| 25 | Treatment/medication code: luteine | Medications |

### LV246

Figure 7: Cell types for LV246. 

Figure 7: **Cell types for LV246.**

Table 6: Pathways aligned to LV246.

|  |  |  |
| --- | --- | --- |
| Pathway | AUC | p-value (adjusted) |
| REACTOME\_FATTY\_ACID\_TRIACYLGLYCEROL\_AND\_KETONE\_BODY\_METABOLISM | 0.89 | 3.97e-16 |
| REACTOME\_METABOLISM\_OF\_LIPIDS\_AND\_LIPOPROTEINS | 0.67 | 1.14e-08 |
| REACTOME\_TRIGLYCERIDE\_BIOSYNTHESIS | 0.86 | 6.52e-04 |
| KEGG\_PYRUVATE\_METABOLISM | 0.82 | 2.66e-03 |
| KEGG\_PROPANOATE\_METABOLISM | 0.83 | 4.27e-03 |

Table 7: Significant trait associations of LV246 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| CH2DB NMR | 24,154 |  | 29 / 16 | 9.36e-11 |
| Non-cancer illness code, self-reported: high cholesterol | 361,141 | 43,957 | 29 / 17 | 5.24e-05 |
| Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Cholesterol lowering medication | 193,148 | 24,247 | 29 / 17 | 9.34e-03 |
| HDL Cholesterol NMR | 19,270 |  | 29 / 16 | 9.34e-03 |
| Fasting Glucose | 46,186 |  | 29 / 11 | 4.13e-02 |

Table 8: Significant trait associations of LV246 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |

### LV678

Figure 8: Cell types for LV678. 

Figure 8: **Cell types for LV678.**

Table 9: Pathways aligned to LV678.

|  |  |  |
| --- | --- | --- |
| Pathway | AUC | p-value (adjusted) |
| KEGG\_OXIDATIVE\_PHOSPHORYLATION | 0.98 | 5.75e-14 |
| REACTOME\_RESPIRATORY\_ELECTRON\_TRANSPORT\_ATP\_SYNTHESIS\_BY\_CHEMIOSMOTIC\_COUPLING\_AND\_HEAT\_PRODUCTION\_BY\_UNCOUPLING\_PROTEINS\_ | 0.99 | 5.94e-11 |
| REACTOME\_RESPIRATORY\_ELECTRON\_TRANSPORT | 1.00 | 3.10e-09 |
| REACTOME\_TCA\_CYCLE\_AND\_RESPIRATORY\_ELECTRON\_TRANSPORT | 0.86 | 9.66e-09 |
| MIPS\_55S\_RIBOSOME\_MITOCHONDRIAL | 0.81 | 8.20e-05 |
| REACTOME\_SRP\_DEPENDENT\_COTRANSLATIONAL\_PROTEIN\_TARGETING\_TO\_MEMBRANE | 0.69 | 6.03e-03 |
| REACTOME\_MITOCHONDRIAL\_PROTEIN\_IMPORT | 0.74 | 1.99e-02 |

Table 10: Significant trait associations of LV678 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| Vascular/heart problems diagnosed by doctor: Heart attack | 360,420 | 8,288 | 29 / 14 | 1.08e-02 |
| Inflammatory Bowel Disease | 34,652 | 12,882 | 29 / 21 | 2.35e-02 |
| Non-cancer illness code, self-reported: heart attack/myocardial infarction | 361,141 | 8,239 | 29 / 14 | 2.35e-02 |

Table 11: Significant trait associations of LV678 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |

### LV116

Figure 9: Cell types for LV116. 

Figure 9: **Cell types for LV116.**

### LV931

Figure 10: Cell types for LV931. 

Figure 10: **Cell types for LV931.**

### LV66

Figure 11: Cell types for LV66. 

Figure 11: **Cell types for LV66.**

### LV928

Figure 12: Cell types for LV928. 

Figure 12: **Cell types for LV928.**

### LV30

Figure 13: Cell types for LV30. 

Figure 13: **Cell types for LV30.**

### LV730

Figure 14: Cell types for LV730. 

Figure 14: **Cell types for LV730.**

### LV598

Figure 15: Cell types for LV598. 

Figure 15: **Cell types for LV598.**

Table 12: Significant trait associations of LV598 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| 6mm strong meridian (right) | 66,256 |  | 29 / 10 | 4.13e-07 |
| 6mm weak meridian (right) | 66,256 |  | 29 / 10 | 2.63e-06 |
| 6mm strong meridian (left) | 65,551 |  | 29 / 10 | 3.13e-06 |
| 3mm strong meridian (left) | 75,398 |  | 29 / 10 | 3.24e-06 |
| 6mm weak meridian (left) | 65,551 |  | 29 / 10 | 1.53e-05 |
| 3mm weak meridian (left) | 75,398 |  | 29 / 10 | 2.00e-05 |
| 3mm strong meridian (right) | 75,410 |  | 29 / 10 | 3.70e-05 |
| 3mm weak meridian (right) | 75,410 |  | 29 / 10 | 4.81e-05 |

### LV155

Figure 16: Cell types for LV155. 

Figure 16: **Cell types for LV155.**

Table 13: Significant trait associations of LV155 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| Non-cancer illness code, self-reported: hypothyroidism/myxoedema | 361,141 | 17,574 | 29 / 13 | 2.01e-03 |
| Non-cancer illness code, self-reported: hyperthyroidism/thyrotoxicosis | 361,141 | 2,730 | 29 / 13 | 1.29e-02 |
| Treatment/medication code: levothyroxine sodium | 361,141 | 14,689 | 29 / 13 | 1.41e-02 |

Table 14: Significant trait associations of LV155 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 244.2 | Acquired hypothyroidism | 45,839 | 1,155 | 2.19e-02 |
| 427.9 | Palpitations | 35,214 | 6,092 | 4.43e-02 |

### LV844

Figure 17: Cell types for LV844.   

Figure 17: **Cell types for LV844.**

Table 15: Significant trait associations of LV844 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| Rheumatoid Arthritis | 80,799 | 19,234 | 29 / 26 | 4.27e-57 |
| Non-cancer illness code, self-reported: malabsorption/coeliac disease | 361,141 | 1,587 | 29 / 8 | 4.83e-43 |
| Coeliac disease | 361,194 | 842 | 29 / 8 | 4.76e-41 |
| Diagnoses - main ICD10: K90 Intestinal malabsorption | 361,194 | 922 | 29 / 8 | 1.41e-39 |
| Started insulin within one year diagnosis of diabetes | 16,415 | 1,999 | 29 / 13 | 1.78e-37 |
| Systemic Lupus Erythematosus | 23,210 | 7,219 | 29 / 26 | 1.41e-34 |
| Age diabetes diagnosed | 16,166 |  | 29 / 13 | 3.93e-34 |
| Never eat eggs, dairy, wheat, sugar: Wheat products | 359,777 | 9,573 | 29 / 13 | 2.78e-31 |
| Non-cancer illness code, self-reported: hyperthyroidism/thyrotoxicosis | 361,141 | 2,730 | 29 / 13 | 6.08e-30 |
| Treatment/medication code: insulin product | 361,141 | 3,545 | 29 / 13 | 3.05e-25 |
| Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Insulin | 193,148 | 1,476 | 29 / 13 | 4.63e-23 |
| Medication for cholesterol, blood pressure or diabetes: Insulin | 165,340 | 2,248 | 29 / 13 | 1.92e-20 |
| Non-cancer illness code, self-reported: hypothyroidism/myxoedema | 361,141 | 17,574 | 29 / 13 | 4.96e-20 |
| Treatment/medication code: levothyroxine sodium | 361,141 | 14,689 | 29 / 13 | 4.01e-19 |
| Non-cancer illness code, self-reported: psoriasis | 361,141 | 4,192 | 29 / 13 | 9.28e-16 |

Table 16: Significant trait associations of LV844 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 714.1 | Rheumatoid arthritis | 49,453 | 2,541 | 8.22e-09 |
| 250.1 | Type 1 diabetes | 42,723 | 2,450 | 2.54e-08 |
| 714 | Rheumatoid arthritis and other inflammatory polyarthropathies | 50,215 | 3,303 | 5.06e-07 |
| 440 | Atherosclerosis | 47,471 | 4,993 | 3.15e-03 |
| 578.8 | Hemorrhage of rectum and anus | 47,545 | 1,991 | 3.15e-03 |
| 585.32 | End stage renal disease | 43,309 | 1,842 | 4.38e-03 |
| 440.2 | Atherosclerosis of the extremities | 45,524 | 3,046 | 5.00e-03 |
| 514.2 | Solitary pulmonary nodule | 50,389 | 2,270 | 6.16e-03 |
| 444 | Arterial embolism and thrombosis | 43,378 | 900 | 1.36e-02 |
| 558 | Noninfectious gastroenteritis | 40,177 | 3,191 | 2.94e-02 |
| 747.11 | Cardiac shunt/ heart septal defect | 58,364 | 1,037 | 3.60e-02 |
| 585 | Renal failure | 51,437 | 9,970 | 3.87e-02 |
| 443.9 | Peripheral vascular disease, unspecified | 46,926 | 4,448 | 4.43e-02 |

### LV57

Figure 18: Cell types for LV57.  

Figure 18: **Cell types for LV57.**

Table 17: Significant trait associations of LV57 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| Non-cancer illness code, self-reported: hypothyroidism/myxoedema | 361,141 | 17,574 | 29 / 13 | 1.17e-24 |
| Treatment/medication code: levothyroxine sodium | 361,141 | 14,689 | 29 / 13 | 6.07e-23 |
| Non-cancer illness code, self-reported: hyperthyroidism/thyrotoxicosis | 361,141 | 2,730 | 29 / 13 | 1.16e-06 |
| Started insulin within one year diagnosis of diabetes | 16,415 | 1,999 | 29 / 13 | 8.17e-05 |
| Treatment/medication code: insulin product | 361,141 | 3,545 | 29 / 13 | 6.33e-04 |
| Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Insulin | 193,148 | 1,476 | 29 / 13 | 1.13e-03 |
| Medication for cholesterol, blood pressure or diabetes: Insulin | 165,340 | 2,248 | 29 / 13 | 4.50e-03 |

Table 18: Significant trait associations of LV57 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 244 | Hypothyroidism | 54,404 | 9,720 | 3.97e-09 |
| 244.4 | Hypothyroidism NOS | 53,968 | 9,284 | 3.97e-09 |
| 279 | Disorders involving the immune mechanism | 56,771 | 3,309 | 4.93e-03 |
| 514.2 | Solitary pulmonary nodule | 50,389 | 2,270 | 1.19e-02 |
| 714 | Rheumatoid arthritis and other inflammatory polyarthropathies | 50,215 | 3,303 | 1.68e-02 |
| 452.2 | Deep vein thrombosis [DVT] | 38,791 | 2,131 | 4.37e-02 |

### LV54

Figure 19: Cell types for LV54.  

Figure 19: **Cell types for LV54.**

Table 19: Significant trait associations of LV54 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| Diagnoses - main ICD10: K90 Intestinal malabsorption | 361,194 | 922 | 29 / 8 | 5.09e-25 |
| Coeliac disease | 361,194 | 842 | 29 / 8 | 7.77e-25 |
| Never eat eggs, dairy, wheat, sugar: Wheat products | 359,777 | 9,573 | 29 / 13 | 6.33e-23 |
| Systemic Lupus Erythematosus | 23,210 | 7,219 | 29 / 26 | 1.32e-22 |
| Started insulin within one year diagnosis of diabetes | 16,415 | 1,999 | 29 / 13 | 3.84e-20 |
| Non-cancer illness code, self-reported: hyperthyroidism/thyrotoxicosis | 361,141 | 2,730 | 29 / 13 | 9.59e-19 |
| Treatment/medication code: insulin product | 361,141 | 3,545 | 29 / 13 | 5.07e-18 |
| Age diabetes diagnosed | 16,166 |  | 29 / 13 | 1.28e-17 |
| Non-cancer illness code, self-reported: malabsorption/coeliac disease | 361,141 | 1,587 | 29 / 8 | 1.36e-14 |
| Medication for cholesterol, blood pressure or diabetes: Insulin | 165,340 | 2,248 | 29 / 13 | 8.67e-14 |
| Non-cancer illness code, self-reported: psoriasis | 361,141 | 4,192 | 29 / 13 | 2.61e-13 |
| Rheumatoid Arthritis | 80,799 | 19,234 | 29 / 26 | 3.11e-13 |
| Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Insulin | 193,148 | 1,476 | 29 / 13 | 3.89e-12 |
| Treatment/medication code: levothyroxine sodium | 361,141 | 14,689 | 29 / 13 | 5.92e-10 |
| Non-cancer illness code, self-reported: hypothyroidism/myxoedema | 361,141 | 17,574 | 29 / 13 | 3.31e-08 |

Table 20: Significant trait associations of LV54 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 250.1 | Type 1 diabetes | 42,723 | 2,450 | 2.04e-13 |
| 244 | Hypothyroidism | 54,404 | 9,720 | 5.10e-06 |
| 244.4 | Hypothyroidism NOS | 53,968 | 9,284 | 5.37e-06 |
| 695 | Erythematous conditions | 48,347 | 4,210 | 4.25e-05 |
| 714 | Rheumatoid arthritis and other inflammatory polyarthropathies | 50,215 | 3,303 | 3.06e-04 |
| 440 | Atherosclerosis | 47,471 | 4,993 | 8.88e-04 |
| 585 | Renal failure | 51,437 | 9,970 | 3.40e-03 |
| 585.32 | End stage renal disease | 43,309 | 1,842 | 3.64e-03 |
| 585.33 | Chronic Kidney Disease, Stage III | 46,279 | 4,812 | 3.64e-03 |
| 285.2 | Anemia of chronic disease | 39,673 | 2,606 | 7.62e-03 |
| 415.1 | Acute pulmonary heart disease | 49,887 | 1,857 | 8.67e-03 |
| 285.21 | Anemia in chronic kidney disease | 38,616 | 1,549 | 1.16e-02 |
| 743 | Osteoporosis, osteopenia and pathological fracture | 55,165 | 11,990 | 1.31e-02 |
| 415.11 | Pulmonary embolism and infarction, acute | 49,867 | 1,837 | 1.39e-02 |
| 577 | Diseases of pancreas | 60,538 | 1,795 | 1.42e-02 |
| 585.1 | Acute renal failure | 46,803 | 5,336 | 1.51e-02 |
| 195 | Cancer, suspected or other | 50,040 | 2,250 | 1.52e-02 |
| 440.2 | Atherosclerosis of the extremities | 45,524 | 3,046 | 1.89e-02 |
| 714.1 | Rheumatoid arthritis | 49,453 | 2,541 | 3.18e-02 |
| 458.9 | Hypotension NOS | 50,150 | 3,241 | 3.32e-02 |

### LV847

Figure 20: Cell types for LV847.  

Figure 20: **Cell types for LV847.**

Table 21: Significant trait associations of LV847 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Blood pressure medication | 193,148 | 33,519 | 29 / 17 | 1.95e-18 |
| Vascular/heart problems diagnosed by doctor: None of the above | 360,420 | 253,565 | 29 / 17 | 4.07e-15 |
| Vascular/heart problems diagnosed by doctor: High blood pressure | 360,420 | 97,139 | 29 / 17 | 6.99e-14 |
| Non-cancer illness code, self-reported: hypertension | 361,141 | 93,560 | 29 / 17 | 1.48e-13 |
| Treatment/medication code: bendroflumethiazide | 361,141 | 20,196 | 29 / 17 | 1.41e-08 |
| Medication for cholesterol, blood pressure or diabetes: Blood pressure medication | 165,340 | 40,987 | 29 / 17 | 1.47e-07 |
| Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: None of the above | 193,148 | 133,338 | 29 / 17 | 1.55e-06 |
| Diastolic blood pressure, automated reading | 340,162 |  | 29 / 17 | 3.76e-06 |
| Medication for cholesterol, blood pressure or diabetes: None of the above | 165,340 | 110,372 | 29 / 17 | 6.36e-06 |

Table 22: Significant trait associations of LV847 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 585.32 | End stage renal disease | 43,309 | 1,842 | 1.88e-08 |
| 442.1 | Aortic aneurysm | 45,589 | 3,111 | 5.23e-06 |
| 411.3 | Angina pectoris | 43,503 | 4,382 | 2.14e-05 |
| 415.11 | Pulmonary embolism and infarction, acute | 49,867 | 1,837 | 5.13e-05 |
| 416 | Cardiomegaly | 53,289 | 5,259 | 6.50e-05 |
| 415.1 | Acute pulmonary heart disease | 49,887 | 1,857 | 7.28e-05 |
| 411 | Ischemic Heart Disease | 54,275 | 15,154 | 5.49e-04 |
| 401.2 | Hypertensive heart and/or renal disease | 30,405 | 6,253 | 1.28e-03 |
| 519 | Other diseases of respiratory system, not elsewhere classified | 56,909 | 2,056 | 1.28e-03 |
| 411.8 | Other chronic ischemic heart disease, unspecified | 44,123 | 5,002 | 1.42e-03 |
| 427.6 | Premature beats | 31,575 | 2,453 | 5.65e-03 |
| 687.1 | Rash and other nonspecific skin eruption | 47,039 | 4,964 | 9.88e-03 |
| 185 | Cancer of prostate | 52,630 | 2,815 | 1.03e-02 |
| 591 | Urinary tract infection | 49,727 | 10,016 | 1.34e-02 |
| 442.11 | Abdominal aortic aneurysm | 44,531 | 2,053 | 2.08e-02 |
| 427.21 | Atrial fibrillation | 37,743 | 8,621 | 2.26e-02 |
| 389.1 | Sensorineural hearing loss | 53,672 | 4,318 | 2.73e-02 |
| 427.2 | Atrial fibrillation and flutter | 37,934 | 8,812 | 4.50e-02 |

### LV136

Figure 21: Cell types for LV136.  Pulmonary microvascular endothelial cells were exposed to hypoxia for 24 hours or more [95];

Figure 21: **Cell types for LV136.** Pulmonary microvascular endothelial cells were exposed to hypoxia for 24 hours or more [[95](#ref-VKYS05n1)];

Table 23: Significant trait associations of LV136 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| 3mm strong meridian (right) | 75,410 |  | 29 / 10 | 9.19e-11 |
| 6mm strong meridian (left) | 65,551 |  | 29 / 10 | 2.06e-09 |
| 6mm strong meridian (right) | 66,256 |  | 29 / 10 | 2.38e-09 |
| 3mm strong meridian (left) | 75,398 |  | 29 / 10 | 1.34e-08 |
| 3mm weak meridian (right) | 75,410 |  | 29 / 10 | 1.67e-08 |
| Coronary Artery Disease | 184,305 | 60,801 | 29 / 11 | 1.67e-08 |
| 6mm weak meridian (right) | 66,256 |  | 29 / 10 | 3.21e-08 |
| 3mm weak meridian (left) | 75,398 |  | 29 / 10 | 5.20e-08 |
| 6mm weak meridian (left) | 65,551 |  | 29 / 10 | 1.21e-07 |
| Coronary atherosclerosis | 361,194 | 14,334 | 29 / 14 | 3.90e-06 |
| Ischaemic heart disease, wide definition | 361,194 | 20,857 | 29 / 14 | 7.22e-06 |
| Vascular/heart problems diagnosed by doctor: Heart attack | 360,420 | 8,288 | 29 / 14 | 2.93e-04 |
| Myocardial infarction | 361,194 | 7,018 | 29 / 14 | 6.33e-04 |
| Myocardial infarction, strict | 361,194 | 7,018 | 29 / 14 | 6.33e-04 |
| Diagnoses - main ICD10: I21 Acute myocardial infarction | 361,194 | 5,948 | 29 / 14 | 9.92e-04 |
| Non-cancer illness code, self-reported: heart attack/myocardial infarction | 361,141 | 8,239 | 29 / 14 | 1.40e-03 |
| Major coronary heart disease event excluding revascularizations | 361,194 | 10,157 | 29 / 14 | 1.85e-02 |
| Major coronary heart disease event | 361,194 | 10,157 | 29 / 14 | 1.85e-02 |
| Fasting Insulin | 38,238 |  | 29 / 11 | 3.85e-02 |

Table 24: Significant trait associations of LV136 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 747.1 | Cardiac congenital anomalies | 59,198 | 1,871 | 4.71e-02 |
| 411.4 | Coronary atherosclerosis | 52,836 | 13,715 | 4.80e-02 |

### LV93

Figure 22: Cell types for LV93. 

Figure 22: **Cell types for LV93.**

Table 25: Significant trait associations of LV93 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| CH2DB NMR | 24,154 |  | 29 / 16 | 9.61e-24 |
| Chronotype | 128,266 |  | 29 / 16 | 1.17e-03 |
| HDL Cholesterol NMR | 19,270 |  | 29 / 16 | 2.99e-03 |

Table 26: Significant trait associations of LV93 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 208 | Benign neoplasm of colon | 55,694 | 8,597 | 6.21e-03 |
| 440.2 | Atherosclerosis of the extremities | 45,524 | 3,046 | 1.31e-02 |
| 444 | Arterial embolism and thrombosis | 43,378 | 900 | 4.06e-02 |

### LV206

Figure 23: Cell types for LV206. 

Figure 23: **Cell types for LV206.**

Table 27: Significant trait associations of LV206 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| CH2DB NMR | 24,154 |  | 29 / 16 | 7.67e-21 |
| HDL Cholesterol NMR | 19,270 |  | 29 / 16 | 6.46e-03 |

Table 28: Significant trait associations of LV206 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 458 | Hypotension | 51,341 | 4,432 | 1.41e-02 |
| 286.9 | Abnormal coagulation profile | 48,006 | 800 | 1.54e-02 |
| 458.9 | Hypotension NOS | 50,150 | 3,241 | 1.58e-02 |
| 428.2 | Heart failure NOS | 48,178 | 3,584 | 1.65e-02 |

### LV260

Figure 24: Cell types for LV260. 

Figure 24: **Cell types for LV260.**

Table 29: Significant trait associations of LV260 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| CH2DB NMR | 24,154 |  | 29 / 16 | 5.96e-17 |
| HDL Cholesterol NMR | 19,270 |  | 29 / 16 | 2.37e-02 |

Table 30: Significant trait associations of LV260 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 427.6 | Premature beats | 31,575 | 2,453 | 2.85e-02 |
| 426.3 | Bundle branch block | 31,827 | 2,705 | 4.80e-02 |

### LV21

Figure 25: Cell types for LV21. 

Figure 25: **Cell types for LV21.**

Table 31: Significant trait associations of LV21 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| Alzheimers Disease | 54,162 | 17,008 | 29 / 16 | 1.64e-19 |
| LDL Cholesterol NMR | 13,527 |  | 29 / 16 | 1.18e-04 |
| Triglycerides NMR | 21,559 |  | 29 / 16 | 2.19e-02 |

Table 32: Significant trait associations of LV21 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 573 | Other disorders of liver | 47,826 | 2,524 | 1.37e-02 |
| 577 | Diseases of pancreas | 60,538 | 1,795 | 2.15e-02 |

### LV5

Figure 26: Cell types for LV5. 

Figure 26: **Cell types for LV5.**

Table 33: Significant trait associations of LV5 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| LDL Cholesterol NMR | 13,527 |  | 29 / 16 | 1.78e-04 |
| Triglycerides NMR | 21,559 |  | 29 / 16 | 5.00e-04 |
| Alzheimers Disease | 54,162 | 17,008 | 29 / 16 | 3.06e-03 |
| Ever had prolonged feelings of sadness or depression | 117,763 | 64,374 | 29 / 27 | 8.69e-03 |
| Substances taken for depression: Medication prescribed to you (for at least two weeks) | 117,763 | 28,351 | 29 / 27 | 1.03e-02 |
| Recent feelings of depression | 117,656 |  | 29 / 27 | 1.32e-02 |
| Ever contemplated self-harm | 117,610 |  | 29 / 27 | 1.89e-02 |
| Recent lack of interest or pleasure in doing things | 117,757 |  | 29 / 27 | 2.08e-02 |
| Amount of alcohol drunk on a typical drinking day | 108,256 |  | 29 / 27 | 3.50e-02 |
| Ever sought or received professional help for mental distress | 117,677 | 46,020 | 29 / 27 | 3.92e-02 |
| General happiness | 117,442 |  | 29 / 27 | 4.74e-02 |

Table 34: Significant trait associations of LV5 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 241 | Nontoxic nodular goiter | 47,842 | 3,158 | 8.98e-03 |
| 241.1 | Nontoxic uninodular goiter | 47,125 | 2,441 | 2.57e-02 |
| 241.2 | Nontoxic multinodular goiter | 46,465 | 1,781 | 4.43e-02 |

### LV434

Figure 27: Cell types for LV434.     HEK293 is a cell line derived from human embryonic kidney cells; 3T3 is a cell line derived from mouse embryonic fibroblasts.

Figure 27: **Cell types for LV434.** HEK293 is a cell line derived from human embryonic kidney cells; 3T3 is a cell line derived from mouse embryonic fibroblasts.

Table 35: Significant trait associations of LV434 in PhenomeXcan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Trait description | Sample size | Cases | Partition/cluster number | p-value (adjusted) |
| Attention Deficit Hyperactivity Disorder | 53,293 | 19,099 | 29 / 21 | 7.01e-03 |

Table 36: Significant trait associations of LV434 in eMERGE.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Phecode | Trait description | Sample size | Cases | p-value (adjusted) |
| 722 | Intervertebral disc disorders | 47,659 | 7,458 | 6.65e-03 |
| 721 | Spondylosis and allied disorders | 47,517 | 7,316 | 7.62e-03 |
| 250.4 | Abnormal glucose | 45,220 | 4,947 | 1.02e-02 |
| 721.1 | Spondylosis without myelopathy | 47,315 | 7,114 | 1.22e-02 |
| 720 | Spinal stenosis | 44,807 | 4,606 | 1.74e-02 |
| 288 | Diseases of white blood cells | 47,288 | 2,802 | 2.10e-02 |
| 796 | Elevated prostate specific antigen [PSA] | 51,990 | 2,175 | 3.09e-02 |
| 288.2 | Elevated white blood cell count | 46,595 | 2,109 | 3.54e-02 |
| 079 | Viral infection | 46,991 | 1,934 | 4.19e-02 |

### Agreement of consensus clustering partitions with the ensemble by number of clusters

Figure 28: Final selected partitions for follow-up analysis.  From all consensus clustering partitions generated with k from 2 to 60, we selected those with a median adjusted Rand index (ARI) with the ensemble members greater the 75th percentile.

Figure 28: **Final selected partitions for follow-up analysis.** From all consensus clustering partitions generated with from 2 to 60, we selected those with a median adjusted Rand index (ARI) with the ensemble members greater the 75th percentile.