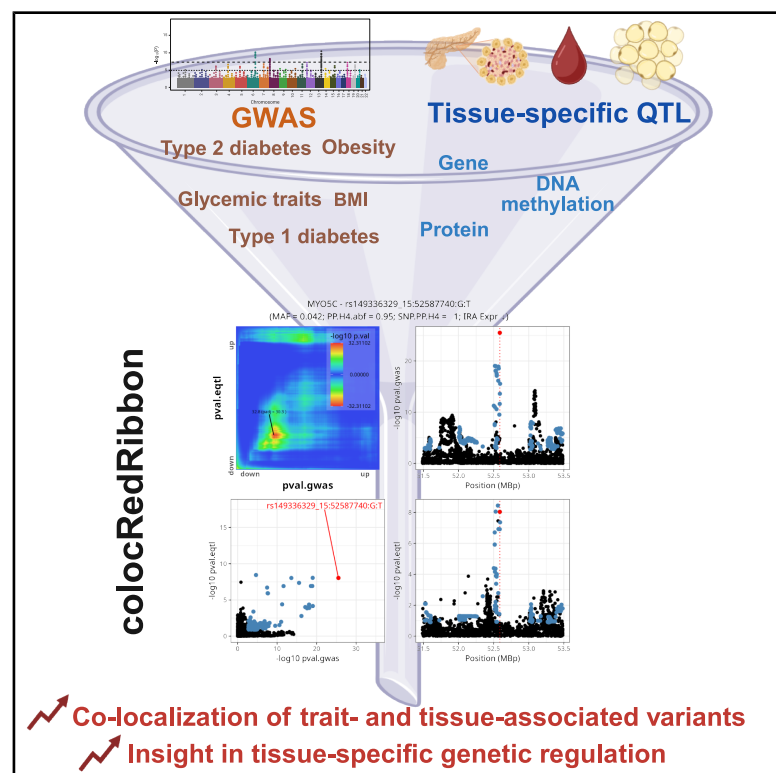


Identification of novel type 1 and type 2 diabetes genes by co-localization of human islet eQTL and GWAS variants with *colocRedRibbon*

Graphical abstract



Authors

Anthony Piron, Florian Szymczak, Lise Folon, ..., Décio L. Eizirik, Josep M. Mercader, Miriam Cnop

Correspondence

anthony.piron@ulb.be (A.P.), miriam.cnop@ulb.be (M.C.)

In brief

Piron et al. present the tool *colocRedRibbon*, which identifies hundreds of gene regions where genetic variation influences diabetes risk and glycemic traits through effects on pancreatic islet gene expression. This approach enables the discovery of tissue-specific mechanisms and advances understanding of the genetic architecture of diabetes.

Highlights

- *colocRedRibbon* is a new tool to match genetic variants with gene expression changes
- The tool uncovers 292 islet gene regions tied to diabetes and glycemic traits
- It can co-localize genetic variants with transcripts, proteins, and DNA methylation
- These co-localizations provide insight into how GWAS variants confer disease risk

Article

Identification of novel type 1 and type 2 diabetes genes by co-localization of human islet eQTL and GWAS variants with *colocRedRibbon*

Anthony Piron,^{1,2,3,4,16,*} Florian Szymczak,^{1,3} Lise Folon,¹ Daniel J.M. Crouch,⁴ Theodora Papadopoulou,¹ Maria Lytrivi,¹ Yue Tong,¹ Maria Inês Alvelos,¹ Maikel L. Colli,¹ Xiaoyan Yi,¹ Marcin L. Pekalski,^{4,5} Konstantinos Hatzikotoulas,⁶ Alicia Huerta-Chagoya,^{7,8,9} Henry J. Taylor,^{11,12,13} Type 2 Diabetes Global Genomics Initiative, Matthieu Defrance,³ John A. Todd,⁴ Décio L. Eizirik,¹ Josep M. Mercader,^{7,8,9,10} and Miriam Cnop^{1,14,15,*}

¹ULB Center for Diabetes Research, Medical Faculty, Université Libre de Bruxelles, 1070 Brussels, Belgium

²Pharmacognosy, Bioanalysis and Drug Discovery, Pharmacy Faculty, Université Libre de Bruxelles, 1050 Brussels, Belgium

³Interuniversity Institute of Bioinformatics in Brussels (IB2), 1050 Brussels, Belgium

⁴JDRF/Wellcome Diabetes and Inflammation Laboratory, Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford OX3 7BN, UK

⁵Military Institute of Medicine, National Research Institute Warsaw, Warsaw, Poland

⁶Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, 85764 Neuherberg, Germany

⁷Diabetes Unit, Massachusetts General Hospital, Boston, MA 02144, USA

⁸Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA 02114, USA

⁹Department of Medicine, Harvard Medical School, Boston, MA 02115, USA

¹⁰Programs in Metabolism and Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA

¹¹Center for Precision Health Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892-2152, USA

¹²British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge CB2 0BB, UK

¹³Heart and Lung Research Institute, University of Cambridge, Cambridge CB2 0BB, UK

¹⁴Division of Endocrinology, Erasmus Hospital, Université Libre de Bruxelles, 1070 Brussels, Belgium

¹⁵WEL Research Institute, 1300 Wavre, Belgium

¹⁶Lead contact

*Correspondence: anthony.piron@ulb.be (A.P.), miriam.cnop@ulb.be (M.C.)

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SUMMARY

Over 1,000 genetic variants have been associated with diabetes by genome-wide association studies (GWASs), but for most, their functional impact is unknown; only 7% alter gene expression in pancreatic islets in expression quantitative trait locus (eQTL) studies. To fill this gap, we developed a co-localization pipeline, *colocRedRibbon*, that prefilters eQTLs by the direction of effect on gene expression and shortlists overlapping eQTL and GWAS variants prior to co-localization. Applying *colocRedRibbon* to recent diabetes and glycemic trait GWASs, we identified 292 co-localizing gene regions, including 24 co-localizations for type 1 diabetes and 268 for type 2 diabetes and glycemic traits, representing a 4-fold increase. A low-frequency type 2 diabetes protective variant increases islet *MYO5C* expression, and a type 1 diabetes protective variant increases *FUT2* expression. These novel co-localizations advance the understanding of diabetes genetics and its impact on human islet biology. *colocRedRibbon* has broad applicability to co-localize GWASs and various QTLs.

INTRODUCTION

Diabetes is a complex, multi-factorial disease characterized by elevated blood glucose levels. More than 589 million people are affected worldwide, and diabetes prevalence is forecasted to reach 1.31 billion by 2050.^{1,2} Common forms are type 1 (10%–15%) and type 2 (>85%) diabetes. Environmental factors such as sedentary lifestyle, obesity, aging, viral infections, and gut microbiome play important roles in the development of diabetes

and underlie the increasing prevalence.^{3–5} Familial clustering and heritability studies have long provided evidence for the role of genetic factors, and type 1 and type 2 diabetes are now established as polygenic. Progressive pancreatic islet dysfunction, caused by environmental and genetic factors, is central in most forms of diabetes.^{6–8} Therefore, the study of human islet pathophysiology is essential to better understand the disease.

Large genome-wide association studies (GWASs) and fine-mapping analyses have associated >700 genetic loci with the

risk for type 1 and type 2 diabetes and glycemic traits,^{9–15} but the mechanism of action for most remains poorly understood. 89% of fine-mapped type 2 diabetes GWAS variants lie in non-coding genomic regions⁹; these are typically named after the closest gene. *Cis*-expression quantitative trait locus (*cis*-eQTL) analyses link variants with gene expression. Such approaches have identified gene expression changes associated with variants lying farther away or in intronic regions of other genes in human tissues¹⁶ and islets,^{17,18} showing that the closest gene is not necessarily the effector. eQTLs further inform about the direction of effect, i.e., whether a variant is associated with lower or higher gene expression. Linking diabetes-associated variants to gene expression is therefore an essential step to understanding diabetes genetics and pathophysiology.

One of the methods to link disease variants with gene expression is to co-localize GWAS and *cis*-eQTL variants. The Genotype-Tissue Expression (GTEx) project generated eQTLs for 54 human tissues,¹⁹ including pancreas. However, pancreatic islets—a key tissue in diabetes pathogenesis—are not part of the GTEx collection. Separate initiatives have identified human islet eQTLs and co-localized them with diabetes GWAS hits, advancing the domain but falling short of expectations: only around 50 are associated with gene expression variation.^{17,18} We hypothesized that this missing link is, at least in part, caused by methodological limitations of the available co-localization approaches. Indeed, we observed that existing co-localization tools miss matching GWAS and eQTL signals when analyzing chromosomal regions that contain multiple strong GWAS signals. These tools also do not consider the direction of effect of variants in a region tested for co-localization.

To test this hypothesis and fill the co-localization gap, we developed a new co-localization pipeline, *colocRedRibbon*. The method uses novel prefiltering steps, shortlisting variants before running an existing co-localization tool. We use *colocRedRibbon* to co-localize human islet *cis*-eQTLs¹⁷ and GWASs for type 1 diabetes,²⁰ type 2 diabetes,¹⁵ and glycemic traits.¹¹ We significantly expand the number of co-localizations to 268 for type 2 diabetes and to 24 for type 1 diabetes, making this study the largest to date and improving knowledge about genetic regulation in human islets.

colocRedRibbon is a versatile tool designed to co-localize a wide range of datasets, extending beyond diabetes and islets. It enables the integration of GWAS data for any trait with various QTL types or with other GWAS datasets. To highlight its broad applicability, we applied *colocRedRibbon* to protein QTLs (pQTLs),²¹ methylation QTLs (meQTLs),²² obesity GWASs,²³ and BMI GWASs.²⁴

RESULTS

Previous studies have linked diabetes GWAS signals to eQTL variants in human islets, a highly disease-relevant tissue that maintains glycemia. The yield of the 2 largest studies to date^{17,18} has been limited, identifying co-localization with eQTL variants for only 7% of GWAS hits. To investigate the hypothesis that methodological limitations in co-localization approaches contributed to the “co-localization missing link,” we developed a novel tool called *colocRedRibbon*. The pipeline employs a

two-step approach for shortlisting variants and then runs the *coloc* co-localization package.²⁵ The novel shortlisting method first categorizes risk variants based on the direction of effect on gene expression and then uses *RedRibbon* rank-rank hypergeometric overlap.²⁶ In this second step, variants are ranked by *p* values for both GWASs or QTLs, and potential overlap between the ranked lists is statistically examined (see the [STAR Methods](#) section). In the last step, *coloc*²⁵ is used to assess the posterior probability (PP) that both dataset signals share the same causal variant, known as hypothesis H4; a PP.H4.abc > 0.8 is considered significant. Additionally, SNP.PP.H4 represents the PP that the lead SNP is the shared causal variant in both datasets. We applied *colocRedRibbon* to recent large-scale eQTL,¹⁷ pQTL,²¹ meQTL,²² and GWAS^{11,15,20,23,24} datasets ([Figure 1](#)). The eQTL dataset is from the translational human pancreatic islet genotype tissue-expression resource (TIGER), which is, with its meta-analysis of eQTLs in 4 cohorts comprising 404 islet samples, one of the largest eQTL analyses of human islets.¹⁷ The European and multi-ancestry type 2 diabetes GWASs were from the Type 2 Diabetes Global Genomic Initiative (T2DGGI).¹⁵ The Wellcome Center for Human Genetics provided the GWAS for type 1 diabetes.²⁰ Quantitative glycemic trait GWASs originate from MAGIC.¹¹ These GWASs are among the biggest to date, having included >2.5 million cases/controls for type 2 diabetes, >170,000 for type 1 diabetes, and up to 200,000 for glycemic traits ([Table S1](#)). The pQTL from deCODE includes data from 35,000 individuals on 4,907 aptamers.²¹ The adipocyte meQTL from the Twins UK cohort comprises 538 participants.²² The obesity GWAS from FinnGen analyzed 500,000 individuals, including 31,000 cases,²³ and the BMI GWAS from GIANT included 700,000 participants.²⁴

The co-localization of variants identifies important diabetes genes

With this new *colocRedRibbon* pipeline, we identified a total of 434 co-localizations between islet eQTL and diabetes and glycemic trait GWAS variants. These co-localizations are shown by their chromosomal position in a circle plot, highlighting the regulated genes for GWAS SNPs for type 1 diabetes (*n* = 24), type 2 diabetes (multi-ancestry GWAS *n* = 216; European ancestry *n* = 143), and the glycemic traits fasting glucose (*n* = 22), post-challenge 2-h glucose (*n* = 4), HbA1c (*n* = 20), and fasting insulin (*n* = 2) ([Figure 2](#); [Tables S2](#) and [S3](#)).

We examined a total of 10,835,771 GWAS variants, including non-significant ones, within a 2 million base-pair region around the transcription start site of genes exhibiting at least one significant GWAS variant and one eQTL. The distribution of the 10,835,771 variants across traits revealed that type 2 diabetes accounts for the majority (73%), with multi-ancestry GWAS contributing 41% and European ancestry 32%. Type 1 diabetes represented 18% of the variants, and glycemic traits were represented to a lesser extent: HbA1c (5%), 2-h glucose (0.5%), fasting glucose (3%), and fasting insulin (0.5%) ([Table S4](#)).

Type 2 diabetes demonstrated the highest number of co-localizations ([Tables S2](#), [S3](#), and [S5](#)). The lowest number was found for fasting insulin, which reflects insulin resistance rather than β cell function. This aligns with the

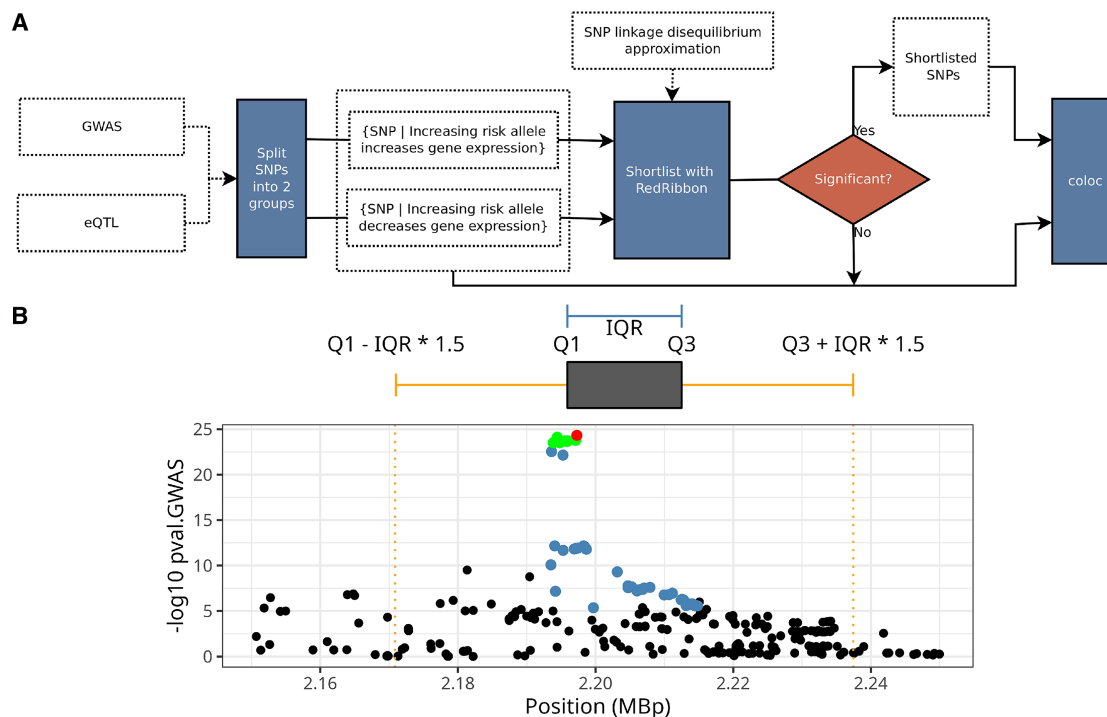


Figure 1. The *colocRedRibbon* pipeline

(A) The workflow of *colocRedRibbon*. GWAS and eQTL SNPs are split into two effect sets depending on the direction of effect on gene expression for the increasing risk allele. The *RedRibbon* rank-rank hypergeometric overlap method is applied on both SNP sets ranked by p values. If significant overlap is detected by *RedRibbon*, shortlisted SNPs are analyzed by *coloc*. Otherwise, *coloc* is applied to the two effect sets without overlap shortlisting.

(B) The interquartile range mode of *colocRedRibbon* adds a background of variants between dotted orange lines, where Q_1 is the 25th percentile (first quartile) of the chromosomal positions of the core set, Q_2 the 75th percentile (third quartile), and IQR the interquartile range.

expectation that insulin resistance would primarily manifest in skeletal muscle, liver, or adipose tissue rather than in pancreatic islets.

***colocRedRibbon* shortlisting steps solve the issue of multiple GWAS signals**

Cis-eQTL signals for a gene typically manifest themselves as a single peak of variants in linkage disequilibrium, whereas GWAS signals often comprise multiple independent peaks. This multiplicity of signals can confound *coloc*, potentially leaving legitimate co-localizations undetected. A prime example is observed in a 2 million base-pair region surrounding the *RPL39L* gene. *coloc* identifies a lead variant in a strong type 2 diabetes GWAS signal (red dot at the top, Figure 3A) but overlooks an adjacent, highly significant—albeit weaker—signal (Figure 3A) that holds potential for a legitimate co-localization given the presence of a matching eQTL at the same chromosomal position (Figure 3A, bottom). *coloc* assumes under the H4 hypothesis that each trait has a single causal variant that is shared between traits. For *coloc* to be reliable, the analysis must be restricted to genomic regions where the single causal variant assumption holds. In the case of *RPL39L*, this could be achieved by narrowing the region and excluding the stronger GWAS signal.

To address this issue, we shortlisted SNPs using *RedRibbon* overlap. This approach involves ranking GWAS and eQTL variant

lists from lowest to highest p value and searching for overlapping SNPs using a rank-rank hypergeometric overlap approach. The resulting overlap map reveals a strong and highly significant overlap among low p values (Figure 3B, top left). By selecting the variants with the most significant overlap (Figure 3B, blue dots at bottom left), we identified matching GWAS and eQTL peaks and the lead SNP (Figure 3B, red dot on the right). This shortlisting step eliminates spurious GWAS signals unrelated to eQTL peaks, enabling *coloc* to detect co-localization. The lead SNP rs3887925 is the only variant in the 99% credible set. The T effector allele that is associated with type 2 diabetes risk upregulates *RPL39L* transcript expression in human islets (Figure 3C). The SNP lies in regulatory genomic regions, and *RPL39L* is differentially expressed in islets from type 2 diabetic vs. non-diabetic donors, pointing to biological relevance (see below).

The *colocRedRibbon* method further refines the analysis through a direction-of-effect step, which splits variants into two disjoint subsets based on whether their risk alleles up- or downregulate a gene. This premise reduces the number of variants considered by *coloc*. For instance, in a region around the gene *TH* with multiple type 2 diabetes GWAS signals (Figure 3D, top), *coloc* fails to detect co-localization due to the confounding effect of the strongest GWAS signal. By only retaining variants for which the risk allele downregulates *TH* expression and excluding many highly significant GWAS

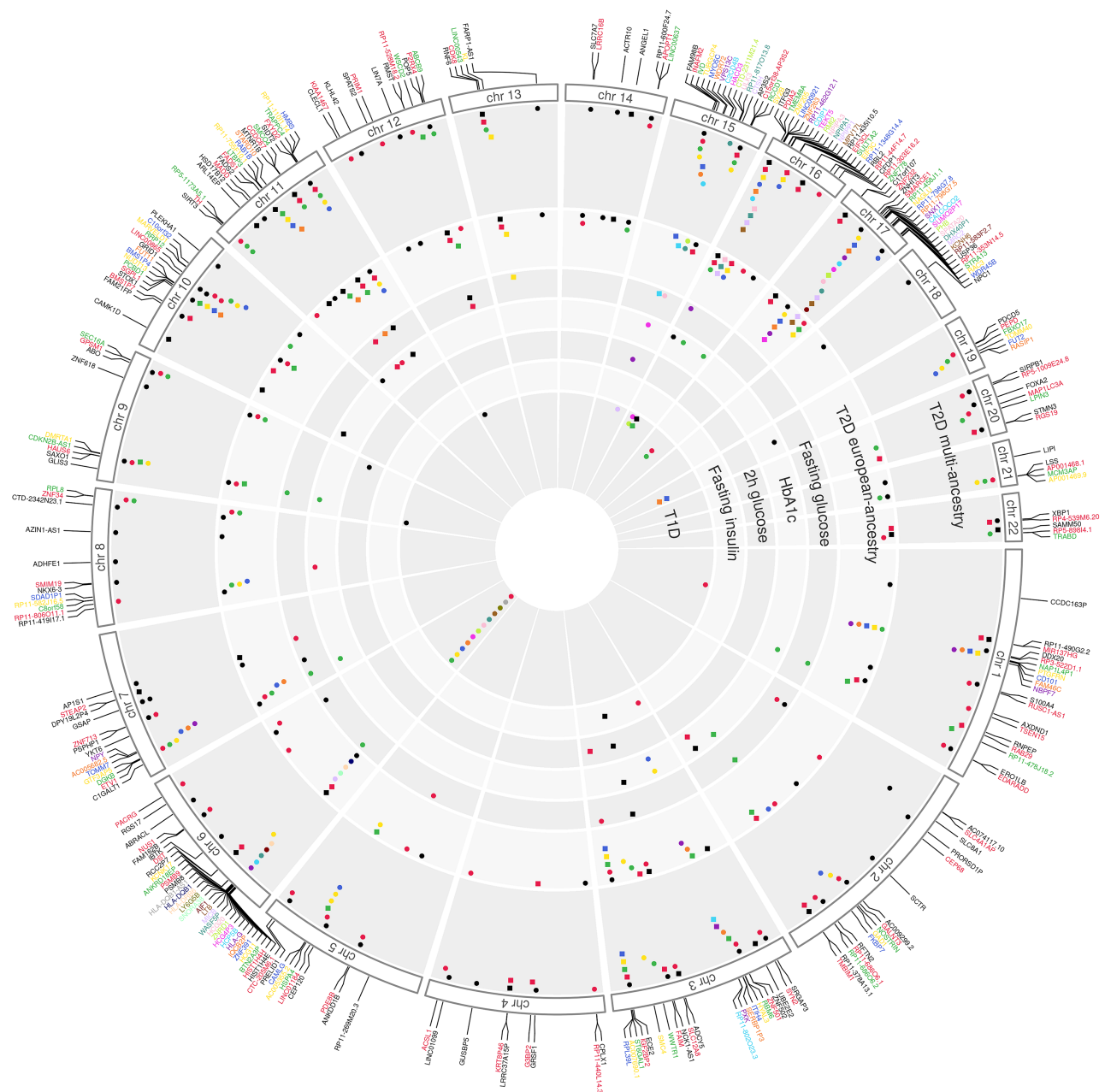


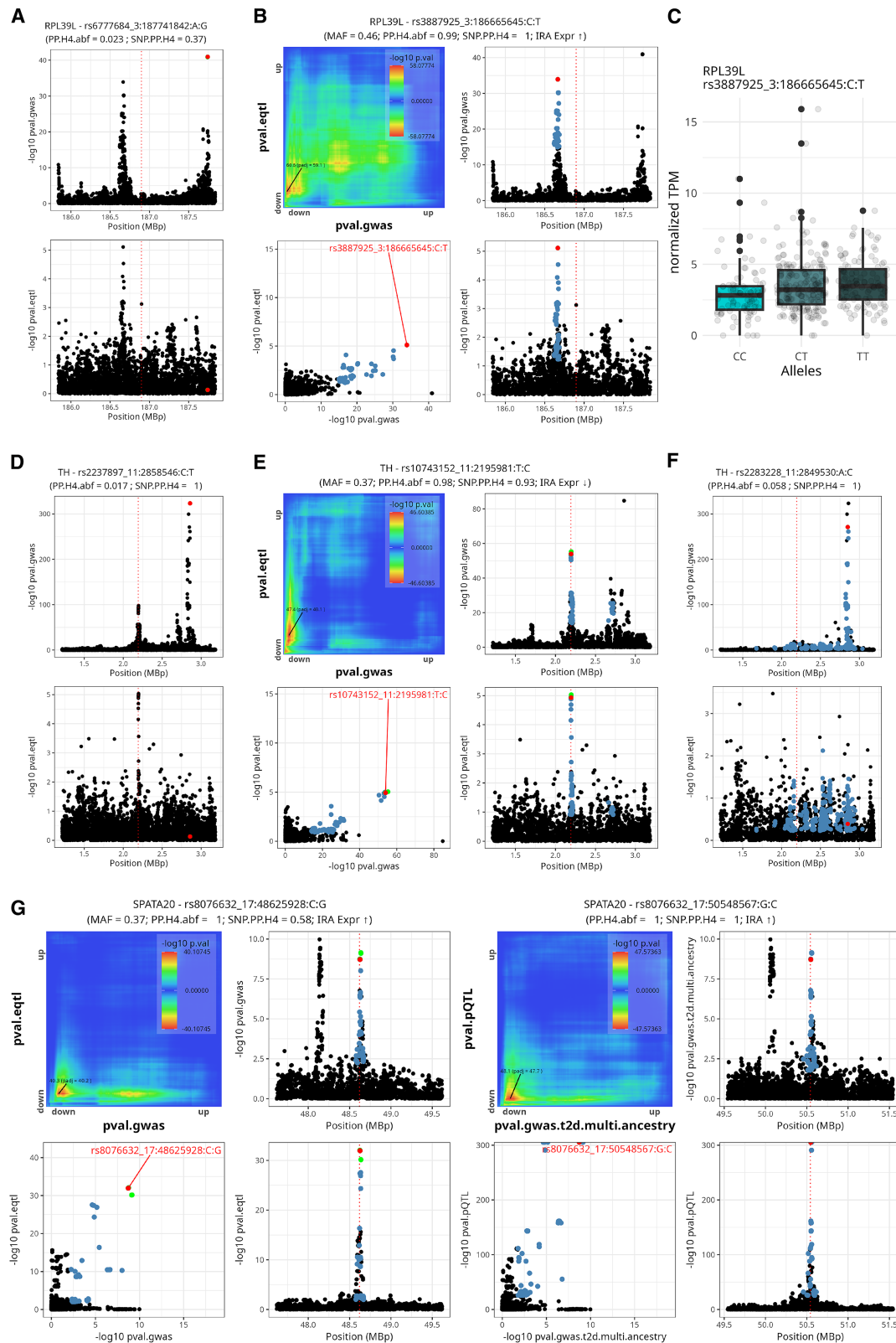
Figure 2. Circle plot of 434 *colocRedRibbon* co-localizations of islet eQTLs with diabetes and glycemic trait GWAS
eQTL genes are positioned at their starting position on the chromosome. Concentric circles correspond to GWASs, each dot to an SNP, and color matches eQTL gene color. Square dots indicate identical SNPs. T1D, type 1 diabetes; T2D, type 2 diabetes. See also [Figures S1–S5](#) and [Table S2](#).

variants, *coloc* detects another significant signal ([Figure 3E](#)). Conversely, variants for which the risk allele upregulates *TH* expression do not exhibit co-localization ([Figure 3F](#)), aligning with the biologically plausible assumption that risk alleles only associate with one direction of effect.

Of note, five genes co-localize for risk allele expression in both downregulation and upregulation. Among these is gamma-secretase activating protein (*GSAP*). *colocRedRibbon* detects two distinct signals going in opposite gene expression directions,

while both increase diabetes risk ([Figure S1](#); [Table S6](#)). This gamma-secretase catalyzes intermembrane cleavage of membrane proteins. *GSAP* plays a role in lipid homeostasis and mitochondrial function.²⁷

This refined approach demonstrates the power of *colocRedRibbon* in uncovering previously undetected co-localizations and providing more nuanced insights into the relationship between genetic variants, gene expression, and disease risk.



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***colocRedRibbon* doubles the number of co-localizations**

The 434 co-localizations between human islet *cis*-eQTLs and GWASs for type 1 and type 2 diabetes and glycemic traits encompass 344 distinct lead variants, mapping to 289 unique genes (Figure 4; Table S3). Only 214 were detected by running *coloc* without shortlisting steps (Figure 4A); in other words, *colocRedRibbon* doubled the detection. Improvements were observed for most GWASs, and the largest was for type 1 diabetes. A total of 307 co-localizations were identified across 236 distinct regions for which no co-localization was previously reported.

Out of the 434 co-localizations, 48 had a unique lead variant in the 99% credible set ($\text{SNP.PP.H4} \geq 0.99$), and 37% had ≤ 5 candidate variants in the 99% credible set. This restricted number narrows the list of potential candidates for experimental validation. For instance, a unique co-localizing lead variant, rs10830963, was detected in *MTNR1B* (Table S2). This SNP has been extensively studied and is associated with increased type 2 diabetes risk.^{30,31}

For type 2 diabetes co-localizations, risk alleles are significantly more associated with increased gene expression (Figure 4B). Half of the glycemic trait genes are also associated with type 2 diabetes (Figure 4C). Type 1 and type 2 diabetes share only 3 genes (*FUT2*, *SULT1A2*, and *WASF5P*; Figure 4D) with differing alleles and effects on gene expression (Table S2).

For type 2 diabetes, 35 genes are specific to European ancestry (Figure 4E; Table S7), and 106 are exclusively detected using multi-ancestry GWAS. This is not unexpected, as the multi-ancestry GWAS encompasses a larger number of samples, including those of European ancestry. For 10 of the 106 co-localizations, the lead variant GWAS *p* value is significant for non-European ancestry and non-significant for European ancestry (Table S8), suggesting potential ancestry specificity. For example, we found a novel co-localization for a variant that increases *PRELID1* expression in islets and is associated with reduced type 2 diabetes risk in East Asians. *PRELID1* is a lipid-shuttling protein needed for mitochondrial structure and function. The minor-allele frequency for 50 of the 106 multi-ancestry co-localizations is at least 1.5 times higher in one or more non-European GWAS cohorts compared with the European cohort. This is illustrated by the novel co-localization for *GRSF1*, another protein needed for mitochondrial function, with an East Asian type 2 diabetes protective variant increasing islet *GRSF1* expression. This variant is more common in South Asian, His-

panic, East Asian, and African American ancestries (with respective minor-allele frequencies of 11%, 14%, 21%, and 49%) as compared with Europeans (minor-allele frequency of 4.5%). These findings underscore the importance of genetic diversity in enhancing the power to discover disease mechanisms.

Co-localizing variants largely lie in regulatory regions

Co-localizing lead variants showed a notable over-representation in regulatory regions of the genome (Figure 4F; Table S9), with 383 lead variants situated in such areas. Significant enrichment was observed in exonic ($n = 71$), promoter ($n = 56$), promoter-flanking ($n = 65$), and transcript ($n = 310$) regions. In this tissue-agnostic analysis, no enrichment was detected in open chromatin, enhancer, or CTCF-binding sites from Ensembl GRCh37 regulatory features.³²

Given the tissue- or cell-type-specific nature of many regulatory regions, we further investigated the distribution of co-localizing lead variants within regions known to modulate human islet chromatin structure.²⁸ This revealed a significant enrichment in the human islet regulome (Figure 4G; Table S10), particularly in active promoters ($n = 30$), active enhancers ($n = 50$), inactive enhancers ($n = 18$), and strong CTCF-binding regions ($n = 29$). No enrichment was observed in open inactive chromatin regions. When applying an enhancer subclassification, the most significant enrichment of co-localizing lead variants was detected in active class I enhancers ($p = 2.16 \times 10^{-18}$; $n = 25$), characterized by higher H3K27ac marks and stronger Mediator protein occupancy, both key factors in gene expression regulation.²⁸

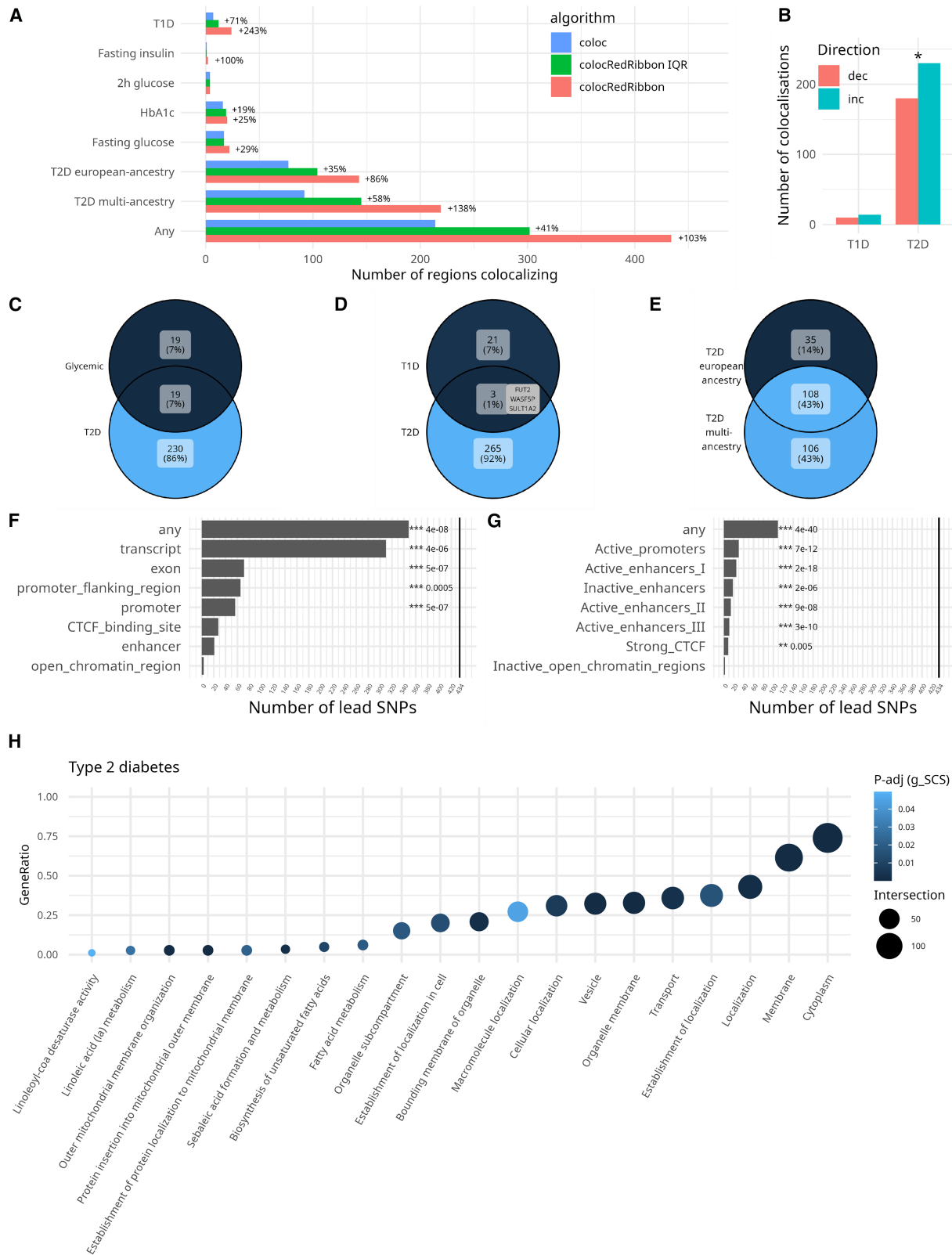
In summary, 361 co-localizing lead variants were found to reside in exons, transcripts, and regulatory and islet-specific chromatin interaction regions that consist of active promoters and enhancers.^{28,32} These findings underscore the functional importance of these variants in gene regulation and their relevance to disease susceptibility.

Co-localizing variants identify important pathways

Gprofiler2 pathway enrichment of pooled co-localizing genes for type 2 diabetes and glycemic traits revealed pathways related to cellular localization, vesicle dynamics, mitochondrial function, fatty acid metabolism, and synthesis (Figures 4H, S2A, and S2B), suggesting a role for these islet cell processes in type 2 diabetes pathogenesis. These pathway enrichments were corroborated by analyses using Metascape and EnrichR (Figures S2C–S2F). Genes downregulated by lead variants

Figure 3. *colocRedRibbon* shortlisting steps identify genuine co-localizations

- (A) GWAS and eQTL Manhattan plots for the *RPL39L* region. Two signals are present for GWAS. *coloc* alone does not detect co-localization: the lead SNP (red dot) on the highest GWAS peak does not have an eQTL signal, while the matching eQTL and GWAS peaks are missed. The red dotted line is the gene transcription start site.
- (B) *colocRedRibbon* shortlisting method applied to *RPL39L* detects a co-localization for the lower GWAS signal. Overlapping—shortlisted—SNPs are shown in blue and the lead SNP in red on the bottom.
- (C) Islet *RPL39L* expression according to lead SNP C or T alleles.
- (D) GWAS and eQTL Manhattan plots for the *TH* gene. *coloc* does not detect a significant co-localization for the eQTL peak and 6 GWAS peaks.
- (E) *colocRedRibbon* shortlisting of SNPs that increase diabetes risk (increasing risk allele [IRA]) and lower *TH* expression unmasks co-localization. The most significant GWAS peak (see D) is dismantled by shortlisting the direction of effect of gene expression. The overlap map in the top left shows significant overlap between GWAS and eQTL SNPs. Shortlisted SNPs are shown in color (bottom left): overlapping SNPs in blue, 99% credible set in green, and lead SNP in red.
- (F) There is no co-localization for risk alleles that decrease *TH* gene expression.
- (G) *SPATA20* shows co-localization for type 2 diabetes GWAS variants with islet eQTLs (left) and plasma pQTLs (right), sharing lead variant rs8076632. See also Figure S1.



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were mainly involved in cellular localization and trafficking, whereas upregulated genes were primarily associated with cytoplasmic function (Figures S2A and S2B). The co-localizing gene set exhibited significant ($p = 0.00783$) overlap with genes differentially expressed in islets from type 2 diabetic vs. non-diabetic donors³³ (Table S2, column fGSEA.t2d). For example, we detected a signal associated with type 2 diabetes risk and decreased *PDE8B* islet expression. *PDE8B* was downregulated in islets from type 2 diabetic vs. non-diabetic donors and upon palmitate exposure of non-diabetic donor islets.³⁴ *PDE8B* encodes a high-affinity cAMP-specific phosphodiesterase that maintains low basal cAMP levels in β cells, with *PDE8B* knockdown disturbing glucose-stimulated sub-plasma-membrane cAMP oscillations and pulsatile insulin secretion.³⁵

Among the type 2 diabetes genes in the vesicle pathway (Figures 4H and S2B) is *MYO5C*. The low minor-allele frequency (5%) T allele confers protection against type 2 diabetes and increases islet *MYO5C* gene expression (Figure S3). *MYO5C* encodes myosin type V, a molecular motor that moves along actin filaments and is involved in secretory granule trafficking.³⁶ The lead variant, rs149336329, is located in promoter and transcript regions, as well as in a human islet-specific active promoter (marked by Mediator, H3K27ac, and H3K4me3) (Tables S10 and S11) near the transcription start site (Figure S3A), making it a plausible causal variant. A different lead SNP (rs3825801) was reported by Mahajan et al.¹⁰ after fine-mapping, but *coloc* co-localization was unsuccessful.

Another type 2 diabetes gene is *RPL39L*, with the T risk allele inducing islet *RPL39L* expression (Figures 3A–3C). This unique variant in the 99% credible set is noteworthy due to its presence in multiple regulatory regions, i.e., promoter flanking region, transcripts, and islet-specific active enhancers. *RPL39L* has been associated with type 2 diabetes in differential gene expression studies of islets from type 2 diabetic vs. non-diabetic donors,³³ a finding corroborated by type 2 diabetes fast gene set enrichment analysis (fGSEA) enrichment analysis (Table S2, column fGSEA.t2d). *RPL39L* encodes ribosomal protein L39-like; its function in islets is unknown. Interestingly, the same variant also affects *ST6GAL1* expression, although *ST6GAL1* is not part of the leading edge in our type 2 diabetes fGSEA enrichment for human islets (Table S12, column fGSEA.t2d). *RPL39L* and *ST6GAL1* are co-expressed in multiple tissues, including thyroid, prostate, ovary, artery, and fibroblasts.³⁷ Notably, *ST6GAL1* belongs to cellular pathways in our enrichment analysis, i.e., organelle sub-compartment, bounding membrane of organelle, organelle membrane, membrane, and cytoplasm (Figure 4H; Table S12).

colocRedRibbon detected 8 co-localizations for type 1 diabetes in the HLA region of chromosome 6 (Figure 2). Pathway enrichment analysis for type 1 diabetes genes did not reach significance due to the relatively limited number ($n = 24$) of co-localizations.

Among the type 1 diabetes co-localizations, variant rs11666792 emerged as the lead variant for both *FUT2* and *RASIP1* (Figure 5). These genes are co-expressed in the esophageal mucosa and skin.³⁷ *RASIP1* encodes Ras-interacting protein 1, which has GTPase-binding and protein homodimerization activities. *FUT2*, one of the three genes that also co-localize for type 2 diabetes (albeit with a distinct lead variant), encodes the enzyme α -1,2-fucosyltransferase. This enzyme is involved in the synthesis of the H antigen, the precursor of secreted ABO blood group antigens. *FUT2* has been associated with type 1 diabetes³⁸; a common nonsense mutation in *FUT2* abolishes the secretion of ABO antigens in saliva and the gut, alters the gut microbiome, and confers susceptibility to type 1 diabetes while protecting from some viral infections.^{38,39} In human islets, the protective G allele of rs11666792 increases *FUT2* expression (Figure 5B). *FUT2* silencing in human EndoC- β H1 β cells increased coxsackievirus B1-induced apoptosis, suggesting that *FUT2* might protect β cells against potentially diabetogenic viruses (Figures S4A and 5C). *FUT2* silencing did not affect β cell function: insulin content and glucose- and glucose+forskolin-stimulated insulin secretion were comparable in *FUT2*-depleted and -competent EndoC- β H1 cells (Figures S4B and S4C).

Cathepsin H (encoded by *CTSH*), a type 1 diabetes candidate gene,^{40,41} exhibits a co-localization for lead variant rs34593439, having a 0.10 minor-allele frequency and a small 99% credible set (5 variants, Figure S5A). The protective allele A (type 1 diabetes odds ratio = 0.84) lowers islet *CTSH* expression (Figure S5B). *CTSH* displays complex regulation in response to inflammatory stimuli. It is downregulated in EndoC- β H1 cells upon exposure to pro-inflammatory cytokines interleukin (IL)-1 β + interferon (IFN) γ .²⁶ The risk allele T of variant rs3825932 has been shown to reduce islet *CTSH* expression⁴⁰; this variant is in linkage disequilibrium with rs34593439. Lower methylation variability may make individuals with the protective allele potentially less sensitive to cytokines.⁴¹ The gene is also associated with celiac disease⁴²; type 1 narcolepsy,⁴³ where the rs34593439 A allele increases risk; and rheumatoid arthritis.⁴⁴ This association with multiple autoimmune diseases makes the gene and variant good candidates for further investigation.

Figure 4. *colocRedRibbon* doubles the number of co-localizations and detected variants that lie in islet-specific regulatory regions

(A) Number of co-localizing regions. *colocRedRibbon* (red) significantly improves detection of co-localizations compared with *coloc* (blue). The more conservative *colocRedRibbon* interquartile range (IQR) method (green) is also better than *coloc*. The percentage increase is shown for GWAS hits for European and multi-ancestry type 2 diabetes (T2D), type 1 diabetes (T1D), and glycemic traits HbA1c, fasting glucose, 2-h glucose post-challenge, and fasting insulin. “Any” includes all GWAS SNPs combined. Co-localizations overall increased by 103%.

(B) Direction of effect of the risk allele on gene expression. Inc, increased gene expression; dec, decreased gene expression.

(C–E) The number of regulated genes in common for glycemic traits and diabetes GWAS.

(F) Enrichment in regulatory regions for lead SNPs. “Any” means any of the regions.

(G) Human islet-specific regulome enrichment.^{28,29} *** $p \leq 0.001$, ** $p \leq 0.01$, and * $p \leq 0.05$.

(H) Gprofiler2 enrichment in co-localizing genes for type 2 diabetes and glycemic traits.

See also Figures S2 and S3.

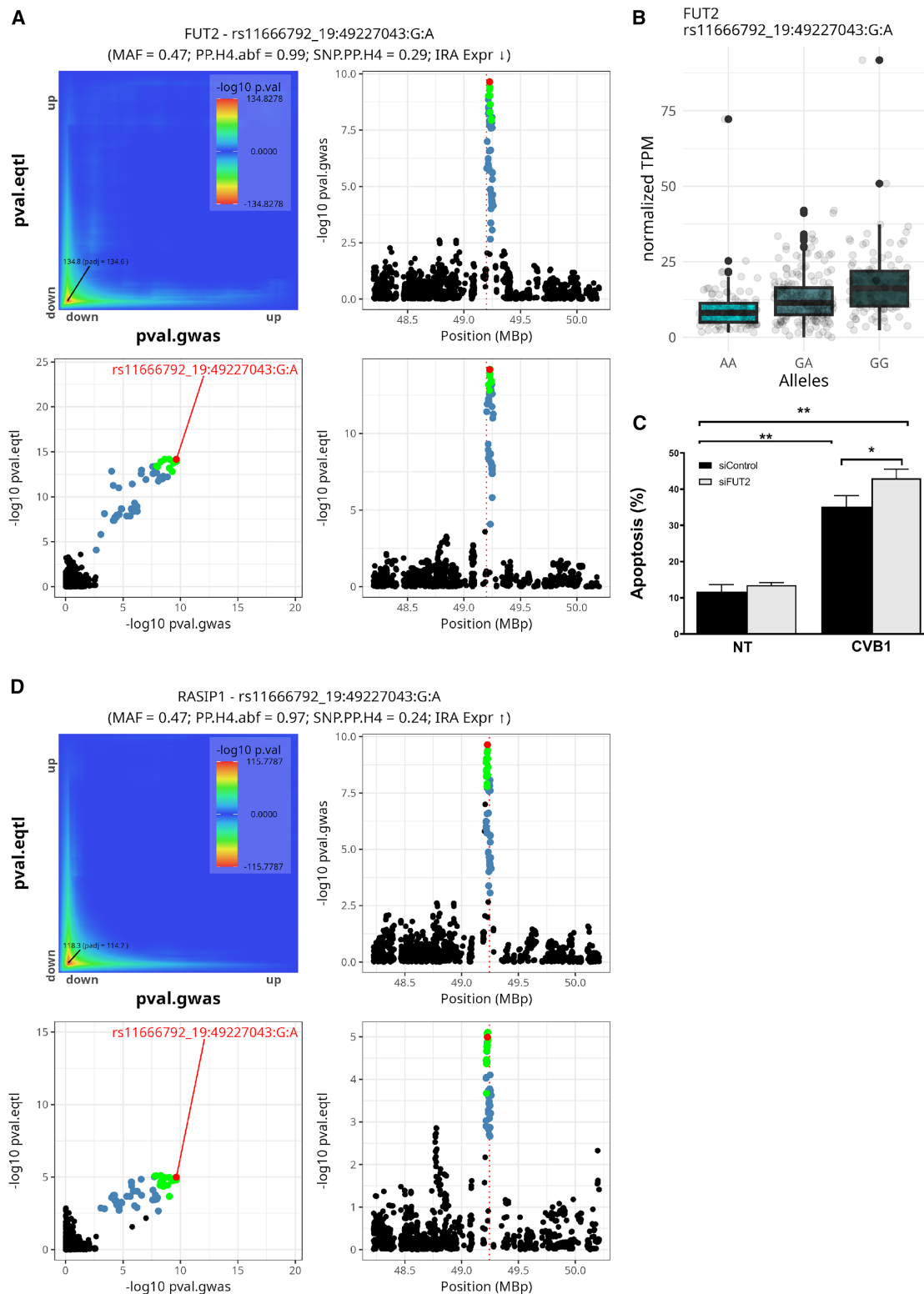


Figure 5. Co-localization for co-expressed *FUT2*/*RASIP1* eQTL and type 1 diabetes GWAS

(A) Co-localization plots for *FUT2*, showing lead SNP in red, 99% credible set in green, and *RedRibbon* overlap in blue. The red dotted line is the gene transcription start site.

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Glycemic trait genes are shared with type 2, but not type 1, diabetes

Among the 48 co-localizations identified for glycemic traits, only *SULT1A2* was present among type 1 diabetes genes. In contrast, 19 (50%) glycemic trait genes were detected for type 2 diabetes, with 11 sharing an identical lead variant. A striking example of this overlap is single lead variant rs11708067 affecting *ADCY5* expression,⁴⁵ which co-localizes for type 2 diabetes and all glycemic traits (Figure 6). The type 2 diabetes risk allele A decreases human islet *ADCY5* expression (Figures 6A and 6B). Consistent with its effect on type 2 diabetes risk, the A allele is associated with increased HbA1c and fasting and 2-h glucose and decreased islet *ADCY5* expression (Figures 6C–6E). Conversely, the A allele is associated with increased fasting insulin and increased *ADCY5* expression (Figure 6F). *ADCY5* encodes adenylate cyclase 5, an enzyme that converts ATP to cAMP, generating an essential amplifier of insulin secretion. Decreased *ADCY5* expression impairs glucose-induced cAMP production and insulin secretion.⁴⁶ These congruent co-localization data strongly support rs11708067 as the causal variant that increases diabetes risk by decreasing *ADCY5* expression. It underscores the importance of *ADCY5* in glucose homeostasis, highlighting how a single genetic variant can have pleiotropic effects on related traits.

Concordance between transcriptomic and proteomic co-localizations in diabetes

To determine whether co-localization signals at the transcriptome level are reflected in the proteome, we used *colocRedRibbon* to co-localize GWAS SNPs with plasma pQTLs.²¹ Of 268 unique co-localizing genes for type 2 diabetes and glycemic traits and 24 for type 1 diabetes, 68 with at least one significant pQTL (Table S13) were detected by aptamers in plasma.²¹ Of these, 21 regions showed co-localization with pQTLs, resulting in a total of 40 co-localizations across all traits (Tables S13 and 1). Variant rs8076632 co-localizes with the SPT20 protein and the corresponding spermatogenesis-associated 20 (*SPATA20*) gene (Figure 3G), with the type 2 diabetes risk allele located in an exon concordantly increasing mRNA and protein expression. While a previous study reported no co-localization in this region,⁴⁷ another did, albeit with an unconvincing lead variant.⁴⁸ The mechanism by which *SPATA20* alters type 2 diabetes risk remains to be elucidated.

CTSH protein contains the type 1 diabetes-associated variant rs2289702 within its 99% credible set. The risk allele again demonstrates a concordant direction of effects on gene and protein expression.

Concordance was also seen for PDCD5 and ABO, the latter in multiple GWASs (Table S13).

ColocRedRibbon enables co-localization for diverse diseases and traits

To demonstrate the broader applicability and versatility of *colocRedRibbon*, we used it for other combinations of GWASs and/or QTLs.

We first examined co-localizations between different GWASs using *colocRedRibbon*. We analyzed the region around *FTO*, known to be associated with type 2 diabetes and BMI (Table S14). Strong overlap was seen for variants from obesity²³ and type 2 diabetes GWASs, with rs11642015 being the lead SNP (Figure S6). The risk alleles are concordant, suggesting that this variant confers susceptibility to obesity and type 2 diabetes.

We next investigated the relationship between the obesity GWAS²³ and islet eQTLs,¹⁷ expecting fewer co-localizations than for diabetes, given the central role of the brain and adipocytes in obesity. This identified 12 co-localizations (Table S15). Obesity-associated variants in a chromosome 16 locus increase islet *EIF3C* and *EIF3CL* expression and decrease lincRNA *ENSG00000251417* (Figure S7); these islet eQTLs also co-localize with type 2 diabetes (Table S2). The increased *EIF3C* transcript expression associated with the lead risk allele rs62036658 is concordant with obesity and type 2 diabetes. *EIF3C* encodes subunit c of eukaryotic translation initiation factor 3, a critical protein for mRNA start codon selection and ribosome assembly.⁴⁹

Finally, we co-localized the BMI GWAS²⁴ with subcutaneous adipose tissue meQTLs for 28 regions targeted in McAllan et al.,²² identifying 5 co-localizations (Table S16). The BMI-increasing rs12450225 allele augments methylation at the cg14884929 site (Figure S8). cg14884929 is located near *MIR10A*, encoding microRNA 10a that regulates adipose tissue inflammation and homeostasis.^{50,51} These results suggest that genetic variants influencing BMI may, in part, exert their effects through the modulation of adipocyte DNA methylation.

Taking these results together, we show that *colocRedRibbon* has broad applicability for co-localization analyses across multiple omics and is versatile in uncovering tissue-specific or shared genetic mechanisms underlying disease phenotypes.

DISCUSSION

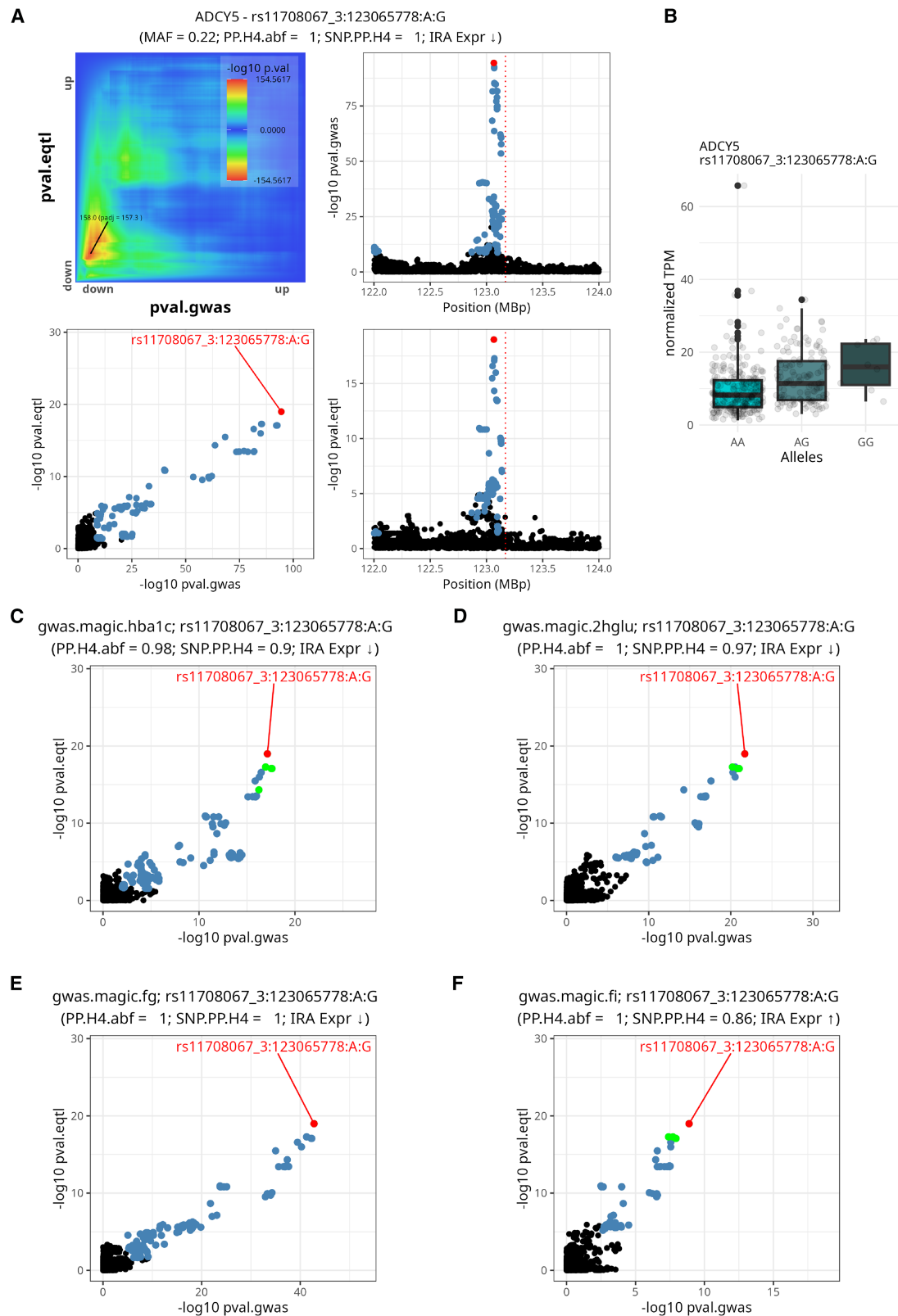
Over the past decades, a plethora of GWASs have linked common genetic variation to complex diseases and traits. Because 90% of all GWAS hits lie in non-coding regions, the identification of genes that mediate susceptibility is not straightforward. eQTL studies in disease-relevant tissues can connect SNPs to functional genes, but the yield of GWAS and eQTL variant co-localization studies tends to be low. This is illustrated by the >700 variants identified in the diabetes GWAS, of which only around

(B) *FUT2* expression plot for co-localizing SNP.

(C) Human EndoC-βH1 β cell apoptosis 24 h after control or *FUT2* small interfering RNA (siRNA) transfection and infection or not (NT) with coxsackievirus B1 (*n* = 5). ***p* ≤ 0.01 and **p* ≤ 0.05.

(D) Co-localization plots for *RASIP1*. SNPs are referenced by rsids, and PP.H4.abf and SNP PP.H4 are the posterior probabilities for *coloc* tool hypothesis 4. MAF, minor-allele frequency; IRA, increasing risk allele expression regulation direction. An arrow pointing up or down means increased or decreased gene expression for the risk allele, respectively.

See also Figure S4.



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50 have so far been linked to changes in pancreatic islet gene expression. Here, we significantly expanded the number of co-localizations for type 2 diabetes and identified many novel type 1 diabetes co-localizations using the novel *colocRedRibbon* pipeline. This pipeline detected 434 co-localizations corresponding to 289 genes and 344 distinct lead variants. This increase is attributed to a combination of new computational methods and larger, multi-ethnic, and multi-trait GWASs. Without the methodological advancements of *colocRedRibbon*, we would have identified 214 co-localizations (128 distinct gene regions), i.e., less than half, highlighting the importance of these improvements in uncovering novel associations. *colocRedRibbon* filters variants or delimits regions (interquartile range [IQR] mode, Figure 1B) to be further analyzed for co-localization. We used *coloc*, but any other tool may be used (e.g., *SuSiE* + *coloc*^{52,53} or *smr*⁵⁴).

Our analysis revealed that 88% of lead variants are localized in regulatory regions, including those specific to islets. For type 2 diabetes and glycemic traits, genes are involved in cellular localization, vesicle dynamics, mitochondrial function, fatty acid metabolism, and synthesis (Figure S1). The enrichment in regulatory regions and pathways crucial for β cell function/survival demonstrates the potential of *colocRedRibbon* to identify disease-relevant mechanisms. When comparing detected genes with those reported as differentially expressed in islets in type 2 diabetes,³³ 51 genes overlapped, pertaining primarily to cellular localization and vesicle pathways. This is substantial, considering the relatively modest transcriptome sample size (28 type 2 diabetic and 58 non-diabetic donors) compared to the large GWAS and eQTL datasets.

Co-localizing lead variants were also found in genes potentially involved in monogenic diabetes, such as *FOXA2* and *PCBD1*. The transcription factor *FOXA2* contributes to pancreas development and islet gene expression. *FOXA2* mutations have been implicated in diabetes and congenital hyperinsulinism.⁵⁵ *PCBD1* acts as a cofactor of transcription factor HNF1A, which is essential for pancreatic development and function.⁵⁶ These findings underscore parallels between monogenic and polygenic diabetes, as have been described for uncommon variants in monogenic diabetes genes that increase type 2 diabetes risk, on average, by 3-fold.⁵⁷

The HLA region on chromosome 6 resulted in 8 co-localizations for type 1 diabetes (Figure 2). This region poses a significant challenge for co-localization analyses due to the complex structure of the linkage disequilibrium. It contains numerous immunity-related genes that are under strong selective pressure,⁵⁸ leading to highly intricate linkage disequilibrium patterns. For several co-localizations (e.g., *BTN2A3P* and *HCG20*), *colocRedRibbon* detected significant subsets of variants through the

overlap prefiltering step. The visual representation of these co-localizations (see [data and code availability](#)) appears inconclusive, however, as the *colocRedRibbon*-identified variants lie within stronger GWAS signals. This could be a side effect of the simplification used to assess linkage disequilibrium in adjusted *p* value computation, overestimating the overlap significance or, alternatively, acting as a reflection of the method's ability to discern multiple overlapping GWAS signals, resulting in valid co-localization. Other co-localizations in the HLA region (e.g., *PSMB9* and *HLA-DQB1-AS1*) appear more convincing, with well-isolated GWAS signals and the lead variant close to the top. Future validation of HLA region co-localizations is required, probably using specialized tools tailored to handle the unique challenges posed by this genomic locus. Adapting and fine-tuning *colocRedRibbon* may help to address the complexities of the HLA region, but this will require a dedicated effort.

colocRedRibbon can now be applied to eQTL studies in other disease-relevant tissues, such as the immune system for type 1 diabetes,⁵⁹ as well as muscle, liver, and adipose tissue for type 2 diabetes and glycemic traits.^{60–65} The use of the same pipeline across multiple tissues and QTLs will comprehensively characterize the tissue-specific genetic architecture of these diseases.

The tool is also applicable to QTLs for protein, open chromatin, and DNA methylation; the method only requires that GWAS and QTL data share common genomic positional features. A limitation is the current scarcity of pQTLs, open chromatin, and meQTLs in relevant tissues. We applied *colocRedRibbon* to plasma pQTLs,²¹ meQTLs,²² and obesity²³ and BMI²⁴ GWASs, showcasing its adaptability to different QTL types and its applicability across diseases or traits. The method is equally suitable for investigating chromosomal regions located farther away from the gene—such as those with *trans*-QTL signals. Users can specify any region of interest, including the union of regions around *trans*-QTL variants associated with the gene under study. This flexibility allows *colocRedRibbon* to be readily adapted for both *cis*- and *trans*-QTL co-localization analyses.

In summary, this study leveraged the novel *colocRedRibbon* pipeline to analyze a large dataset from human pancreatic islets, a tissue central in the pathogenesis of diabetes, allowing us to investigate the expression regulatory variation underlying this complex disease. *colocRedRibbon* significantly enhanced the detection of co-localizations of eQTL and GWAS variants compared with previous methods, refining the mapping of lead variants and uncovering numerous novel co-localizations. These results are a critical step toward understanding how diabetes-associated variants impact pancreatic islet cell function, elucidating the mechanisms linking genetic variation with diabetes and, potentially, guiding the translation of GWAS hits to (personalized) diabetes therapy.

Figure 6. Co-localization of *ADCY5* eQTL and type 2 diabetes and glycemic trait GWAS SNPs

Co-localization plots for *ADCY5* show the same lead SNP in red, the 99% credible set in green, and *RedRibbon* overlap in blue. The red dotted line is the gene transcription start site.

(A) Type 2 diabetes co-localization.

(B) Expression level for alleles regulating *ADCY5*.

(C–F) Co-localization for (C) glycated hemoglobin (HbA1c), (D) 2-h glucose (2hGlu), (E) fasting glucose (FG), and (F) fasting insulin (FI). SNPs are referenced by rsids, and PP.H4.abf and SNP PP.H4 are the posterior probabilities for *coloc* tool hypothesis 4. MAF, minor-allele frequency; IRA, increasing risk allele expression regulation direction. An arrow pointing up or down means increased or decreased gene expression for the risk allele, respectively.

Table 1. Selected co-localizations for diabetes and glycemic traits

Co-localization				PP.H4		Cross-analyses		
GWAS	Gene (pQTL)	Lead SNP	IRA	abf	SNP	Other GWASs	Previously reported	Regions
T2D	<i>CCDC67</i>	rs11600595	inc	86%	91%	T2D Eur.	INSPIre	–
T2D	<i>TH</i>	rs10840495	dec	97%	98%	T2D Eur.	–	–
T2D	<i>GSAP</i>	rs3912067	inc	82%	21%	T2D Eur.	–	promoter flanking region
T2D	<i>GSAP</i>	rs9641219	dec	93%	92%	T2D Eur.	–	promoter, transcript, active promoters
T2D	<i>MTNR1B</i>	rs10830963	inc	99%	100%	FG, HbA1c, T2D Eur.	TIGER	transcript, inactive enhancers
T2D	<i>FUT2</i>	rs681343	inc	99%	25%	T1D	–	exon, transcript
T2D	<i>WASF5P</i>	rs2905758	inc	97%	56%	T1D	–	transcript
T2D	<i>PRELID1</i>	rs28607106	dec	91%	62%	–	–	–
T2D	<i>GRSF1</i>	rs10433674	dec	97%	34%	–	GSEA	promoter flanking region, active enhancers
T2D	<i>PDE8B</i>	rs7732130	inc	96%	99%	FG, T2D Eur.	INSPIre, GSEA	enhancer, transcript, active enhancers
T2D	<i>MYO5C</i>	rs149336329	dec	94%	99%	T2D Eur.	–	promoter, transcript, active promoters
T2D	<i>RPL39L</i>	rs3887925	inc	99%	98%	T2D Eur.	GSEA	promoter flanking region, transcript, active enhancers
T2D	<i>ST6GAL1</i>	rs3887925	inc	99%	99%	T2D Eur.	TIGER	promoter flanking region, transcript, active enhancers
T2D	<i>ADCY5</i>	rs11708067	dec	99%	99%	2hglu, FG, FI, HbA1c, T2D Eur.	TIGER, INSPIre, GSEA	promoter flanking region, transcript, inactive enhancers
T2D	<i>FOXA2</i>	rs6048206	inc	89%	32%	–	GSEA	–
T2D	<i>PCBD1</i> (PHS)	rs827241	dec	98%	53%	T2D Eur.	TIGER, GSEA	promoter, exon, transcript, active promoters
T2D	<i>SPATA20</i> (SPT20)	rs8076632	inc	99%	58%	–	GSEA	exon, transcript
HbA1c	<i>SULT1A2</i>	rs4149406	inc	86%	22%	T1D	GSEA	promoter, transcript
T1D	<i>FUT2</i>	rs11666792	dec	98%	29%	T2D	–	transcript
T1D	<i>SULT1A2</i>	rs13331170	dec	81%	12%	HbA1c	–	–
T1D	<i>WASF5P</i>	rs3130297	inc	93%	99%	T2D	–	–
T1D	<i>RASIP1</i>	rs11666792	inc	96%	23%	–	–	transcript
T1D	<i>CTSH</i> (cathepsin H)	rs34593439	inc	99%	25%	–	–	transcript
T1D	<i>PSMB9</i>	rs2071465	inc	99%	99%	–	–	promoter, transcript
T1D	<i>HLA-DQB1-AS1</i>	rs17206350	inc	99%	100%	–	–	–

Gene shows gene symbol. If a protein quantitative trait locus (pQTL) also co-localizes, the protein name is displayed in parentheses. GWASs are for type 2 diabetes multi-ancestry (T2D), type 2 diabetes European ancestry (T2D Eur.), type 1 diabetes (T1D), fasting glucose (FG), fasting insulin (FI), 2-h glucose (2hglu), and HbA1c. IRA indicates the direction of gene expression associated with the risk-increasing allele, where “inc” denotes increased and “dec” decreased expression. GSEA refers to our fast gene set enrichment analysis (fGSEA) comparing type 2 diabetic vs. non-diabetic islet differential gene expression.³³ INSPIre data are from Viñuela et al.¹⁸ and TIGER data from Alonso et al.¹⁷ Genomic regions are defined based on GENCODE genome annotation and chromatin regulation data.²⁸

colocRedRibbon is a powerful new tool for integrating genetic and gene expression data to elucidate the complex interplay between genetic variation and disease risk. It is poised to expand knowledge of the genetic architecture of many complex diseases and highlight avenues for therapeutic development.

Limitations of the study

colocRedRibbon uses the *RedRibbon* approach that employs an evolutionary algorithm to identify the minimal hypergeometric *p* value within the overlap map. As a result, *colocRedRibbon* is subject to the inherent non-determinism

associated with such algorithms. This stochastic variability can be managed effectively by performing multiple independent runs of the overlap analysis to ensure the robustness of the results.

Another limitation lies in the limited availability of pQTL, open chromatin, and meQTL data in relevant tissues. This restricts the comprehensiveness of our analyses and, consequently, limits our ability to fully capture the regulatory landscape in all biologically relevant contexts.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Anthony Piron (anthony.piron@ulb.be).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The eQTL dataset is from Alonso et al.,¹⁷ pQTLs from Ferkingstad et al.,²¹ meQTLs from McAllan et al.,²² and GWASs from Chen et al.,¹¹ Suzuki et al.,¹⁵ Kurki et al.,²³ Yengo et al.,²⁴ and GCST90013791. The co-localization list, plots, and source code to generate these data are available on Zenodo via accession number <https://doi.org/10.5281/zenodo.13987433>.
- The R package code is open to the community with a permissive license (GPL3) and available for download from GitHub <https://github.com/antpiron/colocRedRibbon> (also available on Zenodo <https://doi.org/10.5281/zenodo.13987433>). This package depends on <https://github.com/antpiron/RedRibbon> (*colocRedRibbon* R package also contains this code).
- Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization, A.P., J.M.M., and M.C.; methodology, A.P., J.M.M., and M.C.; formal analysis, A.P.; data curation, A.P.; software, A.P.; software documentation, T.P.; visualization, A.P., L.F., and M.L.; investigation, A.P., F.S., L.F. M.L., and Y.T.; writing – original draft, A.P., F.S., L.F., and M.C.; writing – review & editing, D.J.M.C., T.P., M.L., Y.T., M.I.A., M.L.C., M.L.P., K.H., A.H.-C., H.J.T., M.D., D.L.E., J.M.M., and M.C.; resources, X.Y., D.J.M.C., J.A.T., and M.C.; supervision, M.C.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- **KEY RESOURCES TABLE**
- **EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS**
- **METHOD DETAILS**
 - *colocRedRibbon* workflow
 - *colocRedRibbon* shortlisting
 - *colocRedRibbon* R package
 - Pathway and regulatory elements enrichment
 - Normalization of gene expression
 - Viral infection and FUT2 knockdown in human beta cells
- **QUANTIFICATION AND STATISTICAL ANALYSIS**
 - Co-localization
 - Enrichment analyses
 - *FUT2* statistical analyses

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.xgen.2025.101004>.

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REFERENCES

1. IDF (2025). IDF Diabetes Atlas (International Diabetes Federation). <https://diabetesatlas.org/>.
2. Ong, K.L., Stafford, L.K., McLaughlin, S.A., Boyko, E.J., Vollset, S.E., Smith, A.E., Dalton, B.E., Duprey, J., Cruz, J.A., Hagins, H., et al. (2023). Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 402, 203–234. [https://doi.org/10.1016/S0140-6736\(23\)01301-6](https://doi.org/10.1016/S0140-6736(23)01301-6).
3. Ilonen, J., Lempainen, J., and Veijola, R. (2019). The heterogeneous pathogenesis of type 1 diabetes mellitus. *Nat. Rev. Endocrinol.* 15, 635–650. <https://doi.org/10.1038/s41574-019-0254-y>.
4. Byndloss, M., Devkota, S., Duca, F., Niess, J.H., Nieuwdorp, M., Orho-Melander, M., Sanz, Y., Tremaroli, V., and Zhao, L. (2024). The gut microbiota and diabetes: research, translation, and clinical applications - 2023 Diabetes, Diabetes Care, and Diabetologia Expert Forum. *Diabetologia* 67, 1760–1782. <https://doi.org/10.1007/s00125-024-06198-1>.
5. Xourafa, G., Korbmacher, M., and Roden, M. (2024). Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* 20, 27–49. <https://doi.org/10.1038/s41574-023-00898-1>.
6. Cohrs, C.M., Panzer, J.K., Drotar, D.M., Enos, S.J., Kipke, N., Chen, C., Bozsak, R., Schöniger, E., Ehehalt, F., Distler, M., et al. (2020).

- Dysfunction of Persisting β Cells Is a Key Feature of Early Type 2 Diabetes Pathogenesis. *Cell Rep.* 31, 107469. <https://doi.org/10.1016/j.celrep.2020.03.033>.
7. Eizirik, D.L., Pasquali, L., and Cnop, M. (2020). Pancreatic β -cells in type 1 and type 2 diabetes mellitus: different pathways to failure. *Nat. Rev. Endocrinol.* 16, 349–362. <https://doi.org/10.1038/s41574-020-0355-7>.
 8. Suleiman, M., Marselli, L., Cnop, M., Eizirik, D.L., De Luca, C., Femia, F.R., Tesi, M., Del Guerra, S., and Marchetti, P. (2022). The Role of Beta Cell Recovery in Type 2 Diabetes Remission. *Int. J. Mol. Sci.* 23, 7435.
 9. Mahajan, A., Taliun, D., Thurner, M., Robertson, N.R., Torres, J.M., Rayner, N.W., Payne, A.J., Steinthorsdottir, V., Scott, R.A., Grarup, N., et al. (2018). Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat. Genet.* 50, 1505–1513. <https://doi.org/10.1038/s41588-018-0241-6>.
 10. Mahajan, A., Spracklen, C.N., Zhang, W., Ng, M.C.Y., Petty, L.E., Kitajima, H., Yu, G.Z., Rüeger, S., Speidel, L., Kim, Y.J., et al. (2022). Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation. *Nat. Genet.* 54, 560–572. <https://doi.org/10.1038/s41588-022-01058-3>.
 11. Chen, J., Spracklen, C.N., Marenne, G., Varshney, A., Corbin, L.J., Luan, J., Willems, S.M., Wu, Y., Zhang, X., Horikoshi, M., et al. (2021). The trans-ancestral genomic architecture of glycemic traits. *Nat. Genet.* 53, 840–860. <https://doi.org/10.1038/s41588-021-00852-9>.
 12. Chiou, J., Geusz, R.J., Okino, M.-L., Han, J.Y., Miller, M., Melton, R., Beebe, E., Benaglio, P., Huang, S., Korgaonkar, K., et al. (2021). Interpreting type 1 diabetes risk with genetics and single-cell epigenomics. *Nature* 594, 398–402. <https://doi.org/10.1038/s41586-021-03552-w>.
 13. Bonas-Guarch, S., Guindo-Martinez, M., Miguel-Escalada, I., Grarup, N., Sebastian, D., Rodriguez-Fos, E., Sanchez, F., Planas-Felix, M., Cortes-Sanchez, P., Gonzalez, S., et al. (2018). Re-analysis of public genetic data reveals a rare X-chromosomal variant associated with type 2 diabetes. *Nat. Commun.* 9, 321. <https://doi.org/10.1038/s41467-017-02380-9>.
 14. Vujkovic, M., Keaton, J.M., Lynch, J.A., Miller, D.R., Zhou, J., Tcheandjie, C., Huffman, J.E., Assimes, T.L., Lorenz, K., Zhu, X., et al. (2020). Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat. Genet.* 52, 680–691. <https://doi.org/10.1038/s41588-020-0637-y>.
 15. Suzuki, K., Hatzikotoulas, K., Southam, L., Taylor, H.J., Yin, X., Lorenz, K.M., Mandla, R., Huerta-Chagoya, A., Melloni, G.E.M., Kanoni, S., et al. (2024). Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. *Nature* 627, 347–357. <https://doi.org/10.1038/s41586-024-07019-6>.
 16. GTEx Consortium (2020). The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* 369, 1318–1330. <https://doi.org/10.1126/science.aaz1776>.
 17. Alonso, L., Piron, A., Morán, I., Guindo-Martínez, M., Bonàs-Guarch, S., Atla, G., Miguel-Escalada, I., Royo, R., Puiggròs, M., Garcia-Hurtado, X., et al. (2021). TIGER: The gene expression regulatory variation landscape of human pancreatic islets. *Cell Rep.* 37, 109807. <https://doi.org/10.1016/j.celrep.2021.109807>.
 18. Viñuela, A., Varshney, A., van de Bunt, M., Prasad, R.B., Asplund, O., Bennett, A., Boehnke, M., Brown, A.A., Erdos, M.R., Fadista, J., et al. (2020). Genetic variant effects on gene expression in human pancreatic islets and their implications for T2D. *Nat. Commun.* 11, 4912. <https://doi.org/10.1038/s41467-020-18581-8>.
 19. Lonsdale, J., Thomas, J., Salvatore, M., Phillips, R., Lo, E., Shad, S., Hasz, R., Walters, G., Garcia, F., Young, N., et al. (2013). The Genotype-Tissue Expression (GTEx) project. *Nature Genet.* 45, 580–585. <https://doi.org/10.1038/ng.2653>.
 20. Crouch, D.J.M., Inshaw, J.R.J., Robertson, C.C., Zhang, J.-Y., Chen, W.-M., Onengut-Gumuscu, S., Cutler, A.J., Sidore, C., Cucca, F., Pociot, F., et al. (2022). Enhanced genetic analysis of type 1 diabetes by selecting variants on both effect size and significance, and by integration with autoimmune thyroid disease. Preprint at bioRxiv. <https://doi.org/10.1101/2021.02.05.429962>.
 21. Ferkingstad, E., Sulem, P., Atlason, B.A., Sveinbjornsson, G., Magnusson, M.I., Styrismisdottir, E.L., Gunnarsdottir, K., Helgason, A., Oddsson, A., Halldorsson, B.V., et al. (2021). Large-scale integration of the plasma proteome with genetics and disease. *Nat. Genet.* 53, 1712–1721. <https://doi.org/10.1038/s41588-021-00978-w>.
 22. McAllan, L., Baranasic, D., Villicaña, S., Brown, S., Zhang, W., Lehne, B., Adamo, M., Jenkinson, A., Elkalaawy, M., Mohammadi, B., et al. (2023). Integrative genomic analyses in adipocytes implicate DNA methylation in human obesity and diabetes. *Nat. Commun.* 14, 2784. <https://doi.org/10.1038/s41467-023-38439-z>.
 23. Kurki, M.I., Karjalainen, J., Palta, P., Sipilä, T.P., Kristiansson, K., Donner, K.M., Reeve, M.P., Laivuori, H., Aavikko, M., Kaunisto, M.A., et al. (2023). FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* 613, 508–518. <https://doi.org/10.1038/s41586-022-05473-8>.
 24. Yengo, L., Sidorenko, J., Kemper, K.E., Zheng, Z., Wood, A.R., Weedon, M.N., Frayling, T.M., Hirschhorn, J., Yang, J., and Visscher, P.M.; GIANT Consortium (2018). Meta-analysis of genome-wide association studies for height and body mass index in ~700,000 individuals of European ancestry. *Hum. Mol. Genet.* 27, 3641–3649. <https://doi.org/10.1093/hmg/ddy271>.
 25. Giambartolomei, C., Vukcevic, D., Schadt, E.E., Franke, L., Hingorani, A.D., Wallace, C., and Plagnol, V. (2014). Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet.* 10, e1004383. <https://doi.org/10.1371/journal.pgen.1004383>.
 26. Piron, A., Szymczak, F., Papadopolou, T., Alvelos, M.I., Defrance, M., Le-naerts, T., Eizirik, D.L., and Cnop, M. (2024). RedRibbon: A new rank–rank hypergeometric overlap for gene and transcript expression signatures. *Life Sci. Alliance* 7, e202302203. <https://doi.org/10.26508/lsa.202302203>.
 27. Xu, P., Chang, J.C., Zhou, X., Wang, W., Bamkole, M., Wong, E., Bettayeb, K., Jiang, L.L., Huang, T., Luo, W., et al. (2021). GSAP regulates lipid homeostasis and mitochondrial function associated with Alzheimer’s disease. *J. Exp. Med.* 218, e20202446. <https://doi.org/10.1084/jem.20202446>.
 28. Miguel-Escalada, I., Bonàs-Guarch, S., Cebola, I., Ponsa-Cobas, J., Mendieta-Esteban, J., Atla, G., Javierre, B.M., Rolando, D.M.Y., Farabella, I., Morgan, C.C., et al. (2019). Human pancreatic islet three-dimensional chromatin architecture provides insights into the genetics of type 2 diabetes. *Nat. Genet.* 51, 1137–1148. <https://doi.org/10.1038/s41588-019-0457-0>.
 29. Pasquali, L., Gaulton, K.J., Rodríguez-Seguí, S.A., Mularoni, L., Miguel-Escalada, I., Akerman, I., Tena, J.J., Morán, I., Gómez-Marín, C., van de Bunt, M., et al. (2014). Pancreatic islet enhancer clusters enriched in type 2 diabetes risk-associated variants. *Nat. Genet.* 46, 136–143. <https://doi.org/10.1038/ng.2870>.
 30. Lyssenko, V., Nagorny, C.L.F., Erdos, M.R., Wierup, N., Jonsson, A., Spé-gel, P., Bugliani, M., Saxena, R., Fex, M., Pulizzi, N., et al. (2009). Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat. Genet.* 41, 82–88. <https://doi.org/10.1038/ng.288>.
 31. Sparso, T., Bonnefond, A., Andersson, E., Bouatia-Naji, N., Holmkvist, J., Wegner, L., Grarup, N., Gjesing, A.P., Banasik, K., Cavalcanti-Proença, C., et al. (2009). G-allele of intronic rs10830963 in MTNR1B confers increased risk of impaired fasting glycemia and type 2 diabetes through an impaired glucose-stimulated insulin release: studies involving 19,605 Europeans. *Diabetes* 58, 1450–1456. <https://doi.org/10.2337/db08-1660>.
 32. Zerbino, D.R., Wilder, S.P., Johnson, N., Juettemann, T., and Flicek, P.R. (2015). The ensembl regulatory build. *Genome Biol.* 16, 56. <https://doi.org/10.1186/s13059-015-0621-5>.
 33. Marselli, L., Piron, A., Suleiman, M., Colli, M.L., Yi, X., Khamis, A., Carrat, G.R., Rutter, G.A., Bugliani, M., Giusti, L., et al. (2020). Persistent or

- Transient Human β Cell Dysfunction Induced by Metabolic Stress: Specific Signatures and Shared Gene Expression with Type 2 Diabetes. *Cell Rep.* 33, 108466. <https://doi.org/10.1016/j.celrep.2020.108466>.
34. American Diabetes Association (2009). Diagnosis and classification of diabetes mellitus. *Diabetes Care* 32, S62–S67. <https://doi.org/10.2337/dc09-S062>.
 35. Tian, G., S  getorp, J., Xu, Y., Shuai, H., Degerman, E., and Tengholm, A. (2012). Role of phosphodiesterases in the shaping of sub-plasma-membrane cAMP oscillations and pulsatile insulin secretion. *J. Cell Sci.* 125, 5084–5095. <https://doi.org/10.1242/jcs.107201>.
 36. Jacobs, D.T., Weigert, R., Grode, K.D., Donaldson, J.G., and Cheney, R.E. (2009). Myosin Vc is a molecular motor that functions in secretory granule trafficking. *Mol. Biol. Cell* 20, 4471–4488. <https://doi.org/10.1091/mbc.e08-08-0865>.
 37. M Ribeiro, D., Ziyani, C., and Delaneau, O. (2022). Shared regulation and functional relevance of local gene co-expression revealed by single cell analysis. *Commun. Biol.* 5, 876. <https://doi.org/10.1038/s42003-022-03831-w>.
 38. Smyth, D.J., Cooper, J.D., Howson, J.M.M., Clarke, P., Downes, K., Mistry, T., Stevens, H., Walker, N.M., and Todd, J.A. (2011). FUT2 Nonsecretor Status Links Type 1 Diabetes Susceptibility and Resistance to Infection. *Diabetes* 60, 3081–3084. <https://doi.org/10.2337/db11-0638>.
 39. Yang, P., Li, H.-L., and Wang, C.-Y. (2011). FUT2 Nonfunctional Variant: A “Missing Link” Between Genes and Environment in Type 1 Diabetes? *Diabetes* 60, 2685–2687. <https://doi.org/10.2337/db11-1104>.
 40. Fl  yel, T., Brorsson, C., Nielsen, L.B., Miani, M., Bang-Berthelsen, C.H., Friedrichsen, M., Overgaard, A.J., Berchtold, L.A., Wiberg, A., Poulsen, P., et al. (2014). CTSH regulates β -cell function and disease progression in newly diagnosed type 1 diabetes patients. *Proc. Natl. Acad. Sci. USA* 111, 10305–10310. <https://doi.org/10.1073/pnas.1402571111>.
 41. Ye, J., Stefan-Lifshitz, M., and Tomer, Y. (2021). Genetic and environmental factors regulate the type 1 diabetes gene CTSH via differential DNA methylation. *J. Biol. Chem.* 296, 100774. <https://doi.org/10.1016/j.jbc.2021.100774>.
 42. M  rquez, A., Kerick, M., Zhernakova, A., Gutierrez-Achury, J., Chen, W.M., Onengut-Gumuscu, S., Gonz  lez-  lvaro, I., Rodr  guez-Rodr  guez, L., Rios-Fern  ndez, R., Gonz  lez-Gay, M.A., et al. (2018). Meta-analysis of ImmunoChip data of four autoimmune diseases reveals novel single-disease and cross-phenotype associations. *Genome Med.* 10, 97. <https://doi.org/10.1186/s13073-018-0604-8>.
 43. Miyagawa, T., and Tokunaga, K. (2019). Genetics of narcolepsy. *Hum. Genome Var.* 6, 4. <https://doi.org/10.1038/s41439-018-0033-7>.
 44. Szymczak, F., Colli, M.L., Mamula, M.J., Evans-Molina, C., and Eizirik, D.L. (2021). Gene expression signatures of target tissues in type 1 diabetes, lupus erythematosus, multiple sclerosis, and rheumatoid arthritis. *Sci. Adv.* 7, eabd7600. <https://doi.org/10.1126/sciadv.abd7600>.
 45. Xue, D., Narisu, N., Taylor, D.L., Zhang, M., Grenko, C., Taylor, H.J., Yan, T., Tang, X., Sinha, N., Zhu, J., et al. (2023). Functional interrogation of twenty type 2 diabetes-associated genes using isogenic human embryonic stem cell-derived β -like cells. *Cell Metab.* 35, 1897–1914.e11. <https://doi.org/10.1016/j.cmet.2023.09.013>.
 46. Hodson, D.J., Mitchell, R.K., Marselli, L., Pullen, T.J., Gimeno Brias, S., Semplici, F., Everett, K.L., Cooper, D.M.F., Bugliani, M., Marchetti, P., et al. (2014). ADCY5 couples glucose to insulin secretion in human islets. *Diabetes* 63, 3009–3021. <https://doi.org/10.2337/db13-1607>.
 47. Li, Y., Miao, Y., Feng, Q., Zhu, W., Chen, Y., Kang, Q., Wang, Z., Lu, F., and Zhang, Q. (2024). Mitochondrial dysfunction and onset of type 2 diabetes along with its complications: a multi-omics Mendelian randomization and colocalization study. *Front. Endocrinol.* 15, 1401531. <https://doi.org/10.3389/fendo.2024.1401531>.
 48. Ghanbari, F., Yazdanpanah, N., Yazdanpanah, M., Richards, J.B., and Manousaki, D. (2022). Connecting Genomics and Proteomics to Identify Protein Biomarkers for Adult and Youth-Onset Type 2 Diabetes: A Two-Sample Mendelian Randomization Study. *Diabetes* 71, 1324–1337. <https://doi.org/10.2337/db21-1046>.
 49. Petrychenko, V., Yi, S.H., Liedtke, D., Peng, B.Z., Rodnina, M.V., and Fischer, N. (2025). Structural basis for translational control by the human 48S initiation complex. *Nat. Struct. Mol. Biol.* 32, 62–72. <https://doi.org/10.1038/s41594-024-01378-4>.
 50. Kiran, S., Mandal, M., Rakib, A., Bajwa, A., and Singh, U.P. (2023). miR-10a-3p modulates adiposity and suppresses adipose inflammation through TGF- β 1/Smad3 signaling pathway. *Front. Immunol.* 14, 1213415. <https://doi.org/10.3389/fimmu.2023.1213415>.
 51. Lee, S., Cho, Y.K., Kim, H., Choi, C., Kim, S., and Lee, Y.-H. (2024). miR-10a regulates cell death and inflammation in adipose tissue of male mice with diet-induced obesity. *Mol. Metab.* 90, 102039. <https://doi.org/10.1016/j.molmet.2024.102039>.
 52. Wallace, C. (2021). A more accurate method for colocalisation analysis allowing for multiple causal variants. *PLoS Genet.* 17, e1009440. <https://doi.org/10.1371/journal.pgen.1009440>.
 53. Wang, G., Sarkar, A., Carbonetto, P., and Stephens, M. (2020). A simple new approach to variable selection in regression, with application to genetic fine mapping. *J. R. Stat. Soc. Series B Stat. Methodol.* 82, 1273–1300. <https://doi.org/10.1111/rssb.12388>.
 54. Zhu, Z., Zhang, F., Hu, H., Bakshi, A., Robinson, M.R., Powell, J.E., Montgomery, G.W., Goddard, M.E., Wray, N.R., Visscher, P.M., and Yang, J. (2016). Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* 48, 481–487. <https://doi.org/10.1038/ng.3538>.
 55. Stekelenburg, C., Gerster, K., Blouin, J.L., Lang-Muritano, M., Guipponi, M., Santoni, F., and Schwitzgebel, V.M. (2019). Exome sequencing identifies a de novo FOXA2 variant in a patient with syndromic diabetes. *Pediatr. Diabetes* 20, 366–369. <https://doi.org/10.1111/pedi.12814>.
 56. Simaite, D., Kofent, J., Gong, M., R  schendorf, F., Jia, S., Arn, P., Bentler, K., Ellaway, C., K  hnen, P., Hoffmann, G.F., et al. (2014). Recessive mutations in PCBD1 cause a new type of early-onset diabetes. *Diabetes* 63, 3557–3564. <https://doi.org/10.2337/db13-1784>.
 57. Huerta-Chagoya, A., Schroeder, P., Mandla, R., Li, J., Morris, L., Vora, M., Alkanaq, A., Nagy, D., Szczepinski, L., Madsen, J.G.S., et al. (2024). Rare variant analyses in 51,256 type 2 diabetes cases and 370,487 controls reveal the pathogenicity spectrum of monogenic diabetes genes. *Nat. Genet.* 56, 2370–2379. <https://doi.org/10.1038/s41588-024-01947-9>.
 58. Evseeva, I., Nicodemus, K.K., Bonilla, C., Tonks, S., and Bodmer, W.F. (2010). Linkage disequilibrium and age of HLA region SNPs in relation to classic HLA gene alleles within Europe. *Eur. J. Hum. Genet.* 18, 924–932. <https://doi.org/10.1038/ejhg.2010.32>.
 59. Robertson, C.C., Inshaw, J.R.J., Onengut-Gumuscu, S., Chen, W.M., Santa Cruz, D.F., Yang, H., Cutler, A.J., Crouch, D.J.M., Farber, E., Bridges, S.L., Jr., et al. (2021). Fine-mapping, trans-ancestral and genomic analyses identify causal variants, cells, genes and drug targets for type 1 diabetes. *Nat. Genet.* 53, 962–971. <https://doi.org/10.1038/s41588-021-00880-5>.
 60. Greenawalt, D.M., Dobrin, R., Chudin, E., Hatoum, I.J., Suver, C., Beaulaurier, J., Zhang, B., Castro, V., Zhu, J., Sieberts, S.K., et al. (2011). A survey of the genetics of stomach, liver, and adipose gene expression from a morbidly obese cohort. *Genome Res.* 21, 1008–1016. <https://doi.org/10.1101/gr.112821.110>.
 61. Chen, J., Meng, Y., Zhou, J., Zhuo, M., Ling, F., Zhang, Y., Du, H., and Wang, X. (2013). Identifying candidate genes for Type 2 Diabetes Mellitus and obesity through gene expression profiling in multiple tissues or cells. *J. Diabetes Res.* 2013, 970435. <https://doi.org/10.1155/2013/970435>.
 62. Sajuthi, S.P., Sharma, N.K., Chou, J.W., Palmer, N.D., McWilliams, D.R., Beal, J., Comeau, M.E., Ma, L., Calles-Escandon, J., Demons, J., et al. (2016). Mapping adipose and muscle tissue expression quantitative trait loci in African Americans to identify genes for type 2 diabetes and obesity. *Hum. Genet.* 135, 869–880. <https://doi.org/10.1007/s00439-016-1680-8>.

63. Taylor, D.L., Jackson, A.U., Narisu, N., Hemani, G., Erdos, M.R., Chines, P.S., Swift, A., Idol, J., Didion, J.P., Welch, R.P., et al. (2019). Integrative analysis of gene expression, DNA methylation, physiological traits, and genetic variation in human skeletal muscle. *Proc. Natl. Acad. Sci. USA* **116**, 10883–10888. <https://doi.org/10.1073/pnas.1814263116>.
64. Raulerson, C.K., Ko, A., Kidd, J.C., Currin, K.W., Brotman, S.M., Cannon, M.E., Wu, Y., Spracklen, C.N., Jackson, A.U., Stringham, H.M., et al. (2019). Adipose Tissue Gene Expression Associations Reveal Hundreds of Candidate Genes for Cardiometabolic Traits. *Am. J. Hum. Genet.* **105**, 773–787. <https://doi.org/10.1016/j.ajhg.2019.09.001>.
65. Torres, J.M., Abdalla, M., Payne, A., Fernandez-Tajes, J., Thurner, M., Nylander, V., Gloyn, A.L., Mahajan, A., and McCarthy, M.I. (2020). A Multi-omic Integrative Scheme Characterizes Tissues of Action at Loci Associated with Type 2 Diabetes. *Am. J. Hum. Genet.* **107**, 1011–1028. <https://doi.org/10.1016/j.ajhg.2020.10.009>.
66. Ravassard, P., Hazhouz, Y., Pechberty, S., Bricout-Neveu, E., Armanet, M., Czernichow, P., and Scharfmann, R. (2011). A genetically engineered human pancreatic β cell line exhibiting glucose-inducible insulin secretion. *J. Clin. Investig.* **121**, 3589–3597. <https://doi.org/10.1172/JCI58447>.
67. Costa-Junior, J.M., Coomans de Brachène, A., Musuaya, A.E., Zimath, P.L., Martin-Vazquez, E., Oliveira, J.G., Carpentier, J., Faoro, V., Klass, M., Cnop, M., and Eizirik, D.L. (2025). Exercise-induced meteorin-like protein protects human pancreatic beta cells from cytokine-induced apoptosis. *Diabetologia* **68**, 1524–1529. <https://doi.org/10.1007/s00125-025-06426-2>.
68. Kolberg, L., Raudvere, U., Kuzmin, I., Vilo, J., and Peterson, H. (2020). gprofiler2 – an R package for gene list functional enrichment analysis and namespace conversion toolset g:Profiler. *F1000Res.* **9**, ELIXIR-709. <https://doi.org/10.12688/f1000research.24956.2>.
69. Korotkevich, G., Sukhov, V., Budin, N., Shpak, B., Artyomov, M.N., and Sergushichev, A. (2021). Fast gene set enrichment analysis. Preprint at bioRxiv. <https://doi.org/10.1101/060012>.
70. Alvelos, M.I., Szymczak, F., Castela, Â., Marín-Cañás, S., de Souza, B.M., Gkantounas, I., Colli, M., Fantuzzi, F., Cosentino, C., Igoillo-Esteve, M., et al. (2021). A functional genomic approach to identify reference genes for human pancreatic beta cell real-time quantitative RT-PCR analysis. *Islets* **13**, 51–65. <https://doi.org/10.1080/19382014.2021.1948282>.
71. Moore, F., Naamane, N., Colli, M.L., Bouckennooghe, T., Ortis, F., Gurzov, E.N., Igoillo-Esteve, M., Mathieu, C., Bontempi, G., Thykjaer, T., et al. (2011). STAT1 is a master regulator of pancreatic β -cell apoptosis and islet inflammation. *J. Biol. Chem.* **286**, 929–941. <https://doi.org/10.1074/jbc.M110.162131>.
72. Cunha, D.A., Hekerman, P., Ladière, L., Bazarra-Castro, A., Ortis, F., Wakeham, M.C., Moore, F., Rasschaert, J., Cardozo, A.K., Bellomo, E., et al. (2008). Initiation and execution of lipotoxic ER stress in pancreatic beta-cells. *J. Cell Sci.* **121**, 2308–2318. <https://doi.org/10.1242/jcs.026062>.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Bacterial and virus strains		
Prototype strain of enterovirus, CVB1/Conn-5	ATCC	ATCC VR-28
Chemicals, peptides, and recombinant proteins		
Lipofectamine RNAiMAX Transfection Reagent	Invitrogen	Cat #13778150
Propidium iodide	Sigma-Aldrich	Cat#P4170; CAS: 25535-16-4
Hoechst 33342 (bisBenzimide H 33342 trihydrochloride)	Sigma-Aldrich	Cat#14533; CAS: 875756-97-1
Forskolin	Sigma-Aldrich	Cat#F6886; CAS: 66575-29-9
Beta Krebs	Human Cell Design Group	Cat#BK-100
SsoAdvanced Universal SYBR Green Supermix	Bio-Rad	CAT#1725274
Critical commercial assays		
Human Insulin ELISA	Mercodia	Cat #10-1113-10
Invitrogen™ PureLink™ RNA Micro Scale Kit	Invitrogen	Cat#12183016
Applied Biosystems™ TaqMan™ Reverse Transcription Reagents	Applied Biosystems	Cat#4304134
Deposited data		
eQTL	Alonso et al. ¹⁷	http://tiger.bsc.es/
pQTL	Ferkingstad et al. ²¹	N/A
meQTL	McAllan et al. ²²	N/A
GWAS	Chen et al., ¹¹ Suzuki et al., ¹⁵ Kurki et al., ²³ Yengo et al. ²⁴	N/A
Co-localization list, plots and source code	This paper	https://doi.org/10.5281/zenodo.13987433
Experimental models: Cell lines		
EndoC-βH1	Ravassard et al. ⁶⁶	RRID:CVCL_L909
Oligonucleotides		
AllStars Negative Control siRNA	Qiagen	Cat #1027281
Human siFUT2, Stealth siRNA	ThermoFisher Scientific	ID:HSS103862
Human siFUT2#2, Silencer Select siRNA	ThermoFisher Scientific	ID:S533826
Primer for <i>FUT2</i> Forward: AGCGGCTAGCGAA GATTCA	This paper	N/A
Primer for <i>FUT2</i> Reverse: GGTCCCAGTGCCT TTGATGT	This paper	N/A
Primer for <i>ACTB</i> Forward: CTGTACGCCAACA CAGTGCT	Costa-Junior et al. ⁶⁷	N/A
Primer for <i>ACTB</i> Reverse: GCTCAGGAGGAGC AATGATC	Costa-Junior et al. ⁶⁷	N/A
Primer for <i>VAPA</i> Forward: TACCGAAACAAGGA AACTAATGGAA	Costa-Junior et al. ⁶⁷	N/A
Primer for <i>VAPA</i> Reverse: GCCTTAAACCTTCA TCTCTCAGGT	Costa-Junior et al. ⁶⁷	N/A
Software and algorithms		
colocRedRibbon	This paper	https://github.com/antpiron/colocRedRibbon and https://doi.org/10.5281/zenodo.13987433 (version used for this paper)
RedRibbon	Piron et al. ²⁶	https://github.com/antpiron/RedRibbon

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REAGENT or RESOURCE	SOURCE	IDENTIFIER
GProfiler2	Kolberg et al. ⁶⁸	RRID:SCR_018190 https://cran.r-project.org/web/packages/gprofiler2/index.html
Coloc	Wallace ⁵²	RRID:SCR_026041 https://cran.r-project.org/web/packages/coloc/index.html
fgSEA	Korotkevitch et al. ⁶⁹	RRID:SCR_020938 https://bioconductor.org/packages/release/bioc/html/fgsea.html
GraphPad Prism 9	GraphPad Software	RRID:SCR_002798

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

All human sample data and associated metadata are available from the respective data owners, as detailed in the [key resources table](#) section.

METHOD DETAILS

The novel *colocRedRibbon* R package integrates the *coloc* co-localization package²⁵ with a variant shortlisting method. The shortlisting method is based on *RedRibbon* rank-rank hypergeometric overlap²⁶ and uses the direction of effect of GWAS risk alleles in the eQTL analysis and is described in more detail below.

colocRedRibbon workflow

colocRedRibbon is a tool designed to identify common causal candidates by co-localizing GWAS and eQTL (Figure 1A). This approach aims to pinpoint variants associated both with diabetes risk and gene expression. The method employs a two-step approach for shortlisting variants: a risk allele effect step and a *RedRibbon* overlap step. The risk allele effect step categorizes variants into two disjoint sets based on the direction of effect on gene expression of the disease-risk increasing allele, i.e., down- or upregulating. The upregulating variant set comprises the variants whose risk alleles increase gene expression, and the downregulating set risk alleles that decrease gene expression. The subsequent steps are applied independently on both variant sets.

In the shortlisting step, the *RedRibbon* rank-rank hypergeometric overlap method²⁶ is applied on GWAS and eQTL variants. This step involves the ranking of variants by *p*-values for both GWAS or eQTLs and statistically examining potential overlaps between the ranked lists. If significant overlap is detected, the shortlisted SNPs are further analyzed by the *coloc* package. In cases where *RedRibbon* overlap is not significant, *coloc* analysis is performed without prior shortlisting.

colocRedRibbon shortlisting

Risk allele effect shortlisting

The shortlisting step leverages a known biological principle to categorize variants into two disjoint subsets. This principle is based on the expectation that risk alleles of multiple variants within a gene region that are in linkage disequilibrium should produce concordant expression effects, either upregulating or downregulating gene expression. Risk alleles of variants are hence split into two sets, one upregulating and the other downregulating a gene. Only one of these two sets is likely to yield meaningful co-localization results, as relevant associations are expected to have consistent directional effects. Compared to analyses that do not include this step, this division typically halves the number of candidate loci, streamlining subsequent analyses.

RedRibbon overlap shortlisting

The *RedRibbon* method²⁶ ranks GWAS and eQTL variant lists by increasing *p*-value, prioritizing variants with the strongest statical significance. *RedRibbon* aims to uncover the best overlap among variants with the lowest *p*-values in both lists. For each coordinate (*i*, *j*) in the two lists, where *i* represents the GWAS rank and *j* the eQTL rank, an overlap *p*-value is computed using a one-sided hypergeometric statistic. Let *c* be the number of variants common to both lists at the coordinate (*i*, *j*) in a *RedRibbon* overlap map of size *n* × *n*, where *n* is the number of elements in each list, the overlap *p*-value is calculated as:

$$pval = 1 - CDF_{hyper}(c - 1, i, j, n)$$

where *CDF_{hyper}* represents the hypergeometric cumulative distribution function. This *p*-value quantifies the probability of observing *c* or more overlapping variants by chance, given the positions in the ranked lists. *RedRibbon* overlap results in a list of variants corresponding to the minimal *p*-value overlap. This approach allows for a statistical assessment of the overlap between GWAS and eQTL SNPs, facilitating the identification of potential causal variants that influence both disease risk and gene expression.

RedRibbon overlaps shortlisting in interquartile range mode

The list of shortlisted variants can be directly fed into the *coloc* tool. Or, alternatively, the interquartile range (IQR) method can be employed to add background, providing a more comprehensive analysis (Figure 1B). The *RedRibbon*-shortlisted variants

serve as the core set. The core set is expanded with additional variants based on their chromosomal positions, using as lower bound, $Q_1 - 1.5 * IQR$ and upper bound $Q_2 + 1.5 * IQR$ where Q_1 is the 25th percentile (first quartile) of the chromosomal positions of the core set, Q_2 the 75th percentile (third quartile), and IQR is the interquartile range ($Q_3 - Q_1$). This method adds a background of variants while excluding potential outliers, providing a broader genomic context and ensuring a more robust set for *coloc* analysis.

Adjusted P-value computation

The *colocRedRibbon* adjusted minimal p -value is computed, leveraging the p -value adjustment capabilities of the *RedRibbon* package.²⁶ This approach utilizes a hybrid permutation-prediction method that splits the variants into two sets, the permuted and predicted set. The permuted set undergoes, as the name indicates, random permutation. The predicted set is computed from the permuted set values with the following:

$$P_y = |r|P_x + (1 - |r|)\hat{P}$$

where the p -value P_y for variant y is predicted from the p -value P_x for variant x , the coefficient of correlation r representing the linkage disequilibrium, and a random p -value \hat{P} generated from the distribution of all values in the original list.

The hybrid permutation-prediction of *colocRedRibbon* uses a linkage disequilibrium approximation to compute the adjusted p -value. This approximation is given by r function, an approximation of the coefficient of correlation between two variants:

$$r(SNP_1, SNP_2) = \frac{half}{half + distance(SNP_1, SNP_2)}$$

where *distance* is the distance in base pairs between the variants under consideration, and *half* the distance between the variants where r equals 0.5.

The rationale behind the approximation is to trade-off some of the adjusted p -value accuracy for performance, because using real linkage disequilibrium would be computationally expensive as it needs to be computed for all pairs of variants. Subsequent *coloc* analysis is expected to filter out the remaining false positives.

colocRedRibbon R package

colocRedRibbon is available as a user-friendly R package (see data availability section), designed to streamline the process of co-localization analysis. This package seamlessly combines risk allele effect and *RedRibbon* shortlisting steps with the *coloc* package,²⁵ providing a comprehensive analysis pipeline. It leverages the fast and accurate rank-rank overlap method from *RedRibbon* R package.²⁶ The speed of *RedRibbon* allows for thousands of co-localizations to be run within hours on standard computer hardware.

Pathway and regulatory elements enrichment

Pathway enrichment was done with *gprofiler2* (v0.1.9) and regulatory element enrichment with the hypergeometric model using Ensembl Regulatory Build GRCh37³² and human islet chromatin regions from.^{28,29} We used *fGSEA* R package⁶⁹ to overlap the co-localizing genes with type 2 diabetes differential gene expression from.³³

Normalization of gene expression

In the gene expression plots, expression was normalized to the geometric mean of stable genes *VAPA*, *ACTB* and *ARF1* (in transcripts per million).⁷⁰ For each sample numbered j , an adjustment factor β_j is computed with

$$\beta_j = \sqrt[n]{\prod_{i=1}^n Expr_{ref,i,j}}$$

The expression adjustment is computed for each sample j and gene i as $AdjExpr_{i,j} = \beta_j * Exp r_i$. This normalization was used only for the purpose of visualization of gene expression.

Viral infection and FUT2 knockdown in human beta cells

Cell culture

The human EndoC- β H1 beta cell line,⁶⁶ kindly provided by R.Scharfmann (Institut Cochin, Paris), was cultured on Matrigel-fibronectin-coated plates in DMEM with 5.6 mM glucose, 2% fatty acid-free BSA, 50 μ M 2-mercaptoethanol, 10 mM nicotinamide, 5.5 μ g/mL transferrin, 6.7 ng/mL sodium selenite, and antibiotics.

Viral infection

EndoC- β H1 cells were infected with prototype strain of enterovirus CVB1/Conn-5 (ATCC) at 0.1 multiplicity of infection using medium without FBS. After 2-h adsorption at 37°C, the viral inoculum was removed, cells were washed twice and FBS-containing medium was added to allow viral replication. Cytopathogenic effect was assessed 24 h post-infection.

siRNA transfection

EndoC- β H1 were transfected overnight with 60 nM Allstars Negative Control siRNA (Qiagen, Venlo, The Netherlands) or human FUT2 siRNA (siFUT2, Stealth siRNA, ID:HSS103862, or siFUT2 #2, Silencer Select siRNA, ID:S533826, both from ThermoFisher Scientific) using Lipofectamine RNAiMAX (Invitrogen) according to the manufacturer's protocol.⁷¹ After 48–72-h recovery, cells were infected

with CVB1 coxsackieviruses as described above. RNA extraction (Invitrogen) and reverse transcription (Applied Biosystems) were performed following the manufacturer's protocols, and qPCR was carried out as previously described.⁶⁷

Cell viability

Cells were stained with the DNA-binding dyes propidium iodide (5 $\mu\text{g/mL}$) and Hoechst 33342 (5 $\mu\text{g/mL}$, Sigma). The number of viable, apoptotic and necrotic cells was assessed in at least 600 cells by two observers, one of whom was blinded to sample identity. Observer agreement exceeded 90%. This method has been validated by comparison with electron microscopy, caspase-3 cleavage and DNA laddering.⁷²

Insulin secretion

48 h after siRNA transfection, EndoC- β H1 cells were preincubated for 24 h in DMEM containing 2.8 mM glucose, followed by incubation in glucose-free Krebs solution for 1 h. Cells were exposed in parallel to Krebs solution containing 0 or 20 mM glucose or 20 mM glucose + 10 μM forskolin for 1 h. Insulin was measured in cell-free supernatants and acid ethanol-extracted cell lysates by ELISA (Mercodia) and normalized to protein content, determined by Bradford assay.

QUANTIFICATION AND STATISTICAL ANALYSIS

Co-localization

ColocRedRibbon method is fully detailed in the [method details](#) section. Overlap significance in *ColocRedRibbon* is defined as an adjusted p -value ≤ 0.05 , while significance for *coloc* tool is defined as a posterior probability $\text{PP.H4.abc} \geq 0.8$. To address the non-deterministic nature of RedRibbon²⁶ (see [limitations of the study](#) section), *colocRedRibbon* analyses were repeated up to three times in cases where *coloc* returned a posterior probability $0.8 > \text{PP.H4.abf} \geq 0.6$ to ensure result robustness. When minor allele frequencies were not available from QTL analyses, we used the corresponding GWAS minor allele frequencies as proxies. We ran the co-localization over the regions containing at least one significant GWAS (P -value $\leq 10^{-8}$) and one significant QTL, using significance thresholds as defined by the data owner or, if not provided, derived from a false discovery rate criterion.

Enrichment analyses

Gene enrichment analysis for type 2 diabetes was performed using the *fgSEA* software with parameters $\text{minSize} = 15$ and $\text{maxSize} = 1000$.⁶⁹ Pathway enrichment analysis with *gProfiler2* was carried out using the following data sources: GO, KEGG, REAC, MIRNA, HP, HPA, CORUM, and WP.⁶⁸ GProfiler2 visualization plots were generated with a custom plotting function, which is available in our zenodo repository number (<https://doi.org/10.5281/zenodo.13987433>, file `src/r-lib/enrichment.R`). Variant enrichment in regulatory regions was assessed using a one-sided hypergeometric test, with multiple testing correction applied by controlling for false discovery rate ($\text{FDR} \leq 0.05$, zenodo file `src/r-lib/regulatory.R`).

FUT2 statistical analyses

Statistical analyses for *FUT2* (Figure S4) were performed using one-way ANOVA for panels A–B and two-way ANOVA for panel C, followed by Dunnett's post hoc test for pairwise comparisons using GraphPad software. Data are presented as mean \pm SEM, with individual points indicating independent experiments.

Supplemental information

Identification of novel type 1 and type 2 diabetes genes by co-localization of human islet eQTL and GWAS variants with *colocRedRibbon*

Anthony Piron, Florian Szymczak, Lise Folon, Daniel J.M. Crouch, Theodora Papadopoulou, Maria Lytrivi, Yue Tong, Maria Inês Alvelos, Maikel L. Colli, Xiaoyan Yi, Marcin L. Pekalski, Konstantinos Hatzikotoulas, Alicia Huerta-Chagoya, Henry J. Taylor, Type 2 Diabetes Global Genomics Initiative, Matthieu Defrance, John A. Todd, Décio L. Eizirik, Josep M. Mercader, and Miriam Cnop

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Anthony Piron^{1,2,3,4,17}, Florian Szymczak^{1,3}, Lise Folon¹, Daniel J. M. Crouch⁴, Theodora Papadopoulou¹, Maria Lytrivi¹, Yue Tong¹, Maria Inês Alvelos¹, Maikel L. Colli¹, Xiaoyan Yi¹, Marcin L. Pekalski^{5,4}, Konstantinos Hatzikotoulas⁶, Alicia Huerta-Chagoya^{7,8,9}, Henry J. Taylor^{11,12,13}, Type 2 Diabetes Global Genomics Initiative¹⁴, Matthieu Defrance³, John A. Todd⁴, Décio L. Eizirik¹, Josep M. Mercader^{7,10,8,9} and Miriam Cnop^{1,15,16,18}

1. ULB Center for Diabetes Research, Medical Faculty, Université Libre de Bruxelles, Brussels, 1070, Belgium
2. Pharmacognosy, Bioanalysis and Drug Discovery, Pharmacy Faculty, Université Libre de Bruxelles, Brussels, 1050, Belgium
3. Interuniversity Institute of Bioinformatics in Brussels (IB2), Brussels, 1050, Belgium
4. JDRF/Wellcome Diabetes and Inflammation Laboratory, Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, OX3 7BN, Oxford, UK
5. Military Institute of Medicine, National Research Institute Warsaw, Poland
6. Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, 85764, Germany
7. Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, 02144, United States of America
8. Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts, 02114, United States of America
9. Department of Medicine, Harvard Medical School, Boston, Massachusetts, 02115, United States of America
10. Programs in Metabolism and Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, 02142, United States of America
11. Center for Precision Health Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, 20892-2152, USA
12. British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, CB2 0BB, UK
13. Heart and Lung Research Institute, University of Cambridge, Cambridge, CB2 0BB, UK
14. <https://diagram-consortium.org/T2DGGI.html>
15. Division of Endocrinology, Erasmus Hospital, Université Libre de Bruxelles, Brussels, 1070, Belgium
16. WEL Research Institute, Wavre, 1300, Belgium
17. Lead contact: anthony.piron@ulb.be
18. Correspondence: miriam.cnop@ulb.be

SUPPLEMENTAL INFORMATION

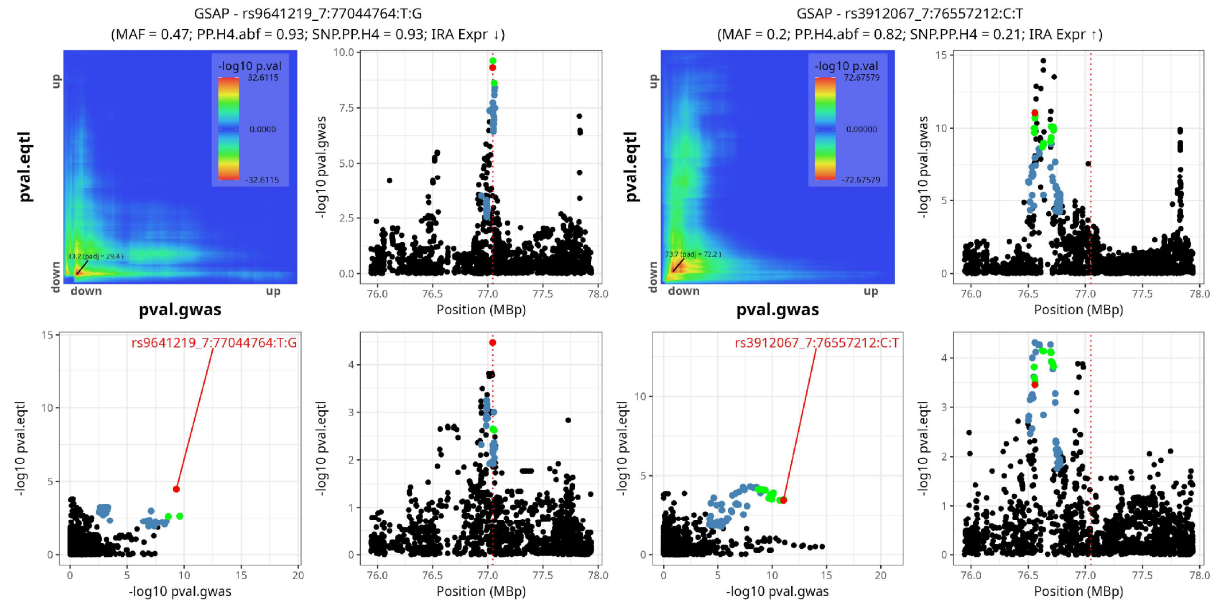


Figure S1. Co-localization plots for GSAP eQTL and type 2 diabetes GWAS, Related to Figure 3. The lead SNP is shown in red, the 99% credible set in green and RedRibbon overlap in blue. GSAP presents two distinct co-localizations in the same region with opposite risk allele expression regulation. SNPs are referenced by rsids, PP.H4 abf and SNP PP.H4 are the posterior probability for coloc tool hypothesis 4, MAF is minor allele frequency. Arrows pointing up or down indicate increased or reduced gene expression, respectively.



Figure S2. Co-localization genes are enriched in important pathways, Related to Figure 4 and Tables S17-18. Directional Gprofiler2 enrichments in co-localizing genes for type 2 diabetes and glycemic trait GWAS. (A) Enrichment for genes upregulated by lead risk allele. (B) Enrichment for genes downregulated by lead risk allele. (C-E) EnricherR enrichments for co-localizing genes of type 2 diabetes and glycemic trait GWAS. Top 10 enriched terms from BioPlanet, WikiPathways, and Reactome gene

set library are displayed by increasing *P*-Value. (F) Metascape enrichment for co-localizing genes of type 2 diabetes and glycemic trait GWAS.

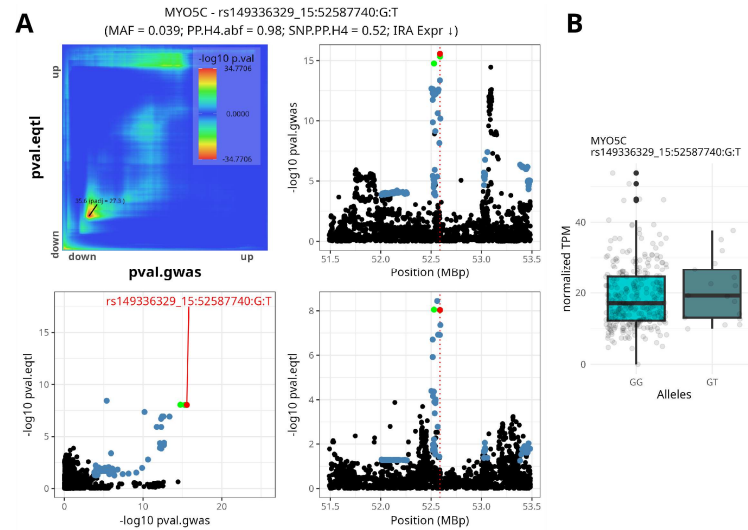


Figure S3. Identification of MYO5C as a novel type 2 diabetes gene, Related to Figure 4H. (A) Co-localization plots for MYO5C, showing lead SNP in red, 99% credible set in green and RedRibbon overlap in blue. The red dotted line is the gene transcription start site. (B) Expression plot for co-localizing SNP. SNPs are referenced by rsids, PP.H4 abf and SNP PP.H4 are the posterior probability for coloc tool hypothesis 4, MAF is minor allele frequency, Increasing Risk Allele expression regulation direction; an arrow pointing down means decreased gene expression for the risk allele

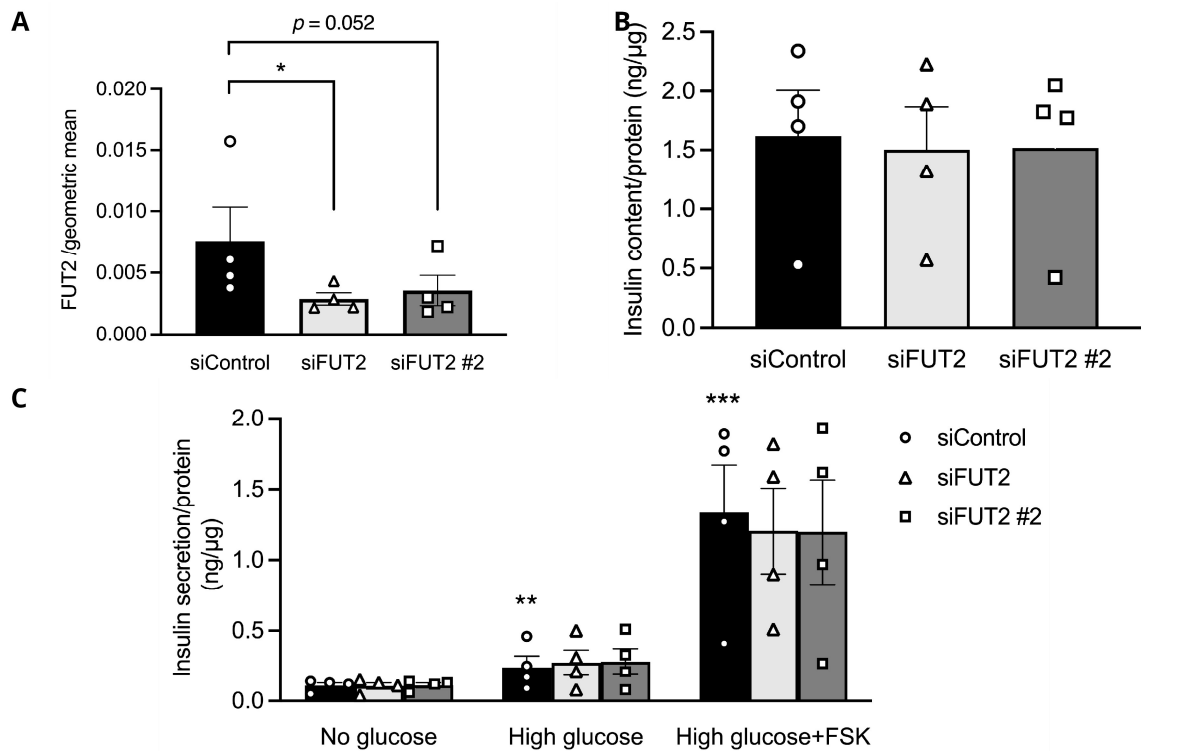


Figure S4. FUT2 depletion does not alter beta-cell function, Related to Figure 5. (A) *FUT2* mRNA expression in EndoC-βH1 cells 48 hours after transfection with siControl or *FUT2* siRNAs (siFUT2 or siFUT2 #2), normalized to the geometric mean of reference genes *ACTB* and *VAPA* (n=4). (B) Insulin content of cell lysates. (C) Insulin secretion induced by 0 or 20 mM (high) glucose or 20 mM glucose + 10 μM forskolin (FSK) (n=4). Statistical analysis by (A-B) one-way or (C) two-way ANOVA followed by Dunnett post hoc test for pairwise comparisons GraphPad software. Data are presented as mean ± SEM, with individual points representing independent experiments. ****P*-Value ≤ 0.001, ***P*-Value ≤ 0.01, **P*-Value ≤ 0.05.

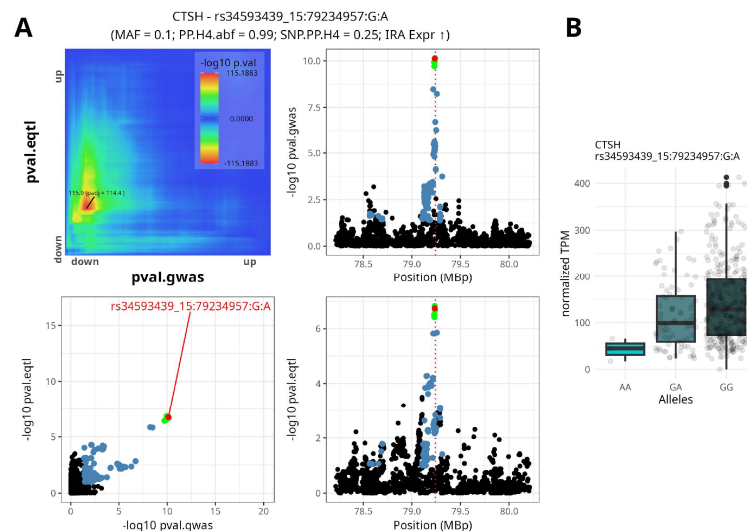


Figure S5. Co-localization for *CTSH* eQTL and type 1 diabetes GWAS, Related to Figure 2. (A) Co-localization plots for *CTSH*, showing the lead SNP in red, the 99% credible set in green and RedRibbon overlap in blue. The red dotted line is the gene transcription start site. (B) Expression plot for co-localizing SNP. SNPs are referenced by rsids, PP.H4 abf and SNP PP.H4 are the posterior probability for *coloc* tool hypothesis 4, MAF is minor allele frequency, IRA indicates the Increasing Risk Allele expression regulation direction; an arrow pointing up means increased gene expression for the risk allele.

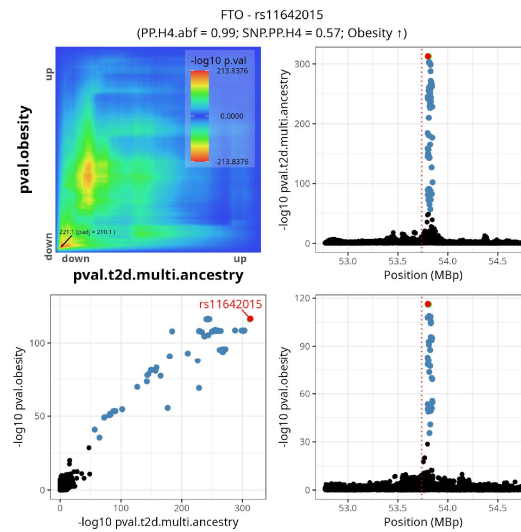


Figure S6. Co-localization for *FTO* region between obesity GWAS and multi-ancestry type 2 diabetes GWAS, Related to Figure 2. Co-localization plots for *FTO*, showing the lead SNP in red, the 99% credible set in green and RedRibbon overlap in blue. The red dotted line is the gene transcription start site. SNPs are referenced by rsids, PP.H4 abf and SNP PP.H4 are the posterior probability for *coloc* tool hypothesis 4; an arrow pointing up means increased gene expression for the risk allele.

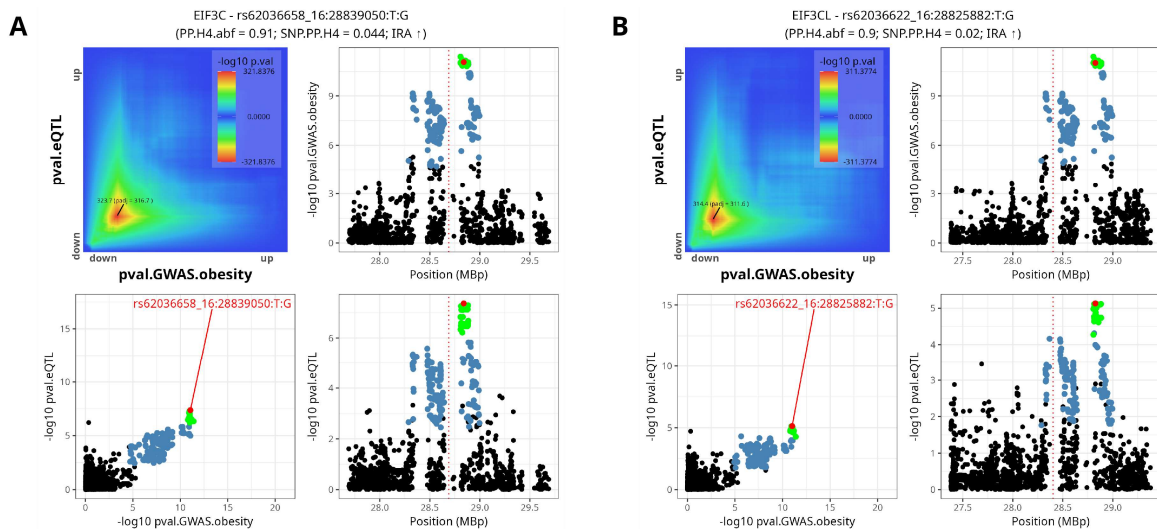


Figure S7. Co-localization for *EIF3C* and *EIF3CL* pancreatic islet eQTL and obesity GWAS, Related to Figure 2 and Graphical Abstract. Co-localization plots for (A) *EIF3C* and (B) *EIF3CL*. The lead SNP in red, 99% credible set in green and RedRibbon overlap in blue. The red dotted line is the gene transcription start site. SNPs are referenced by rsids, PP.H4 abf and SNP PP.H4 are the posterior probability for coloc tool hypothesis 4, IRA indicates the Increasing Risk Allele expression regulation direction; an arrow pointing up means increased gene expression for the risk allele.

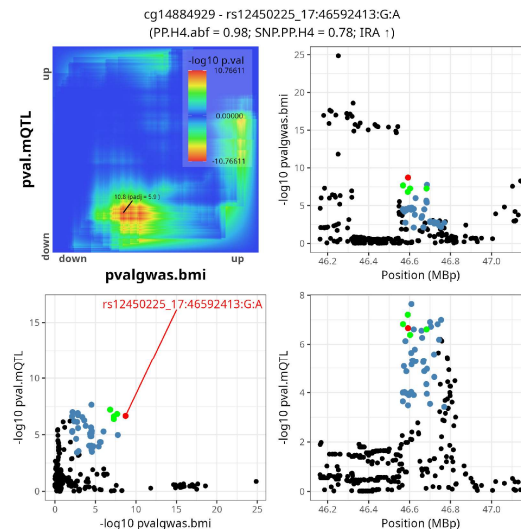


Figure S8. Co-localization for methylation site cg14884929 meQTL and BMI GWAS, Related to STAR Method Key Resources Table and Graphical Abstract. The lead SNP in red, 99% credible set in green and RedRibbon overlap in blue. PP.H4 abf and SNP PP.H4 are the posterior probability for coloc tool hypothesis 4, IRA indicates the Increasing Risk Allele; an arrow pointing up means increased DNA methylation for the risk allele.

T2DGGI Members

Ken Suzuki^{1,2,3}, Konstantinos Hatzikotoulas⁴, Lorraine Southam⁴, Henry J. Taylor^{5,6,7}, Xianying Yin^{8,9}, Kim M. Lorenz^{10,11,12}, Ravi Mandla^{13,14}, Alicia Huerta-Chagoya¹³, Giorgio EM Melloni¹⁵, Stavroula Kanoni¹⁶, Nigel W Rayner⁴, Ozvan Bocher⁴, Ana Luiza Arruda^{4,297,298}, Kyuto Sonehara^{17,3,18,19}, Shinichi Namba³, Simon SK Lee²⁰, Michael H Preuss²⁰, Lauren E Petty²¹, Philip Schroeder^{13,14}, Brett Vanderwerff⁹, Mart Kals²², Fiona Bragg^{23,24}, Kuang Lin²³, Xiuqing Guo²⁵, Weihua Zhang^{26,27}, Jie Yao²⁵, Young Jin Kim²⁸, Mariaelisa Graff²⁹, Fumihiko Takeuchi³⁰, Jana Nano³¹, Amel Lamri^{32,33}, Masahiro Nakatochi³⁴, Sanghoon Moon²⁸, Robert A Scott³⁵, James P Cook³⁶, Jung-Jin Lee³⁷, Ian Pan³⁸, Daniel Taliun⁹, Esteban J Parra³⁹, Jin-Fang Chai⁴⁰, Lawrence F Bielak⁴¹, Yasuharu Tabara⁴², Yang Hai²⁵, Gudmar Thorleifsson⁴³, Niels Grarup⁴⁴, Tamar Sofer^{45,46,47}, Matthias Wuttke⁴⁸, Chloé Sarnowski⁴⁹, Christian Gieger^{50,31,51}, Darryl Noursome⁵², Stella Trompet^{53,54}, Soo-Heon Kwak⁵⁵, Jirong Long⁵⁶, Meng Sun⁵⁷, Lin Tong⁵⁸, Wei-Min Chen⁵⁹, Suraj S Nongmaithem⁶⁰, Raymond Noordam⁵⁴, Victor JY Lim⁴⁰, Claudia HT Tam^{61,62}, Yoonjung Yoonie Joo^{63,64}, Chien-Hsiun Chen⁶⁵, Laura M Raffield⁶⁶, Bram Peter Prins⁶⁷, Aude Nicolas⁶⁸, Lisa R Yanek⁶⁹, Guanjie Chen⁷⁰, Jennifer A Brody⁷¹, Edmond Kabagambe^{72,56}, Ping An⁷³, Anny H Xiang⁷⁴, Hyeok Sun Choi⁷⁵, Brian E Cade^{46,76}, Jingyi Tan²⁵, K Alaine Broadway⁶⁶, Alice Williamson^{35,77}, Zoha Kamali^{78,79}, Jinrui Cui⁸⁰, Manonanthini Thangam⁸¹, Linda S Adair⁸², Adebawale Adeyemo⁷⁰, Carlos A Aguilar-Salinas⁸³, Tarunveer S Ahluwalia^{84,85}, Sonia S Anand^{32,33,86}, Alain Bertoni⁸⁷, Jette Bork-Jensen⁴⁴, Ivan Brandslund^{88,89}, Thomas A Buchanan⁹⁰, Charles F Burant⁹¹, Adam S Butterworth^{6,92,93,7,94}, Mickaël Canouil^{95,96}, Juliana CN Chan^{61,62,97,98}, Li-Ching Chang⁶⁵, Miao-Li Chee⁹⁹, Ji Chen^{100,101}, Shyh-Huei Chen¹⁰², Yuan-Tsong Chen⁶⁵, Zhengming Chen^{23,24}, Lee-Ming Chuang^{103,104}, Mary Cushman¹⁰⁵, John Danesh^{6,92,93,67,7,94}, Swapan K Das¹⁰⁶, H Janaka de Silva¹⁰⁷, George Dedoussis¹⁰⁸, Latchezar Dimitrov¹⁰⁹, Ayo P Doumatey⁷⁰, Shufa Du^{82,110}, Qing Duan⁶⁶, Kai-Uwe Eckardt^{111,112}, Leslie S Emery¹¹³, Daniel S Evans¹¹⁴, Michele K Evans¹¹⁵, Krista Fischer^{22,116}, James S Floyd⁷¹, Ian Ford¹¹⁷, Oscar H Franco¹¹⁸, Timothy M Frayling¹¹⁹, Barry I Freedman¹²⁰, Pauline Genter¹²¹, Hertzfel C Gerstein^{32,33,86}, Vilmantas Giedraitis¹²², Clicerio González-Villalpando¹²³, Maria Elena González-Villalpando¹²³, Penny Gordon-Larsen^{82,110}, Myron Gross¹²⁴, Lindsay A Guare¹²⁵, Sophie Hackinger⁶⁷, Liisa Hakaste^{126,127}, Sohee Han²⁸, Andrew T Hattersley¹²⁸, Christian Herder^{50,129,130}, Momoko Horikoshi¹³¹, Annie-Green Howard^{132,110}, Willa Hsueh¹³³, Mengna Huang^{38,134}, Wei Huang¹³⁵, Yi-Jen Hung^{136,137}, Mi Yeong Hwang¹³⁸, Chii-Min Hwu^{139,140}, Sahoko Ichihara¹⁴¹, Mohammad Arfan Ikram¹¹⁸, Martin Ingelsson¹²², Md. Tariqul Islam¹⁴², Masato Isono³⁰, Hye-Mi Jang¹³⁸, Farzana Jasmine⁵⁸, Guozhi Jiang^{61,62}, Jost B Jonas¹⁴³, Torben Jørgensen^{144,145,146}, Frederick K Kamanu¹⁵, Fouad R Kandeel¹⁴⁷, Anuradhani Kasturiratne¹⁴⁸, Tomohiro Katsuya^{149,150}, Varinderpal Kaur¹⁴, Takahisa Kawaguchi⁴², Jacob M Keaton^{5,56,109}, Abel N Kho^{151,152}, Chiea-Chuen Khor¹⁵³, Muhammad G Kibriya⁵⁸, Duk-Hwan Kim¹⁵⁴, Florian Kronenberg¹⁵⁵, Johanna Kuusisto¹⁵⁶, Kristi Läll²², Leslie A Lange¹⁵⁷, Kyung Min Lee^{158,159}, Myung-Shik Lee^{160,161}, Nanette R Lee¹⁶², Aaron Leong^{163,164}, Liming Li^{165,166}, Yun Li⁶⁶, Ruifang Li-Gao¹⁶⁷, Symen Ligthart¹¹⁸, Cecilia M Lindgren^{168,169,170}, Allan Linneberg^{144,171}, Ching-Ti Liu¹⁷², Jianjun Liu^{153,173}, Adam E Locke^{174,175,302}, Tin Louie¹¹³, Jian'an Luan³⁵, Andrea O Luk^{61,62}, Xi Luo¹⁷⁶, Jun Lv^{165,166}, Julie A Lynch^{158,159}, Valeriya Lyssenko^{177,178}, Shiro Maeda^{179,180,131}, Vasiliki Mamakou¹⁸¹, Sohail Rafik Mansuri^{60,299}, Koichi Matsuda¹⁸², Thomas Meitinger^{183,184,185}, Olle Melander⁸¹, Andres Metspalu²², Huan Mo⁵, Andrew D Morris¹⁸⁶, Filipe A Moura¹⁵, Jerry L Nadler¹⁸⁷, Michael A Nalls^{68,188,189}, Uma Nayak⁵⁹, Ioanna Ntalla¹⁶, Yukinori Okada^{3,17,19,190,18,191}, Lorena Orozco¹⁹², Sanjay R Patel¹⁹³, Snehal Patil⁹, Pei Pei¹⁶⁶, Mark A Pereira¹⁹⁴, Annette Peters^{50,185,31,195}, Fraser J Pirie¹⁹⁶, Hannah G Polikowsky²¹, Bianca Porneala¹⁶⁴, Gauri Prasad^{197,198}, Laura J Rasmussen-Torvik¹⁹⁹, Alexander P Reiner²⁰⁰, Michael Roden^{50,129,130}, Rebecca Rohde²⁹, Katheryn Roll²⁵, Charumathi Sabanayagam^{99,201,202}, Kevin Sandow²⁵, Alagu Sankareswaran^{60,299}, Naveed Sattar²⁰³, Sebastian Schönherr¹⁵⁵, Mohammad Shahriar⁵⁸, Botong Shen¹¹⁵, Jinxiu Shi¹³⁵, Dong Mun Shin¹³⁸, Nobuhiro Shojima², Jennifer A Smith^{41,204}, Wing Yee So^{61,98}, Alena Stančáková¹⁵⁶, Valgerdur Steinthorsdottir⁴³, Adrienne M Stilp¹¹³, Konstantin Strauch^{205,206,207}, Kent D Taylor²⁵, Barbara Thorand^{50,31}, Unnur Thorsteinsdottir^{43,208}, Brian Tomlinson^{61,209}, Tam C. Tran⁵, Fuu-Jen Tsai²¹⁰, Jaakko Tuomilehto^{211,212,213,214}, Teresa Tusie-Luna^{215,216}, Miriam S Udler^{163,13,14}, Adan Valladares-Salgado²¹⁷, Rob M van Dam^{40,173}, Jan B van Klinken^{218,219,220}, Rohit Varma²²¹, Niels Wachter-Rodarte²²², Eleanor Wheeler³⁵, Ananda R Wickremasinghe¹⁴⁸, Ko Willems van Dijk^{218,219,223}, Daniel R Witte^{224,225}, Chittaranjan S Yajnik²²⁶, Ken

Yamamoto²²⁷, Kenichi Yamamoto^{3,228,190}, Kyunghoon Yoon¹³⁸, Canqing Yu^{165,166}, Jian-Min Yuan^{229,230}, Salim Yusuf^{33,32,86}, Matthew Zawistowski⁹, Liang Zhang⁹⁹, Wei Zheng⁵⁶, Leslie J Raffel²³¹, Michiya Igase²³², Eli Ipp¹²¹, Susan Redline^{46,233,76}, Yoon Shin Cho⁷⁵, Lars Lind²³⁴, Michael A Province⁷³, Myriam Fornage²³⁵, Craig L Hanis²³⁶, Erik Ingelsson^{237,238}, Alan B Zonderman¹¹⁵, Bruce M Psaty^{71,239,240}, Ya-Xing Wang²⁴¹, Charles N Rotimi⁷⁰, Diane M Becker⁶⁹, Fumihiko Matsuda⁴², Yongmei Liu^{87,242}, Mitsuhiro Yokota²⁴³, Sharon LR Kardia⁴¹, Patricia A Peyser⁴¹, James S Pankow¹⁹⁴, James C Engert^{244,245}, Amélie Bonnefond^{95,96,246}, Philippe Froguel^{95,96,246}, James G Wilson²⁴⁷, Wayne HH Sheu^{248,140,137}, Jer-Yuarn Wu⁶⁵, M Geoffrey Hayes^{249,250,251}, Ronald CW Ma^{61,62,97,98}, Tien-Yin Wong^{99,201,202}, Dennis O Mook-Kanamori¹⁶⁷, Tiinamaija Tuomi^{252,126,127,81}, Giriraj R Chandak^{60,300}, Francis S Collins⁵, Dwaipayan Bharadwaj²⁵³, Guillaume Paré^{254,33}, Michèle M Sale⁵⁹, Habibul Ahsan⁵⁸, Ayesha A Motala¹⁹⁶, Xiao-Ou Shu⁵⁶, Kyong-Soo Park^{55,255}, J Wouter Jukema^{53,256}, Miguel Cruz²¹⁷, Yii-Der Ida Chen²⁵, Stephen S Rich²⁵⁷, Roberta McKean-Cowdin⁵², Harald Grallert^{31,50,258}, Ching-Yu Cheng^{99,201,202}, Mohsen Ghanbari¹¹⁸, E-Shyong Tai^{173,40,259}, Josee Dupuis^{260,172}, Norihiro Kato³⁰, Markku Laakso¹⁵⁶, Anna Köttgen⁴⁸, Woon-Puay Koh^{261,262}, Donald W Bowden^{109,263,264}, Colin NA Palmer²⁶⁵, Jaspal S Kooner^{27,266,267,268}, Charles Kooperberg²⁰⁰, Simin Liu^{38,134,269}, Kari E North²⁹, Danish Saleheen^{270,271,272}, Torben Hansen⁴⁴, Oluf Pedersen⁴⁴, Nicholas J Wareham³⁵, Juyoung Lee¹³⁸, Bong-Jo Kim¹³⁸, Iona Y Millwood^{23,24}, Robin G Walters^{23,24}, Kari Stefansson^{43,208}, Emma Ahlqvist⁸¹, Mark O Goodarzi⁸⁰, Karen L Mohlke⁶⁶, Claudia Langenberg^{35,273,274}, Christopher A Haiman²⁷⁵, Ruth JF Loos^{20,276,44}, Jose C Florez^{163,13,14}, Daniel J Rader^{277,12,278,279}, Marylyn D Ritchie^{280,12,281}, Sebastian Zöllner^{9,282}, Reedik Mägi²², Nicholas A Marston¹⁵, Christian T Ruff¹⁵, David A van Heel²⁸³, Sarah Finer²⁸⁴, Joshua C Denny^{5,285}, Toshimasa Yamauchi², Takashi Kadowaki^{2,286}, John C Chambers^{287,26,27,266}, Maggie CY Ng^{288,109,264}, Xueling Sim⁴⁰, Jennifer E Below²¹, Philip S Tsao^{289,237,290}, Kyong-Mi Chang^{10,291}, Mark I McCarthy^{168,292,293,301}, James B Meigs^{163,164,13}, Anubha Mahajan^{292,168,301}, Cassandra N Spracklen²⁹⁴, Josep M Mercader^{13,14,76}, Michael Boehnke⁹, Jerome I Rotter²⁵, Marijana Vujkovic^{10,291,295}, Benjamin F Voight^{10,11,12,278}, Andrew P Morris^{1,4,22}, Eleftheria Zeggini^{4,296},

1 Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester, UK

2 Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

3 Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan

4 Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

5 Center for Precision Health Research, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

6 British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

7 Heart and Lung Research Institute, University of Cambridge, Cambridge, UK

8 Department of Epidemiology, School of Public Health, Nanjing Medical University, Nanjing City, China

9 Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA

10 Corporal Michael J Crescenz VA Medical Center, Philadelphia, PA, USA

11 Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

12 Department of Genetics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

13 Programs in Metabolism and Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA, USA

14 Diabetes Unit and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA

15 TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

16 William Harvey Research Institute, Barts and the London School of Medicine and Dentistry,

Queen Mary University of London, London, UK

17 Department of Genome Informatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

18 Integrated Frontier Research for Medical Science Division, Institute for Open and Transdisciplinary Research Initiatives, Osaka University, Suita, Japan

19 Laboratory for Systems Genetics, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan

20 The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

21 Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

22 Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia

23 Nuffield Department of Population Health, University of Oxford, Oxford, UK

24 Medical Research Council Population Health Research Unit, University of Oxford, Oxford, UK

25 The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, The Lundquist Institute for Biomedical Innovation (formerly Los Angeles Biomedical Research Institute) at Harbor-UCLA Medical Center, Torrance, CA, USA

26 Department of Epidemiology and Biostatistics, Imperial College London, London, UK

27 Department of Cardiology, Ealing Hospital, London North West Healthcare NHS Trust, Middlesex, UK

28 Division of Genome Science, Department of Precision Medicine, National Institute of Health, Cheongju-si, South Korea

29 Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

30 Department of Gene Diagnostics and Therapeutics, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan

31 Institute of Epidemiology, Helmholtz Zentrum Munchen, German Research Center for Environmental Health, Neuherberg, Germany

32 Department of Medicine, McMaster University, Hamilton, ON, Canada

33 Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada

34 Public Health Informatics Unit, Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan

35 MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge School of Clinical Medicine, Cambridge, UK

36 Department of Health Data Science, University of Liverpool, Liverpool, UK

37 Division of Translational Medicine and Human Genetics, University of Pennsylvania, Philadelphia, PA, USA

38 Department of Epidemiology, Brown University School of Public Health, Providence, RI, USA

39 Department of Anthropology, University of Toronto at Mississauga, Mississauga, ON, Canada

40 Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore

41 Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA

42 Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

43 deCODE Genetics, Amgen Inc., Reykjavik, Iceland

44 Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

45 Department of Biostatistics, Harvard University, Boston, MA, USA

46 Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, MA, USA

47 Department of Medicine, Harvard University, Boston, MA, USA

48 Institute of Genetic Epidemiology, Department of Data Driven Medicine, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany

49 Department of Epidemiology, Human Genetics, and Environmental Sciences, The University of Texas Health Science Center at Houston School of Public Health, Houston, TX, USA

50 German Center for Diabetes Research (DZD), Neuherberg, Germany

- 51 Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
- 52 Department of Population and Public Health Sciences, Keck School of Medicine of USC, Los Angeles, CA, USA
- 53 Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
- 54 Section of Gerontology and Geriatrics, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands
- 55 Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea
- 56 Division of Epidemiology, Department of Medicine, Institute for Medicine and Public Health, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA
- 57 Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK
- 58 Institute for Population and Precision Health (IPPH), Biological Sciences Division, The University of Chicago, Chicago, IL, USA
- 59 Department of Public Health Sciences and Center for Public Health Genomics, University of Virginia School of Medicine, Charlottesville, VA, USA
- 60 Genomic Research on Complex Diseases (GRC-Group), CSIR-Centre for Cellular and Molecular Biology (CSIR-CCMB), Hyderabad, India
- 61 Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China
- 62 Chinese University of Hong Kong-Shanghai Jiao Tong University Joint Research Centre in Diabetes Genomics and Precision Medicine, The Chinese University of Hong Kong, Hong Kong, China
- 63 Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea
- 64 Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
- 65 Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
- 66 Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
- 67 Department of Human Genetics, Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, UK
- 68 Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA
- 69 Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
- 70 Center for Research on Genomics and Global Health, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA
- 71 Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA
- 72 Division of Academics, Ochsner Health, New Orleans, LA, USA
- 73 Division of Statistical Genomics, Washington University School of Medicine, St. Louis, MO, USA
- 74 Department of Research & Evaluation, Division of Biostatistics Research, Kaiser Permanente of Southern California, Pasadena, CA, USA
- 75 Department of Biomedical Science, Hallym University, Chuncheon, South Korea
- 76 Harvard Medical School, Boston, MA, USA
- 77 Metabolic Research Laboratories, Wellcome Trust-Medical Research Council Institute of Metabolic Science, Department of Clinical Biochemistry, University of Cambridge, Cambridge, UK
- 78 Department of Epidemiology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
- 79 Department of Bioinformatics, Isfahan University of Medical Sciences, Isfahan, Iran
- 80 Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA, USA
- 81 Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden
- 82 Department of Nutrition, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
- 83 Unidad de Investigación en Enfermedades Metabólicas and Departamento de Endocrinología y

Metabolismo., Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. , Mexico City, Mexico

84 Steno Diabetes Center Copenhagen, Herlev, Denmark

85 The Bioinformatics Center, Department of Biology, University of Copenhagen, Copenhagen, Denmark

86 Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada

87 Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA

88 Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark

89 Department of Clinical Biochemistry, Vejle Hospital, Vejle, Denmark

90 Department of Medicine, Division of Endocrinology and Diabetes, Keck School of Medicine of USC, Los Angeles, CA, USA

91 Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

92 British Heart Foundation Centre of Research Excellence, School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

93 Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Hinxton, UK

94 National Institute for Health and Care Research (NIHR) Blood and Transplant Unit (BTRU) in Donor Health and Behaviour, Heart and Lung Research Institute, University of Cambridge, Cambridge, UK

95 Inserm U1283, CNRS UMR 8199, European Genomic Institute for Diabetes (EGID), Institut Pasteur de Lille, Lille University Hospital, Lille, France

96 University of Lille, Lille, France

97 Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China

98 Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong, China

99 Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore

100 Exeter Centre of Excellence in Diabetes (ExCEeD), Exeter Medical School, University of Exeter, Exeter, UK

101 Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, UK

102 Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, USA

103 Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

104 Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan

105 Department of Medicine, University of Vermont, Colchester, VT, USA

106 Section on Endocrinology and Metabolism, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA

107 Department of Medicine, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka

108 Department of Nutrition and Dietetics, Harokopio University of Athens, Athens, Greece

109 Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, NC, USA

110 Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

111 Department of Nephrology and Medical Intensive Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany

112 Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

113 Department of Biostatistics, University of Washington, Seattle, WA, USA

114 California Pacific Medical Center Research Institute, San Francisco, CA, USA

115 Laboratory of Epidemiology and Population Sciences, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

116 Institute of Mathematics and Statistics, University of Tartu, Tartu, Estonia

117 Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK

118 Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

119 Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, Exeter, UK

120 Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA

121 Department of Medicine, Division of Endocrinology and Metabolism, Lundquist Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA

122 Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden

123 Centro de Estudios en Diabetes, Unidad de Investigacion en Diabetes y Riesgo Cardiovascular, Centro de Investigacion en Salud Poblacional, Instituto Nacional de Salud Publica, Mexico City, Mexico

124 Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

125 Genomics and Computational Biology Graduate Group, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

126 Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland

127 Folkhalsan Research Center, Helsinki, Finland

128 University of Exeter Medical School, University of Exeter, Exeter, UK

129 Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany

130 Department of Endocrinology and Diabetology, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

131 Laboratory for Genomics of Diabetes and Metabolism, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan

132 Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

133 Department of Internal Medicine, Diabetes and Metabolism Research Center, The Ohio State University Wexner Medical Center, Columbus, OH, USA

134 Center for Global Cardiometabolic Health, Brown University, Providence, RI, USA

135 Shanghai-MOST Key Laboratory of Health and Disease Genomics, Shanghai Institute for Biomedical and Pharmaceutical Technologies, Shanghai, China

136 Division of Endocrine and Metabolism, Tri-Service General Hospital Songshan Branch, Taipei, Taiwan

137 School of Medicine, National Defense Medical Center, Taipei, Taiwan

138 Division of Genome Science, Department of Precision Medicine, National Institute of Health, Cheongju-si, Korea

139 Section of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

140 School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

141 Department of Environmental and Preventive Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan

142 University of Chicago Research Bangladesh, Dhaka, Bangladesh

143 Institute of Molecular and Clinical Ophthalmology Basel, Basel, Switzerland

144 Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark

145 Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

146 Faculty of Medicine, Aalborg University, Aalborg, Denmark

147 Department of Clinical Diabetes, Endocrinology and Metabolism, Department of Translational Research and Cellular Therapeutics, City of Hope, Duarte, CA, USA

148 Department of Public Health, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka

149 Department of Clinical Gene Therapy, Osaka University Graduate School of Medicine, Osaka, Japan

150 Department of Geriatric and General Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan

151 Division of General Internal Medicine and Geriatrics, Department of Medicine, Northwestern

University Feinberg School of Medicine, Chicago, IL, USA

152 Center for Health Information Partnerships, Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

153 Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore, Singapore

154 Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Suwon, South Korea

155 Institute of Genetic Epidemiology, Medical University of Innsbruck, Innsbruck, Austria

156 Institute of Clinical Medicine, Internal Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland

157 Department of Medicine, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA

158 VA Salt Lake City Health Care System, Salt Lake City, UT, USA

159 Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

160 Soochunhyang Institute of Medi-bio Science and Division of Endocrinology, Department of Internal Medicine, Soochunhyang University College of Medicine, Cheonan, South Korea

161 Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

162 USC-Office of Population Studies Foundation Inc., University of San Carlos, Cebu City, Philippines

163 Department of Medicine, Harvard Medical School, Boston, MA, USA

164 Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA, USA

165 Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China

166 Peking University Center for Public Health and Epidemic Preparedness and Response, Beijing, China

167 Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

168 Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK

169 Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA

170 Big Data Institute, Li Ka Shing Centre For Health Information and Discovery, University of Oxford, Oxford, UK

171 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

172 Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

173 Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore, Singapore

174 McDonnell Genome Institute, Washington University School of Medicine, St. Louis, MO, USA

175 Department of Medicine, Division of Genomics and Bioinformatics, Washington University School of Medicine, St. Louis, MO, USA

176 Department of Biostatistics and Data Science, The University of Texas Health Science Center at Houston School of Public Health, Houston, TX, USA

177 Department of Clinical Sciences, Diabetes and Endocrinology, Lund University Diabetes Centre, Malmö, Sweden

178 Department of Clinical Science, Center for Diabetes Research, University of Bergen, Bergen, Norway

179 Department of Advanced Genomic and Laboratory Medicine, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

180 Division of Clinical Laboratory and Blood Transfusion, University of the Ryukyus Hospital, Okinawa, Japan

181 Dromokaiteio Psychiatric Hospital, National and Kapodistrian University of Athens, Athens, Greece

182 Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The

University of Tokyo, Tokyo, Japan

183 Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

184 Institute of Human Genetics, Technical University Munich, Munich, Germany

185 German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany

186 The Usher Institute to the Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

187 Department of Medicine and Pharmacology, New York Medical College, Valhalla, NY, USA

188 Data Tecnica International LLC, Glen Echo, MD, USA

189 Center for Alzheimer's and Related Dementias, National Institutes of Health, Bethesda, MD, USA

190 Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan

191 Premium Research Institute for Human Metaverse Medicine (WPI-PRIME), Osaka University, Suita, Japan

192 Instituto Nacional de Medicina Genómica, Mexico City, Mexico

193 Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

194 Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA

195 Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Munich, Germany

196 Department of Diabetes and Endocrinology, Nelson R Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

197 Academy of Scientific and Innovative Research, CSIR-Human Resource Development Campus, Ghaziabad, India

198 Genomics and Molecular Medicine Unit, CSIR-Institute of Genomics and Integrative Biology, New Delhi, India

199 Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

200 Fred Hutchinson Cancer Research Center, Seattle, WA, USA

201 Ophthalmology and Visual Sciences Academic Clinical Program (Eye ACP), Duke-NUS Medical School, Singapore, Singapore

202 Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore, Singapore

203 School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK

204 Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, USA

205 Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

206 Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center, Johannes Gutenberg University, Mainz, Germany

207 Chair of Genetic Epidemiology, Institute of Medical Information Processing, Biometry, and Epidemiology, Faculty of Medicine, Ludwig-Maximilians-Universität München, Munich, Germany

208 Faculty of Medicine, University of Iceland, Reykjavik, Iceland

209 Faculty of Medicine, Macau University of Science and Technology, Macau, China

210 Department of Medical Genetics and Medical Research, China Medical University Hospital, Taichung, Taiwan

211 Population Health Unit, Finnish Institute for Health and Welfare, Helsinki, Finland, Finnish Institute for Health and Welfare, Helsinki, Finland

212 National School of Public Health, Madrid, Spain

213 Department of Public Health, University of Helsinki, Helsinki, Finland

214 Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

215 Unidad de Biología Molecular y Medicina Genómica, Instituto Nacional de Ciencias Médicas y

Nutrición Salvador Zubirán, Mexico City, Mexico

216 Departamento de Medicina Genómica y Toxiología Ambiental, Instituto de Investigaciones Biomédicas, UNAM, Mexico City, Mexico

217 Unidad de Investigación Médica en Bioquímica, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico

218 Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands

219 Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands

220 Department of Clinical Chemistry, Laboratory of Genetic Metabolic Disease, Amsterdam University Medical Center, Amsterdam, The Netherlands

221 Southern California Eye Institute, CHA Hollywood Presbyterian Hospital, Los Angeles, CA, USA

222 Unidad de Investigación Médica en Epidemiología Clínica, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico

223 Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden, The Netherlands

224 Department of Public Health, Aarhus University, Aarhus, Denmark

225 Danish Diabetes Academy, Odense, Denmark

226 Diabetology Research Centre, King Edward Memorial Hospital and Research Centre, Pune, India

227 Department of Medical Biochemistry, Kurume University School of Medicine, Kurume, Japan

228 Department of Pediatrics, Osaka University Graduate School of Medicine, Suita, Japan

229 Division of Cancer Control and Population Sciences, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA

230 Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

231 Department of Pediatrics, Division of Genetic and Genomic Medicine, UCI Irvine School of Medicine, Irvine, CA, USA

232 Department of Anti-Aging Medicine, Ehime University Graduate School of Medicine, Toon, Japan

233 Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

234 Department of Medical Sciences, Uppsala University, Uppsala, Sweden

235 Institute of Molecular Medicine, The University of Texas Health Science Center at Houston School of Public Health, Houston, TX, USA

236 Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, US

237 Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA

238 Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden

239 Department of Epidemiology, University of Washington, Seattle, WA, USA

240 Department of Health Systems and Population Health, University of Washington, Seattle, WA, USA

241 Beijing Institute of Ophthalmology, Ophthalmology and Visual Sciences Key Laboratory, Beijing Tongren Hospital, Capital Medical University, Beijing, China

242 Department of Medicine, Division of Cardiology, Duke University School of Medicine, Durham, NC, USA

243 Kurume University School of Medicine, Kurume, Japan

244 Department of Medicine, McGill University, Montreal, QC, Canada

245 Department of Human Genetics, McGill University, Montreal, QC, Canada

246 Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK

247 Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

248 Division of Endocrinology and Metabolism, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

249 Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

250 Center for Genetic Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

251 Department of Anthropology, Northwestern University, Evanston, IL, USA

252 Department of Endocrinology, Helsinki University Hospital, Helsinki, Finland

253 Systems Genomics Laboratory, School of Biotechnology, Jawaharlal Nehru University, New Delhi, India

254 Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada

255 Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, South Korea

256 Netherlands Heart Institute, Utrecht, The Netherlands

257 Center for Public Health Genomics, University of Virginia School of Medicine, Charlottesville, VA, USA

258 Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany

259 Duke-NUS Medical School, Singapore, Singapore

260 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada

261 Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A*STAR), Singapore, Singapore

262 Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

263 Center for Diabetes Research, Wake Forest School of Medicine, Winston-Salem, NC, USA

264 Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, NC, USA

265 Pat Macpherson Centre for Pharmacogenetics and Pharmacogenomics, University of Dundee, Dundee, UK

266 Imperial College Healthcare NHS Trust, Imperial College London, London, UK

267 MRC-PHE Centre for Environment and Health, Imperial College London, London, UK

268 National Heart and Lung Institute, Imperial College London, London, UK

269 Department of Medicine, Brown University Alpert School of Medicine, Providence, RI, USA

270 Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA

271 Department of Cardiology, Columbia University Irving Medical Center, New York, NY, USA

272 Center for Non-Communicable Diseases, Karachi, Pakistan

273 Computational Medicine, Berlin Institute of Health at Charité–Universitätsmedizin, Berlin, Germany

274 Precision Healthcare University Research Institute, Queen Mary University of London, London, UK

275 Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, CA, USA

276 The Mindich Child Health and Development Institute, Ichan School of Medicine at Mount Sinai, New York, NY, USA

277 Division of Translational Medicine and Therapeutics, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

278 Institute for Translational Medicine and Therapeutics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

279 Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

280 Center for Precision Medicine, University of Pennsylvania - Perelman School of Medicine, Philadelphia, PA, USA

281 Institute for Biomedical Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

282 Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

283 Blizard Institute, Queen Mary University of London, London, UK

284 Institute for Population Health Sciences, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

285 All of Us Research Program, National Institutes of Health, Bethesda, MD, USA

286 Toranomon Hospital, Tokyo, Japan

287 Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore
288 Vanderbilt Genetics Institute, Division of Genetic Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
289 VA Palo Alto Health Care System, Palo Alto, CA, USA
290 Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA, USA
291 Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
292 Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
293 Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
294 Department of Biostatistics and Epidemiology, University of Massachusetts Amherst, Amherst, MA, USA
295 Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
296 TUM School of Medicine and Health, Technical University of Munich and Klinikum Rechts der Isar, Munich, Germany
297 Graduate School of Experimental Medicine, Technical University of Munich, Munich, Germany
298 Munich School for Data Science, Helmholtz Munich, Neuherberg, Germany
299 Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, India
300 Science and Engineering Research Board (SERB), Department of Science and Technology, Ministry of Science and Technology, Government of India, New Delhi, India

Present Address:

301 Genentech, South San Francisco, CA, USA
302 Regeneron Genetics Center, Tarrytown, NY, USA