Supplementary Figure 1

Sex-differentiated analyses.

a) Manhattan plot (top panel) of genome-wide association results for T2D (without BMI adjustment) from female-specific meta-analysis of up to 30,053 cases and 434,336 controls. The association p-value (on -log₁₀ scale) for each SNP (y-axis) is plotted against the genomic position (NCBI Build 37; x-axis). Association signals that reached genome-wide significance (p<5x10⁻⁸) in sex-combined analysis are shown in purple or yellow, if novel. b) Manhattan plot (bottom panel) of genome-wide association results for T2D without BMI adjustment from male-specific meta-analysis of up to 41,846 cases and 383,767 controls. c) Z-score for each of the 403 distinct signals from male-specific analysis (y-axis) is plotted against the z-score from the female-specific analysis (y-axis). Colour of each point varies with -log₁₀ gender heterogeneity p-value and diameter of the circle is proportional to sex-combined -log₁₀ p-value.
**Supplementary Figure 2**

**Distributions of the allele frequency, imputation score, and posterior probability of association.**

Distribution of the risk allele frequencies for all variants having >1% posterior probability of association in genetic credible set (x-axis) plotted against average imputation quality (y-axis). Diameter varies with the posterior probability of association assigned to each variant.
Supplementary Figure 3

Islet annotation overlap of variant with the highest probability in genetic credible sets.

Number of variants with posterior probability of association >1% (x-axis) plotted against the highest posterior probability of association (y-axis) assigned to a variant in the credible set. Points are colour coded according to a) islet epigenome states and b) overlap with transcription factor binding sites.
Supplementary Figure 4

Enrichment of cross-tissue epigenetic states in T2D GWAS data.

fGWAS log₂ fold enrichment (based on joint model for each tissue) including 95% confidence intervals (x-axis) of all chromatin states (y-axis) genome-wide. Analyses are based on the Varshney et al.¹ data which combined standard epigenomic annotations for the four principal tissues of interest. These analyses performed separately for each tissue show some enrichment for enhancers and/or promoters in all tissues with strongest and most consistent enrichment observed in islets. The universally enriched “transcript” category refers to coding sequence which is by definition represented by the same sequence in each “tissue-specific” analysis. ¹Varshney, A. et al. Genetic regulatory signatures underlying islet gene expression and type 2 diabetes. Proc Natl Acad Sci U S A 114, 2301-2306 (2017).
Supplementary Figure 5

Enrichment of islet epigenetic states in T2D GWAS data.

GWAS log2 fold enrichment including 95% confidence intervals (x-axis) of all chromatin states (y-axis) genome-wide.
Supplementary Figure 6

Epigenome landscape of ST6GAL1 locus.

For variants included in 99% credible set (PPA>1%) of each distinct signal at ST6GAL1 locus, following information is shown: genomic position of each variant (colour coded for each distinct signal; variant with highest PPA in bold); whole genome bisulphite methylation data (black), 4 human islet ATAC-seq tracks (green, middle), islet chromatin states (from Thurner et al.\textsuperscript{1}, Pasquali et al.\textsuperscript{2}, and Varshney et al.\textsuperscript{3}); and adipose, liver and skeletal muscle chromatin states from Varshney et al.\textsuperscript{3}.

Supplementary Figure 7

Epigenome landscape of ANK1 locus.

For variants included in 99% credible set (PPA>1%) of each distinct signal at ANK1 locus, following information is shown: genomic position of each variant (colour coded for each distinct signal; variant with highest PPA in bold); whole genome bisulphite methylation data (black), 4 human islet ATAC-seq tracks (green, middle), islet chromatin states (from Thurner et al.\(^1\), Pasquali et al.\(^2\), and Varshney et al.\(^3\)); and adipose, liver and skeletal muscle chromatin states from Varshney et al.\(^3\).

Supplementary Figure 8

Epigenome landscape of TCF7L2 locus.

For variants included in 99% credible set (PPA>1%) of each distinct signal at TCF7L2 locus, following information is shown: genomic position of each variant (colour coded for each distinct signal; variant with highest PPA in bold); whole genome bisulphite methylation data (black), 4 human islet ATAC-seq tracks (green, middle), islet chromatin states (from Thurner et al\textsuperscript{1}, Pasquali et al\textsuperscript{2}, and Varshney et al\textsuperscript{3}); and adipose, liver and skeletal muscle chromatin states from Varshney et al\textsuperscript{3}.

\textsuperscript{1} Thurner, M. et al. Integration of human pancreatic islet genomic data refines regulatory mechanisms at Type 2 Diabetes susceptibility loci. \textit{Elife} 7(2018).
Heritability estimates.

Chip heritability estimates for T2D (on the liability scale) at different empirical estimates of population- and sample-level T2D prevalence.
Supplementary Figure 10

Polygenic risk score.

Genome-wide polygenic risk score (PRS) identifies individuals with significantly increased risk of T2D. a) PRS in UK Biobank individuals is normally distributed with a shift towards right, observed for T2D cases. PRS is plotted on the x-axis, with values scaled to a mean of 0 and standard deviation of 1. b) Individuals were binned into 40 groups based on PRS, with each grouping representing 2.5% of population. c) BMI distribution in T2D cases, within each PRS bin.
Genetic correlations between T2D and biomedical-relevant traits estimated by LD score regression implemented in LDHub.

Genetic correlations (z-score) between T2D (y-axis) and range of metabolic and anthropometric traits (x-axis) as estimated using LD Score regression. The genetic correlation estimates are colour coded according to phenotypic area. Allelic direction of effect is aligned to increased T2D risk. Size of the circle denotes the significance level for the correlation.
Impact of BMI adjustment on genetic correlation estimates between various traits and T2D.

Genetic correlations (z-score) between range of metabolic and anthropometric traits and T2D without BMI adjustment (x-axis) and T2D with BMI adjustment (y-axis) as estimated using LD Score regression. The genetic correlation estimates are colour coded according to phenotypic area. Allelic direction of effect is aligned to increased T2D risk. Size of the circle denotes the significance level for the correlation.