

Description of Additional Supplementary Files

File Name: Supplementary Data 1

Description: Sites with differential DNA methylation between pancreatic islets from cases with type 2 diabetes ($n=25$) and non-diabetic controls ($n=75$) ($q<0.05$).

File Name: Supplementary Data 2

Description: KEGG pathway analysis based on genome-wide DNA methylation data for human islets from T2D cases ($n=25$) and non-diabetic controls ($n=75$). Associations with T2D based on FDR-adjusted p -value < 0.05 .

File Name: Supplementary Data 3

Description: Sites with an association between HbA1c and DNA methylation in human pancreatic islets from 114 donors not previously diagnosed with T2D (the Islet HbA1c cohort, $q<0.05$).

File Name: Supplementary Data 4

Description: Sites with both differential DNA methylation between human pancreatic islets from T2D cases ($n=25$) and non-diabetic controls ($n=75$, $q<0.05$) and an association between HbA1c and DNA methylation in human pancreatic islets from 114 donors not previously diagnosed with T2D (The Islet HbA1c cohort, $q<0.05$).

File Name: Supplementary Data 5

Description: KEGG pathway analysis based on genome-wide DNA methylation data for human islets from 114 donors not previously diagnosed with T2D (the Islet HbA1c cohort). Associations with HbA1c were based on FDR-adjusted p -value < 0.05 .

File Name: Supplementary Data 6

Description: Clinical characteristics of the 83 donors of pancreatic islets used for pyrosequencing replication.

File Name: Supplementary Data 7

Description: Sites with differential DNA methylation between pancreatic islets from T2D cases ($n=25$) and controls ($n=75$) in the present study that were also identified using the previous 450k array in human islets from 15 T2D cases and 34 control donors⁴ (Sheet A). Sites with differential DNA methylation between human pancreatic islets from T2D cases ($n=25$) and controls ($n=75$) in previously identified differentially methylated regions (DMRs) between islets from six T2D cases and eight controls⁶ (Sheet B). Sites with an association ($q<0.05$) between HbA1c and DNA methylation in human pancreatic islets from donors not previously diagnosed with T2D (Islet HbA1c cohort, $n=114$) and also identified in differentially methylated regions (DMRs) between islets from six T2D cases and eight control donors⁶ (Sheet C).

File Name: Supplementary Data 8

Description: Sites with differential DNA methylation between pancreatic islets from T2D cases ($n=25$) and non-diabetic controls ($n=75$) in islet open chromatin regions as reported by Bysani et al.¹⁶.

File Name: Supplementary Data 9

Description: Sites with differential DNA methylation between human pancreatic islets from T2D cases ($n=25$) and non-diabetic controls ($n=75$) within 10 kb of genes that are also differentially expressed based on RNA-seq data for 97 samples from the Islet T2D case-control cohort ($q<0.05$).

File Name: Supplementary Data 10

Description: Weighted combined methylation risk score (MRS) for each gene with altered expression and more than five differentially methylated CpG sites within or near (± 10 kb) that gene in the Islet T2D case-control cohort.

File Name: Supplementary Data 11

Description: Sites with differential DNA methylation between human pancreatic islets from T2D cases ($n=25$) and controls ($n=75$) in regions bound by islet-specific transcription factors²⁴.

File Name: Supplementary Data 12

Description: Sites with differential DNA methylation between human pancreatic islets from T2D cases ($n=25$) and controls ($n=75$) within islet regulatory elements²⁶.

File Name: Supplementary Data 13

Description: Characteristics of participants in the prospective matched case-control study of EPIC-Potsdam.

File Name: Supplementary Data 14

Description: Overlap of T2D-associated genes and specific CpG sites from previously conducted prospective or incident T2D studies in blood and differential methylation in the present ***Islet T2D case-control cohort***.

File Name: Supplementary Data 15

Description: Differential gene expression in human islets from non-diabetic donors after silencing by siRNA for *CABLES1*, *FOXP1*, *RHOT1*, or *TBC1D4* (five experiments in $n=5$ different donors per group).

File Name: Supplementary Data 16

Description: Transcription factor binding sites in positions -1000 to 0 of *RHOT1*³⁹ in regions defined as promoters in human islets based on ATAC-Seq and histone modifications²⁶, and overlap with differentially expressed genes after silencing of *FOXP1*, *CABLES1* or *TBC1D4*.

File Name: Supplementary Data 17

Description: Metabolomics of INS-1 β -cells transfected with siRhot1 or siNC (nontemplate control).