**Additional Supplementary Methods**

**Donor Clinical information**. Pancreatic tissue and isolated islets from a 33-year-old Caucasian male (BMI 25.8 kg/$m^2$) diagnosed with type 1 diabetes (T1D) at age 16 were procured in collaboration with the Institute for the Advancement of Medicine (IIAM) during organ donation post head trauma secondary to a motorcycle accident. Based on the redacted medical record, the individual's diabetes was treated with insulin (A1C of 8.9%) and described as poorly controlled; he was reported to experience "tingling in feet and hands." He had concurrent hypertension diagnosed at age 16, a kidney infection at age 20, and a family history of diabetes (mother, maternal aunt, cousins, and grandmother). During the terminal hospital admission of four days, the donor was in the intensive care unit on respiratory support and treated with corticosteroids, antibiotics, and vasopressors. His blood glucose ranged from 105-582 mg/dL and he was treated with intravenous insulin. Renal (Cr 1.07 mg/dL) and hepatic (AST 26 u/L, ALT 24 u/L, ALP 53 u/L) function were normal. He was pronounced brain dead and organs were procured for transplantation. Blood samples collected at the time of organ donation showed the donor carried high-risk HLA haplotypes for T1D (HLA Class II DR4, DQA1 03; DR4-DQ8), had detectable C-peptide (0.4 ng/mL), and was negative for T1D-associated autoantibodies (GAD65, mIAA, ZnT8, ICA512).

**Human Pancreatic Islet Procurement**. Pancreata and islets from normal donors and the case donor were obtained through a partnership with the International Institute for Advancement of Medicine (IIAM), National Disease Research Interchange (NDRI),

Integrated Islet Distribution Program (IIDP), and Network for Pancreatic Organ Donors with Diabetes (nPOD). For most donors, including the one outlined in this report, islets and tissue specimens were procured from the same organ as described (1). Human islets and tissue obtained for all studies are described in **Table S1**. For the reported donor, the pancreas had normal weight (75.4 g), unusual for 17 years of T1D as observed by our group (adult (≥18yrs of age) control: 84.2±4.6g, n=20 versus adult with ≥10yrs duration T1D: 45.6±2.7g, n=20; ****, $p<0.0001$ two-tailed Student's *t*-test) and others (2, 3), and the islet-enriched digestion fraction contained 54,200 islet equivalents (IEQs) with 70% purity. The Vanderbilt University Institutional Review Board declared studies on de-identified human pancreatic specimens does not qualify as human subject research. Donor information was provided by IIDP for islets accepted from this organization. A redacted medical record was provided for the de-identified case received in collaboration with IIAM (**Table S1**).

**DNA sequencing**. DNA was extracted from snap-frozen donor tissue using Wizard Genomic DNA purification kit (Promega, A1120) and the sample was sequenced using a custom designed next-generation sequencing (NGS) targeted panel that includes 148 genes implicated in monogenic forms of diabetes (neonatal diabetes and MODY), insulin resistance, lipodystrophy, obesity, rare syndromic forms of diabetes, and diabetes candidate genes (4). All variants were interpreted according to the guidelines of the American College of Medical Genetics. The pathogenic variant identified by NGS in this donor was classified as described (5) and was confirmed by Sanger sequencing. All sequencing results for the case donor are listed in **Table S2**.

**Immunohistochemical Analysis.** Immunohistochemical analysis of the pancreas was performed on serial 5 μm cryosections from multiple blocks from head, body and tail regions as described (6). Primary antibodies to all antigens and their concentrations are listed in **Table S3** and were visualized using the appropriate secondary antibodies listed in **Table S4**. Digital images were acquired with a Zeiss LSM510 META laser scanning confocal microscope (Carl Zeiss) or Fluorescent ScanScope (Aperio). Apoptosis was assessed by TUNEL stain (Millipore, S1675).

**Assessment of pancreatic islet function *in vitro.*** Function of islets from this donor and normal controls (**Table S1**) were studied in a dynamic cell perifusion system at a perifusate flow rate of 1 mL/min (7). The effluent was collected at 3-minute intervals using an automatic fraction collector. Insulin and glucagon concentrations in each perifusion fraction and islet extracts were measured by radioimmunoassay (insulin, RI-13K, Millipore; glucagon, GL-32K, Millipore). Area under the curve (AUC) above baseline hormone release was calculated with the trapezoidal method by GraphPad Prism 7.0.

**β and α cell sorting by flow cytometry for RNA-sequencing.** As described previously (1), human islets were dispersed using 0.025% trypsin and sorted for α and β cells using primary and secondary antibodies characterized previously by our group and others and used to isolate high-quality RNA from islet cells (8, 9) (**Tables S3** and **S4**). Appropriate single color compensation controls were run alongside samples. Prior to sorting, propidium iodide (0.05 ug/100,000 cells; BD Biosciences) was added to

samples for non-viable cell exclusion. Flow analysis was performed using an LSRFortessa cell analyzer (BD Biosciences), and a FACSAria III cell sorter (BD Biosciences) was used for FACS. Analysis of flow cytometry data was completed using FlowJo 10.1.5 (Tree Star).

**RNA-Sequencing.** Sorted α and β cells (5,000-125,000) were added to 200 µL lysis/binding solution in the RNAqueous micro-scale phenol-free total RNA isolation kit (Ambion) as previously described (1). RNA integrity was evaluated (Agilent 2100 Bioanalyzer – control α cells: 8.36±0.22 RIN, and *HNF1A*$^{+/T260M}$ α cells: RIN 8.3; control β cells: RIN 7.86±0.67, and *HNF1A*$^{+/T260M}$ β cells: RIN 7.40) and high-integrity total RNA was amplified (Ovation system; NuGen Technologies) per standard protocol as described previously (6). Amplified cDNA was sheared to target 200bp fragment size and libraries were prepared using NEBNext DNA Library Prep (New England BioLabs). 50bp Paired End (PE) sequencing was performed on an Illumina HiSeq 2500 using traditional Illumina methods (10) to generate approximately 50 million reads per sample. Raw reads were mapped to the reference human genome hg19 using TopHat v2.1 (11). Aligned reads were then imported onto the Avadis NGS analysis platform (Strand life Sciences) and filtered based on read quality followed by read statistics to remove duplicates. Transcript abundance was quantified using the TMM (Trimmed Mean of M-values) algorithm (12, 13) as the normalization method.

**Cell lines**. A non-islet cell line, HeLa, and pancreatic islet cell line, MIN6, were cultured in a monolayer under conditions described previously (14).

**Site Directed Mutagenesis.** Point mutation of HNF1α-T260M expressing plasmid was generated by QuickChange II Site-Directed Mutagenesis Kit (Agilent) based on a Myc-tagged human HNF1α expressing plasmid (Addgene, FR_HNF1A).

**Electrophoretic Mobility Shift Assay (EMSA) and Western Blot.** HeLa or MIN6 cells were transfected with either wildtype (WT) or mutant (T260M) Myc-tagged HNF1α plasmid. Forty-eight hours post transfection, nuclear extract preparation and DNA binding reactions were performed as described (15). Briefly, 10μg of nuclear extract and 400fmol (150000-200000cpm) of $^{32}$P labeled double strand DNA probe (WT Oligo: 5'-TCGACTTGGTTAATAATTCACCAGAG-3') were mixed with a 20μl reaction system containing 10 mM HEPES (pH 7.9), 10% glycerol, 120 mM NaCl, 2 mM DTT, 1 mM of EDTA and 0.8μg of poly(dI-dC). The nuclear extract was pre-incubated in buffer for 20 min on ice with antibody as appropriate then the $^{32}$P labeled DNA probe was added and incubated for an additional 20 min on ice. The un-labeled DNA oligo competitors were added together with the probe at 20-fold molar excess (Comp Oligo: 5'-TCGACTTGCGGACGACGGCACCAGAG-3'). EMSA reactions were separated on 5% or 6% native acrylamide gels in 0.5% Tris borate-EDTA buffer (TBE) at 200 V for 1.5 h. The protein:DNA complexes were visualized by autoradiography. Western blot analysis was performed as described (16). Primary antibodies used in EMSA and western blots are listed in **Table S3**.

**Luciferase Reporter Assays.** HeLa cells were co-transfected with the WT or site mutant (*MAFA* R3 M2G$^{-7816}$) of the mouse *MAFA* Region 3 (R3) enhancer driven pFox-Prl-Firefly Luciferase plasmid (15), the phRL-TK Renilla luciferase internal control plasmid, and CMV-driven HNF1A$^{WT}$ and/or HNF1A$^{T260M}$ expression plasmids. Transcriptional activity was evaluated 48-hrs after transfection using a dual-luciferase assay according to the manufacturer's protocol (Promega). Each transfection was repeated at least three times. Firefly luciferase measurements were normalized to the Renilla internal control (phRL-TK). HNF1A$^{WT}$ and HNF1A$^{T260M}$ were produced at similar levels (**Figure S2G**).

**Quantification of nuclear protein expression.** Protein expression of nuclear factors in α and β cells was quantified using MetaMorph 7.1 imaging software (Molecular Devices) using manual cell counting (1) where an average of 216.25±99 α cells and 763±140 β cells were counted per normal donor (n=7 donors, **Table S1**) for each transcription factor, and 382 α cells and an average of 1169±318 β cells were counted for the *HNF1A$^{+/T260M}$* (n=1 donor) for each transcription factor.

**Quantification of islet cell mass.** To quantify endocrine cell area, 1-2 entire pancreatic sections from four blocks of the head, body, and tail regions of the donor pancreas and normal controls (n=7 donors, **Table S1**) were imaged using a Fluorescent ScanScope (Aperio). The ratio of hormone-positive cells for each hormone (insulin, glucagon, or somatostatin) over the total number of cells discovered by DAPI nuclear stain was

measured using imaging software Cytonuclear v3 algorithm (Indica Labs) and represented the fraction of total pancreatic parenchyma for each hormone (i.e. hormone-positive area). Donor islet density and size did not differ from controls. Cells calculated as double-positive for hormone were excluded in this analysis. Endocrine cell mass was determined as a product of the fraction of hormone-positive area and the measured pancreas weight taken before islet isolation (1g weight = 1cm$^3$ volume).

**Structural Analysis.** The X-ray structure of human HNF1A protein (PDB ID-1IC8) was retrieved from the PDB database (https://www.rcsb.org/). PyMOL Molecular Graphics System (Schrodinger, LLC; https://sourceforge.net/projects/pymol/) was used to visualize the DNA-protein complex to analyze interactions between the WT protein, mutant protein (T260M), and DNA.

**RNA-sequencing Analysis.** Genes with normalized expression values less than 25 were removed prior to differential expression analysis between controls and *HNF1A*$^{+/T260M}$ α or β cells. Fold change (cutoff ≥ ±1.5) was calculated based on p-value estimated by z-score calculations (cutoff 0.05) as determined by Benjamini Hochberg false discovery rate (FDR) correction of 0.05. Differentially expressed genes were further analyzed through Ingenuity Pathway Analysis (IPA, Qiagen) and Gene Ontology (GO) analysis using DAVID v6.8 (17).

**Statistics.** Values are shown as mean ± standard error of the mean (SEM) for control samples. Data from a sample size of n=1 for the *HNF1A*$^{+/T260M}$ donor precluded formal

statistical analysis. Two-tailed Student's t test was used for analysis of statistical significance for two-group comparison between controls and long-standing T1Ds when assessing pancreatic weight. A p-value less than 0.05 was considered significant.

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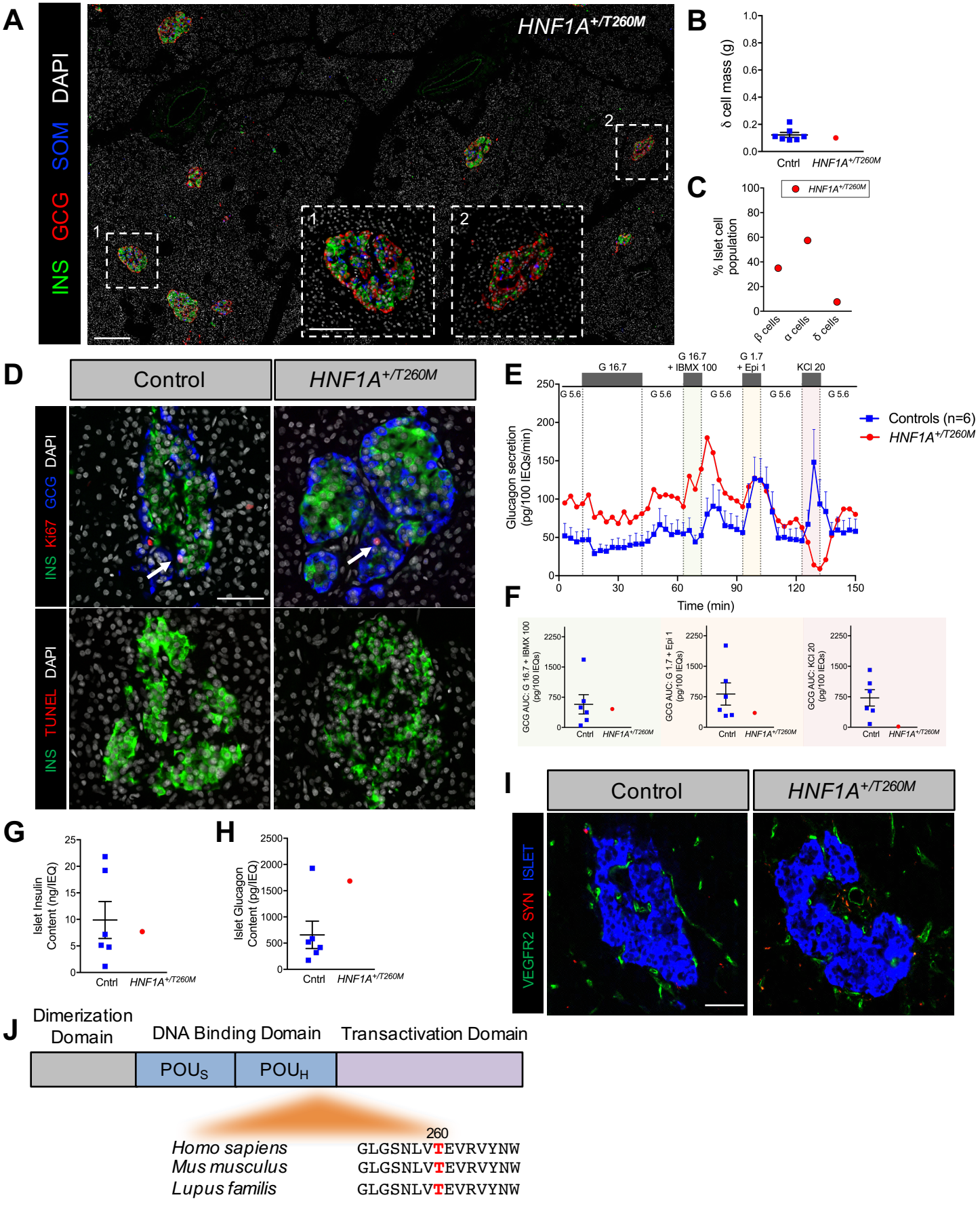

A
INS GCG SOM DAPI
HNF1A+/T260M
1
2
B
δ cell mass (g)
Cntrl
HNF1A+/T260M
C
% Islet cell population
β cells
α cells
δ cells
D
Control
HNF1A+/T260M
INS Ki67 GCG DAPI
INS TUNEL DAPI
E
G 16.7
G 16.7 + IBMX 100
G 1.7 + Epi 1
KCl 20
G 5.6
Glucagon secretion (pg/100 IEQs/min)
Time (min)
Controls (n=6)
HNF1A+/T260M
F
GCG AUC: G 16.7 + IBMX 100 (pg/100 IEQs)
GCG AUC: G 1.7 + Epi 1 (pg/100 IEQs)
GCG AUC: KCl 20 (pg/100 IEQs)
G
Islet Insulin Content (ng/IEQ)
H
Islet Glucagon Content (pg/IEQ)
I
Control
HNF1A+/T260M
VEGFR2 SYN ISLET
J
Dimerization Domain
DNA Binding Domain
Transactivation Domain
POUS
POUH
260
Homo sapiens GLGSNLVTEVRVYNW
Mus musculus GLGSNLVTEVRVYNW
Lupus familis GLGSNLVTEVRVYNW

**Figure S1. Immunohistochemical and functional analysis of *HNF1A*$^{+/T260M}$ pancreas.** (**A**) Pancreatic tissue section of *HNF1A*$^{+/T260M}$ donor stained for insulin (INS), glucagon (GCG), and somatostatin (SOM) and counterstained with nuclear marker DAPI. All islets identified in this donor were insulin+. Scale bar is 250 μm. Boxed and numbered islets represent islet heterogeneity. Magnified images of each islet in insets show islet #1 has more insulin-positive cells than islet #2. Scale bar for insets is 100 μm. (**B**) δ cell mass was calculated as described in **Figure 1**. (**C**) Endocrine cell populations in dispersed isolated islets from *HNF1A*$^{+/T260M}$ donor contained 34.9% β cells, 57.4% α cells, and 7.6% δ cells. Normal control islets collected by this method had a range of 53.4±2.6% β cells, 38.5±2.7% α cells, and 7.5±0.9% δ cells (18). (**D**) The native pancreatic tissue from *HNF1A*$^{+/T260M}$ donor was assessed for proliferative marker Ki67 and apoptotic signal TUNEL. Scale bar is 50 μm. Arrow depicts Ki67+ islet cells. (**E**) The same islets shown in **Figure 1C** were simultaneously analyzed for glucagon secretion and normalized to overall islet cell volume (expressed as islet equivalents, IEQs). As in **Figure 1**, **F** depicts integrated glucagon release as area under the curve from basal glucagon release for indicated secretagogues (corresponding to shaded color-matched regions of perifusion trace). Insulin (**G**) and glucagon (**H**) content in control and *HNF1A*$^{+/T260M}$ islets were in the range of normal. (**I**) Normal innervation (synapsin) and vasculature (VEGFR2) were observed in islets (detected by insulin and glucagon) in donor. SYN – synapsin. Scale bar is 50 μm. (**J**) HNF1A protein domain architecture and conservation of the T260 residue across species. Results of the control samples are expressed as mean ± standard error of the mean.

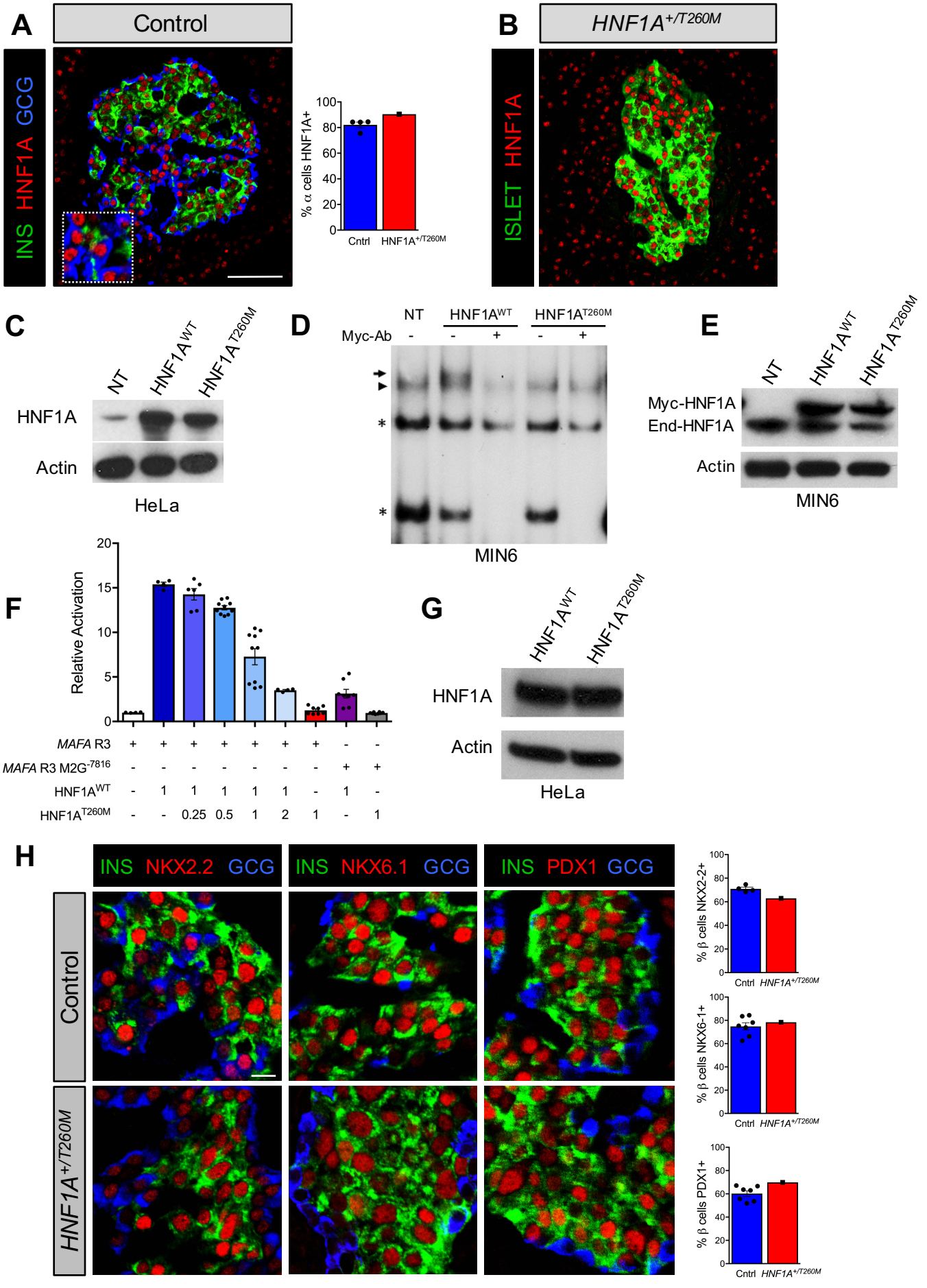
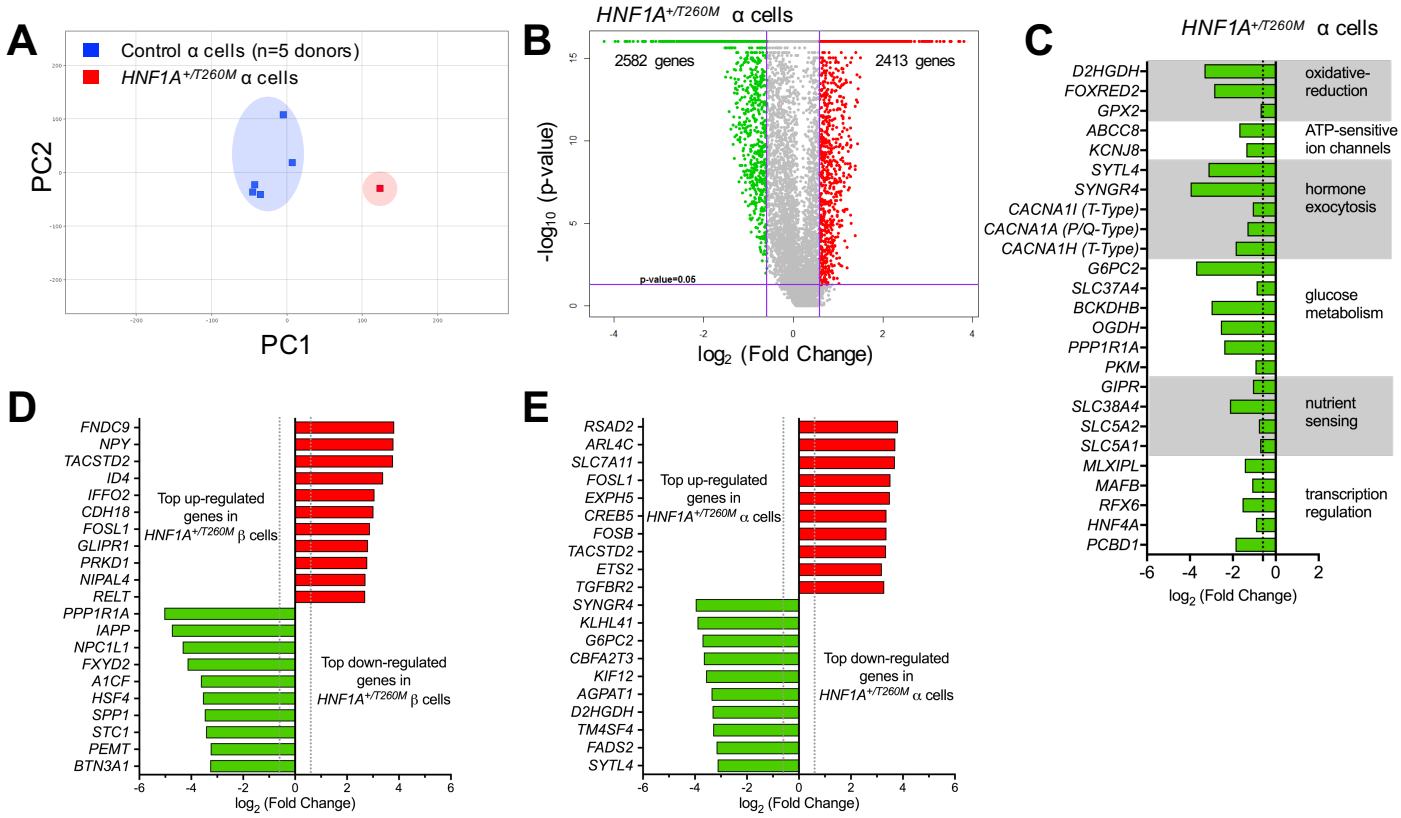
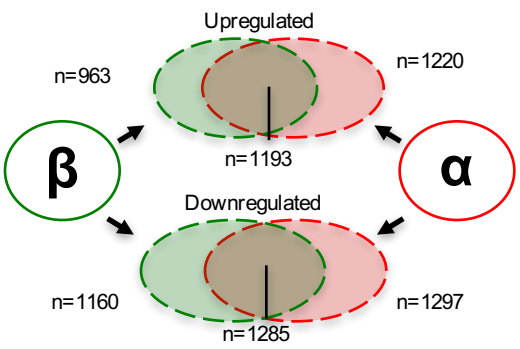

A
Control
INS HNF1A GCG
% α cells HNF1A+
100
80
60
40
20
0
Cntrl
HNF1A+/T260M
B
HNF1A+/T260M
ISLET HNF1A
C
NT
HNF1AWT
HNF1AT260M
HNF1A
Actin
HeLa
D
NT
HNF1AWT
HNF1AT260M
Myc-Ab
-
-
+
-
+
*
*
MIN6
E
NT
HNF1AWT
HNF1AT260M
Myc-HNF1A
End-HNF1A
Actin
MIN6
F
Relative Activation
20
15
10
5
0
MAFA R3 + + + + + + + - -
MAFA R3 M2G-7816 - - - - - - - + +
HNF1AWT - 1 1 1 1 1 - 1 -
HNF1AT260M - - 0.25 0.5 1 2 1 - 1
G
HNF1AWT
HNF1AT260M
HNF1A
Actin
HeLa
H
INS NKX2.2 GCG
INS NKX6.1 GCG
INS PDX1 GCG
Control
HNF1A+/T260M
% β cells NKX2-2+
% β cells NKX6-1+
% β cells PDX1+
100
80
60
40
20
0
Cntrl
HNF1A+/T260M

**Figure S2. Expression and functional characterization of HNF1A$^{T260M}$ variant.** (**A**) Example of control staining for **Figure 2A** with quantification of HNF1A protein expression in α cells. Scale bar represents 50 μm and applies to **B**. (**B**) HNF1A nuclei associated with hormone-positive endocrine cells in donor islets, marked here with insulin, glucagon, somatostatin, and ghrelin on the same channel. (**C**) Corresponding western blot of HeLa cells without transfection and transfection with either wildtype (WT) or T260M mutant Myc-tagged HNF1A from **Figure 2B**. EMSA of HNF1A$^{WT}$ or HNF1A$^{T260M}$ transfected MIN6 cells confirmed the effects of the mutant protein on DNA-binding in an immortalized β cell line (**D**) with corresponding western blot (**E**). Specific elimination of the Myc-tagged HNF1A-DNA complex with Myc antibody (arrow) was observed only in WT transfected MIN6 cells, but not in Myc-tagged HNF1A$^{T260M}$ expressing conditions. The endogenous HNF1α-DNA complex remained. Arrow – Myc-tagged HNF1A-DNA complex; arrow head – endogenous HNF1A-DNA complex in MIN6 cells; asterisk – nonspecific complexes; Myc-HNF1A – Myc-tagged HNF1A; End-HNF1A – Endogenous HNF1A of MIN6 cells; NT – non-transfected cells. (**F**) HNF1A$^{T260M}$ reduced *MAFA* R3-driven reporter activity in a dose and *cis*-element site dependent manner in HeLa cells. MAFA R3 M2G$^{-7816}$ – *MAFA* R3 site mutation. (**G**) Immunoblot analysis of HeLa cells transfected only with HNF1A$^{WT}$ or HNF1A$^{T260M}$, which corresponds to the darkest blue and red bar conditions of panel **F**. (**H**) Analysis of native pancreatic tissue from *HNF1A$^{+/T260M}$* donor for expression of β cell-enriched transcription factors. *HNF1A$^{+/T260M}$* β cells expressed β cell markers NKX2.2, NKX6.1, and PDX1 similar to controls (n=7 donors; ages 8-55yrs). Scale bar represents 10 μm and corresponds to all panels in **H**. Images represent one of three replicates. Results of the control samples are expressed as mean ± standard error of the mean.




**G**

| Top 10 Common DAVID GO Analysis Molecular Functions in *HNF1A+/T260M* β and α cells | β cells p-value | α cells p-value |
|---|---|---|
| GO:0005515:protein binding | 5.40E-32 | 7.07E-29 |
| GO:0044822:poly(A) RNA binding | 7.04E-11 | 1.01E-13 |
| GO:0005524:ATP binding | 5.48E-07 | 4.84E-10 |
| GO:0000287:magnesium ion binding | 1.76E-05 | 3.68E-05 |
| GO:0004674:protein serine/threonine kinase activity | 2.56E-05 | 4.20E-06 |
| GO:0004672:protein kinase activity | 2.99E-05 | 3.11E-05 |
| Go:0046872:metal ion binding | 3.28E-05 | 2.57E-06 |
| GO:0016301:kinase activity | 8.90E-05 | 1.39E-05 |
| GO:0051287:NAD binding | 2.93E-04 | 6.61E-05 |
| GO:0098641:cadherin binding involved in cell-cell adhesion | 3.48E-04 | 2.40E-08 |

**Figure S3. Transcriptome analysis of purified *HNF1A+/T260M* β and α cells by RNA-sequencing.** (**A**) PCA plot and (**B**) volcano plot of *HNF1A+/T260M* α cells as described in main **Figure 3**. (**C**) Graph represents down-regulation of HNF1A associated-targets in α cells from the *HNF1A+/T260M* donor. Graphs represent most significantly up- and down-regulated genes in the *HNF1A+/T260M* β cells (**D**) and α cells (**E**) compared to controls (n=5 donors; ages 26-55yrs). The same set of control donor islets were used for α and β cell transcriptomic analysis and are also published elsewhere (1, 9). (**F**) Venn diagrams depict the number of genes up- and down- regulated in *HNF1A+/T260M* α and β cells highlighting approximately 50% overlap of up- and down-regulated genes between cell types. (**G**) Table represents the top 10 common Molecular Functions in *HNF1A+/T260M* β and α cells identified by DAVID GO term analysis. Corresponding p-values, Ensembl Gene IDs and process GO accession numbers are listed in **Tables S5** and **S6**.

**Table S1. Demographic and source information of all donors**

| Donors | Age (years) | Ethnicity/ Race | Gender | BMI | Cause of Death | Tissue/Islet Sources* |
|---|---|---|---|---|---|---|
| **Normal Controls for Islet Perifusion** | 8 | African American | M | 17.2 | Anoxia | NDRI |
| | 16 | African American | M | 23.2 | Head Trauma | IIAM |
| | 19 | Caucasian | M | 21.2 | Anoxia | NDRI |
| | 19 | Caucasian | M | 20.1 | Head Trauma | NDRI |
| | 52 | African American | M | 29.2 | Stroke | TDS |
| | 55 | African American | F | 24.2 | Stroke | TDS |
| **Normal Controls for Histology** | 8 | African American | M | 17.2 | Anoxia | NDRI |
| | 10 | Caucasian | M | 19.3 | Head Trauma | NDRI |
| | 19 | Caucasian | M | 21.2 | Anoxia | NDRI |
| | 19 | Caucasian | M | 20.1 | Head Trauma | NDRI |
| | 20 | Hispanic/ Latino | M | 19.4 | Head Trauma | IIAM |
| | 24 | Caucasian | M | 35.5 | Head Trauma | IIAM |
| | 35 | Caucasian | M | 26.8 | Head Trauma | IIAM |
| | 55 | African American | M | 35.6 | Stroke | IIAM |
| **Normal Controls for RNA-seq** | 26 | Hispanic/Latino | F | 35.9 | Anoxia | IIDP |
| | 35 | Caucasian | F | 23.6 | Anoxia | IIDP |
| | 49 | Caucasian | F | 31.6 | Stroke | IIDP |
| | 50 | African American | M | 30.2 | Stroke | IIDP |
| | 55 | Caucasian | M | 27.8 | Stroke | IIDP |
| **HNF1A/ MODY3 Donor** | 33 | Caucasian | M | 25.6 | Head Trauma | IIAM |

*All NDRI, IIAM, and TDS islets were isolated by Rita Bottino at Allegheny Health Network in Pittsburgh, PA, USA. NDRI – National Disease Research Interchange; IIAM – International Institute for the Advancement of Medicine; IIDP – Integrated Islet Distribution Program; TDS – Tennessee Donor Services

**Table S2. DNA sequencing of donor for variants associated with monogenic diabetes.**

| Donor | Gene | Chr | Transcript | Nucleotide | Amino Acid Change | dbSNP ID | MAF | POLY Score |
|---|---|---|---|---|---|---|---|---|
| HNF1A/ MODY3 | *ALMS1* | 2 | NM_015120.4 | c.2041C>T | p.Arg681* | - | 0 | 0 |
| | *DYRK1B* | 19 | NM_004714.1 | c.*9C>G | - | rs370237703 | 0 | 0 |
| | *FBN1* | 15 | NM_000138.4 | c.5343G>A | p.Val1781Val | rs140649 | 0.003 | 0 |
| | *HNF1A* | 12 | NM_000545.6 | c.779C>T | p.Thr260Met | rs886039544 | 0 | 1 |
| | *IFIH1* | 2 | NM_022168.3 | c.1491G>A | p.Thr497Thr | - | 0 | 0 |
| | *INS* | 11 | NM_000207.2 | c.-414C>A | - | - | 0 | 0 |
| | *KCNJ11* | 11 | NM_000525.3 | c.-179C>T | - | - | 0 | 0 |
| | *LRBA* | 4 | NM_006726.4 | c.217-10del | - | - | 0 | 0 |
| | *PCNT* | 21 | NM_006031.5 | c.1754G>A | p.Arg585Gln | - | 0 | 0 |
| | *PTEN* | 10 | NM_000314.4 | c.579G>A | p.Leu193Leu | - | 0 | 0 |
| | *SLC29A3* | 10 | NM_018344.5 | c.300+10del | - | - | 0 | 0 |
| | *WFS1* | 4 | NM_006005.3 | c.2052G>A | p.Ala684Ala | rs71539668 | 0.002 | 0 |

Chr – Chromosome, MAF – Minor allele frequency; DNA isolated from pancreatic samples of donor was subjected to DNA sequencing covering coding regions and splice junctions of 148 genes associated with monogenic diabetes (4). *nonsense mutation

**Table S3. Sources and concentrations of primary antibodies**

| Antigen | Host Species | Working Dilutions | | | Vendor | Catalog # |
|---|---|---|---|---|---|---|
| | | Cryo-sections | Western Blot; EMSA | Flow Cytometry | | |
| **CD45** | Rabbit | 1:100 | - | - | Dako | A0452 |
| **Glucagon** | Rabbit | 1:200 | - | - | Cell Signaling | 2760 |
| **Glucagon** | Mouse | 1:500 | - | - | Abcam | ab10988 |
| **Glucagon-Pacific Blue** | Mouse | - | - | 1:600 | Sigma-Aldrich | G2654 |
| **Insulin-647** | Rabbit | 1:65 | - | - | Cell Signaling | 9008 |
| **Insulin** | Guinea pig | 1:1000 | - | - | Dako | A0564 |
| **Insulin** | Chicken | - | - | 1:10 | Gallus Immunotech | ABI |
| **Ghrelin** | Mouse | 1:1000 | - | - | Abcam | 57222 |
| **VEGFR2** | Goat | 1:200 | - | - | R&D Systems | AF644 |
| **Synapsin-1,2** | Rabbit | 1:2000 | - | - | Synaptic Systems | 106 002 |
| **Ki67** | Mouse | 1:5000 | - | - | Dako | M7240 |
| **HNF1A** | Rabbit | 1:500 | - | - | Abcam | Ab204306 |
| **HNF1A** | Mouse | - | 1:2000 | - | Thermo Fisher | GT4110 |
| **HNF1A** | Rabbit | - | N/A; 1:40 | - | Proteintech | 22426-1-AP |
| **c-Myc** | Mouse | - | 1:2000; 1:40 | - | Santa Cruz | 9E10 |
| **β-Actin** | Rabbit | - | 1:4000 | - | Cell Signaling | 4967 |
| **NKX2.2** | Mouse | 1:100 | - | - | Developmental Studies Hybridoma Bank | 74-5A5 |
| **NKX6.1** | Rabbit | 1:2000 | - | - | BCBC/Palle Serup | N/A |
| **PDX1** | Rabbit | 1:5000 | - | - | C. V. E. Wright* | N/A |
| **Somatostatin** | Goat | 1:500 | - | - | Santa Cruz | sc-7819 |
| **Somatostatin-AlexaFluor 488** | Mouse | - | - | 1:200 | LS Bio | LS-C169129-100 |
| **HIC3-2D12 (Hpa3)** | Mouse | - | - | 1:200 | Gift from Dr. Philip Streeter** | N/A |
| **HIC0-4F9 (Hpi1) - Biotin** | Mouse | - | - | 1:100 | Novus | NBP1-18872B |
| **CD39L3** | Mouse | - | - | 1:100 | Gift from Jean Sévigny[#] | N/A |

BCBC – Beta Cell Biology Consortium, N/A – not applicable; *Vanderbilt University, Nashville, TN, USA; **Oregon Health & Science University, Portland, OR, USA; [#]Laval University, Québec, Canada

**Table S4. Sources and concentrations of secondary antibodies**

| Host Species | Primary Ab Species | Fluorophore/ Chromogen | Working Dilutions | | Vendor | Catalog # |
|---|---|---|---|---|---|---|
| | | | Cryo-sections | Flow Cytometry | | |
| Donkey | Chicken | APC | - | 1:25 | Jackson Immuno-Research | 703-136-155 |
| Donkey | Goat | Cy5 | 1:200 | - | Jackson Immuno-Research | 705-605-003 |
| Donkey | Goat | Cy2 | 1:500 | - | Jackson Immuno-Research | 705-225-147 |
| Donkey | Guinea pig | Cy2 | 1:500 | - | Jackson Immuno-Research | 706-225-148 |
| Donkey | Guinea pig | Cy5 | 1:200 | - | Jackson Immuno-Research | 706-175-148 |
| Donkey | Rabbit | Cy3 | 1:500 | - | Jackson Immuno-Research | 711-165-152 |
| Donkey | Mouse | Cy5 | 1:200 | - | Jackson Immuno-Research | 715-175-151 |
| Donkey | Mouse | Cy3 | 1:500 | - | Jackson Immuno-Research | 715-165-150 |
| Goat | Mouse | PE | - | 1:1000 | BD Bio-sciences | 550589 |
| Goat | Mouse | Streptavadin BV421 | - | 1:500 | BD Bio-sciences | 563259 |
| Goat | Mouse | APC | - | 1:500 | BD Bio-sciences | 550826 |

**Table S5. DAVID Gene Ontology of *HNF1A*$^{+/T260M}$ β cells** (excel)

**Table S6. DAVID Gene Ontology of *HNF1A*$^{+/T260M}$ α cells** (excel)

**Table S7. Top 10 Significant IPA Canonical Pathways of *HNF1A*$^{+/T260M}$ β and α cells** (excel)