## ESM Methods

### Mice

All animal experiments were conducted at BC Children's Hospital Research Institute where mice were housed under 12-h light 12-h dark conditions at room temperature, with ad libitum access to chow (Teklad, #2918, Envigo, Indianapolis, IN, US; Calorie distribution: 24% protein, 18% fat, 58% carbohydrate) and water. Where indicated, mice were placed on high fat diet (HFD; D12451, Research Diets, New Brunswick, NJ, USA: Calorie distribution: 20% protein, 45% fat, 35% carbohydrate) for 2 weeks. C57BL/6J (#000664), NOD/ShiLtJ (NOD, #001976), NOD.Cg-*Prkdcscid*/J (NOD SCID, #001303), B6.Cg-Tg(TcraTcrb)425Cbn/J (OT-II, #004194), FVB/N-Tg(Ins2-IAPP)RHFSoel/J (hIAPP Tg/0, RIPHAT, #008232), BALB/cJ (#000651) mice were purchased from Jackson Laboratory, Bar Harbor, Maine, USA.

### Randomisation

All animals were assigned to their respective groups depending on genotypes and littermate controls were used for all in vivo experiments.

### Masking/blinding

Group assignment was based on genotype, and therefore not anonymised. Researchers were masked to the group assignment during in vivo blood glucose measurements. Masking was not carried out for other experiments.

### Inclusion and exclusion criteria

All mice were included in studies unless they had unexplained illness, physical abnormalities or weight loss (unrelated to diabetes), no sex-matched littermate control available, or if genotyping was unclear.

### Single cell RNA-sequencing

hIAPP Tg/0 and hIAPP 0/0 littermates on an F1 C57BL/6J x FVB/NJ background, were generated by crossing hIAPP Tg/0 transgenic mice on the FVB/NJ background with C75BL/6J mice. After HFD, islets were isolated and pooled (5 mice per sample, n=3 samples per genotype) for FACS enrichment of islet immune cells via BD FACS ARIA II (BD Biosciences, San Jose, CA, USA) into PBS containing 2% FBS (Thermo Fisher Scientific, Canada), pH 7.4. Based on the total amount of cells sorted into the CD45+ fraction, the amount of CD45- cells to spike back in was calculated to achieve a final ratio of 70% CD45+ cells to 30% CD45- cells. Each combined sample was loaded onto the Chromium Controller for single-cell RNA sequencing library preparation using the Chromium Single Cell 3' V2 Reagent Kit (10X Genomics). Sample libraries were then sequenced on an Illumina NextSeq500 to a read-depth minimum of 80,000 reads per cell. Reads were aligned to a reference genome using CellRanger v2.1.1 (10X Genomics). Resulting sample gene expression matrices were then each individually processed in R.

### Transcriptomic analysis

Sample gene expression matrices were each individually processed in R using various packages before downstream analysis to remove confounding variables. First, the effect of ambient mRNA detected in droplets was mitigated using *SoupX* (1.6.2) [1]. Next, gene expression matrices were imported into RStudio using *Seurat* (4.3.0) [2]. For each sample, low quality cells were removed prior to applying *DoubletFinder* (2.0.4), to detect and remove artificial multiplets before performing SCTransform, selecting 3000 integration features, and integrating samples into one dataset [2][3][4]. Next, a standard

workflow was run for visualization and clustering: principle component analysis (*Seurat*, RunPCA, npcs=30), dimensionality reduction (*Seurat*, RunUMAP, reduction = "pca", dims = 1:30), construction of nearest neighbour graph (*Seurat*, FindNeighbors, reduction = "pca", dims=1:30) and cluster detection (*Seurat*, FindClusters, res=0.8, algorithm=1) [2]. Cell types were annotated based on known marker genes. Gene counts of all the cells from the same sample for each cell type were summed (*Seurat*, AggregateExpression) to generate psudobulk gene expression profiles [5]. Differentially expressed genes (DEGs) between the transgenic and wild type conditions for each type were calculated on the pseudobulk dataset (*Seurat*, FindMarkers) using the *DESeq2* test (1.36.0) [2][6]. Gene set enrichment analysis (GSEA) was performed using *fGSEA* (1.31.3) [7].

**Processing of islets, spleen and lymph nodes for flow cytometry**

Briefly, islets were harvested from mice and hand-picked to purity in complete RPMI 1640 media (Thermo Fisher Scientific Canada) and subsequently exocrine-free islets were selected and dispersed with 0.02 % trypsin for 3 min at 37 °C and washed with FACS buffer (2% FBS, 2 mmol/l EDTA in PBS, pH7.4) for downstream staining and analysis. Spleens and lymph nodes were harvested from mice and homogenized through a 40 µm cell strainer. Cells were washed once with PBS, pH7.4, then lysed in ammonium chloride solution (Stemcell Techonologies, Canada) at 4 °C for 10 minutes. Following lysis, cells were washed once with PBS and resuspended in PBS for counting and flow cytometry.

Cells were incubated in mouse Fc block diluted 1:100 in PBS or FACS buffer for 10 min prior to addition of antibodies for extracellular markers. Fixable viability dye (FVD) eFlour780 (Invitrogen #65-0865) or 7-AAD (Invitrogen #699-50)) were used according to manufacturer instructions to measure viability. For intracellular markers, cells were fixed in freshly prepared Fix concentrate (Invitrogen #5123-43), diluted in Fix Diluent (Invitrogen #5223-56), and subsequently resuspended in permeabilization buffer (Invitrogen #8333-56) containing intracellular staining antibodies. Flow cytometry was conducted on a LSR Fortessa (BD Biosciences, USA), CytoFLEX (Beckman Coulter, USA) or cells were sorted by FACS by BD FACS ARIA II (BD Biosciences, USA). Data were analyzed by FlowJo software (BD Biosciences, USA).

**Adoptive Transfers**

NOD SCID.hIAPP Tg/0 and NOD SCID.hIAPP 0/0 littermates were generated by backcrossing the NOD.hIAPP Tg/0 transgenic mice with homozygous NOD.Cg-*Prkdc*$^{scid/scid}$ (NOD SCID) mice to generate 50% NOD.*Prkdc*$^{scid/wt}$ ; hIAPP Tg/0 mice which were then crossed again to NOD SCID mice to generate NOD.*Prkdc*$^{scid/scid}$; hIAPP Tg/0 and NOD.*Prkdc*$^{scid/scid}$; hIAPP 0/0 mice which were then intercrossed to maintain homozygosity for the *Prkdc*$^{scid}$ allele.

Splenocytes from diabetic 18-week old female NOD/ShiLtJ mice were isolated and injected (10x10$^6$ cells via tail vein) in 17-week old female NOD SCID.hIAPP Tg/0 and NOD SCID.hIAPP 0/0 female mice. In another experiment, splenocytes from non-diabetic 19-week old female NOD.hIAPP Tg/0 and NOD.hIAPP 0/0 mice were injected (10x10$^6$ cells via tail vein) in 25-week old female NOD SCID mice.

**Glucose tolerance tests and glucose-stimulated insulin secretion**

For glucose tolerance tests, all mice were fasted for 6 h and subsequently injected intraperitoneally with glucose dissolved in PBS (dose is indicated in the figure legend). Blood glucose was measured at indicated time points post injection. To measure in vivo glucose-stimulated insulin levels (GSIL), blood was collected from the saphenous vein after a 6-h fast and after injection of glucose for the

measurement of plasma insulin via Stellux Chemiluminescent Rodent Insulin ELISA (#80-INSMR-CH01, Alpco, Salem, NH, USA). Ex vivo glucose-stimulated insulin secretion (GSIS) was measured as previously described [25].

**T cell proliferation assay**

Synthetic hIAPP and rIAPP (Bachem, Switzerland) were prepared as previously published [8]. Bone marrow-derived dendritic cells (BMDCs) were generated from C57BL/6J mice, and treated with synthetic hIAPP, rIAPP (10 µM) or vehicle as indicated for 24 h, with or without 10 ng/ml LPS (Sigma). Subsequently, BMDCs were washed and stained for flow cytometry or co-cultured at a 1:5 ratio with CFDA-SE (Stemcell Technologies, Canada)-labelled CD4 T cells isolated from a B6. Cg-Tg(TcraTcrb)425Cbn/J (OT-II) donor mouse in RPMI-1640, (Thermo Fisher Scientific) supplemented with 10% heat inactivated FBS (Thermo Fisher Scientific, Burnaby, BC, Canada), 100U penicillin/streptomycin (Thermo Fisher Scientific), 10 mM HEPES (Thermo Fisher Scientific), 50 µM β-mercaptoethanol (MilliporeSigma, Canada), 1x Glutamax (Thermo Fisher Scientific, Canada), and 10mM sodium pyruvate (Thermo Fisher Scientific). After 3 days, cells were stained for flow cytometry as above with CD4 antibody (Table 1), fixable viability dye eFlour780 (Thermo Fisher, US) and analyzed by flow cytometry on a CytoFLEX (Beckman Coulter). Proliferation was determined by CFSE dilution as a percent CD4 cells, after gating on viable singlets.

**Lipid nanoparticle formulation**

Ovalbumin (Ova) mRNA with 5' methoxy-uridine (5moU) base modification (Trilink BioTechnologies, USA) was formulated into lipid nanoparticles by Integrated Nanotherapeutics (Canada) with their proprietary ionizable lipid using a rapid mixing process [9]. Briefly, all lipid components, were dissolved in ethanol while the mRNA was dissolved in pH 4.0 citrate buffer. The ethanol and citrate solutions were rapidly mixed at a ratio of 1:3, respectively. The resultant LNP solutions were dialyzed overnight in pH 7.4 tris buffer to remove residual ethanol and to increase the pH to physiological levels. All LNP-mRNA were formulated at an amine-to-phosphate ratio (N/P) of 6. Lipid concentrations were determined by measuring cholesterol content (Cholesterol Total E Assay, Wako Chemicals, Richmond, VA, USA) and RNA entrapment and concentrations were determined using Ribogreen (Thermo Fisher Scientific, Burnaby, BC, Canada). Final LNP-mRNA were stored frozen at -70°C.

**Immunofluorescence**

Pancreases were harvested immediately after euthanasia, and processed and stained as previously described [10] then fixed with 4% paraformaldehyde for 24h. Samples were washed with 70% ethanol prior to paraffin embedding and sectioning (5 µm). Following removal of paraffin layer and rehydration, samples were washed with PBS (Thermo Fisher Scientific) and blocked for 1h at room temperature (Dako Protein block, Agilent Technologies, USA). Samples were incubated overnight at 4°C in anti-insulin antibody (#A0564, 1:500 Dako, Agilent Technologies), washed in 3 times in PBS and incubated for 1 h at room temperature in Alexa 594 goat anti-guinea pig secondary antibody (#A-110761:200, Thermo Fisher Scientific) in a dark humid chamber, followed by incubation in 0.5% (wt/vol) thioflavin S (Sigma) for 2 min, and washed with 70% ethanol and water prior to mounting. Images were acquired on a BX61 microscope (Olympus, Richmond Hill, ON, Canada) using 10× air objective.

**Statistical methods**

With the exception of gene expression data, all statistical analyses were performed using GraphPad Prism 10.0 (GraphPad Software, La Jolla, CA, USA). Data are presented as mean ± SEM, with individual

data points from biological replicates, unless otherwise indicated. For comparisons of only two groups, normally distributed data were analyzed by t-test with Welch's correction whereas non-normal data were analyzed by Mann-Whitney test. Data were tested for normality by the Shapiro-Wilk test. For comparisons of more than two groups, normally distributed data were analyzed by one-way ANOVA and non-normal data analyzed by Kruskal-Wallis test. For repeated measures of two or more groups data were analyzed by two-way repeated measures ANOVA with Geisser-Greenhouse correction for non-sphericity. Diabetes incidence data were analysed via logrank test. The number of observations (n) are provided in figure legends.

**ESM References**


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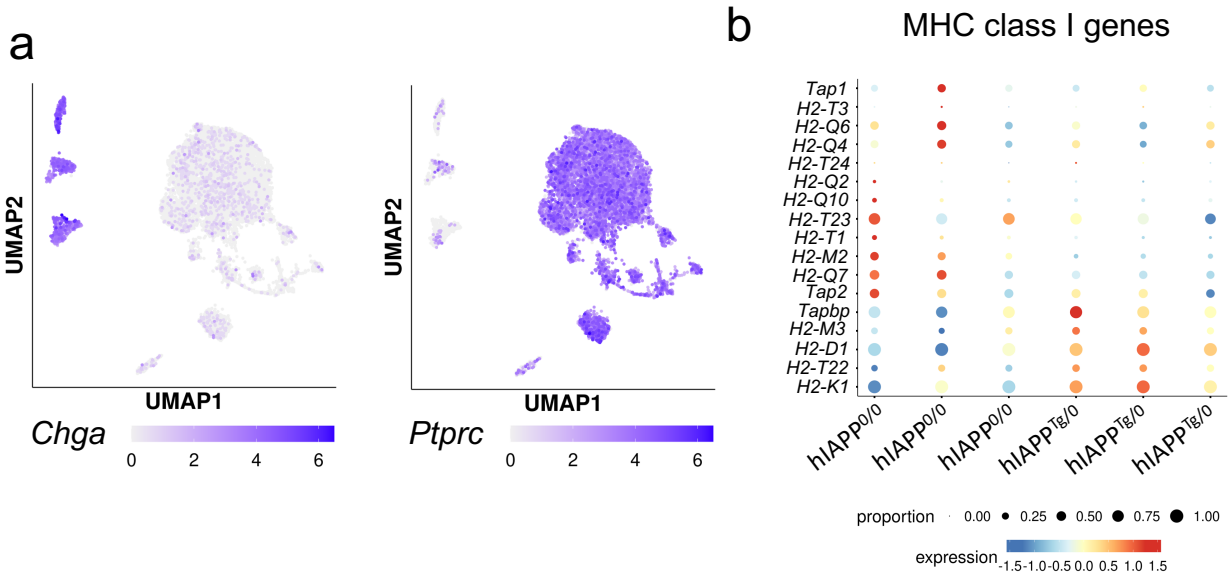
**ESM Tables**

**ESM Table 1**

| ***Gene target*** | ***Forward Primer*** | ***Reverse Primer*** |
|---|---|---|
| control gene (*Pcsk2*) | CGCTGCAACAAGAAGGATT | TAGAGAAACTTACCAGGTACC |
| hIAPP Transgene) | GAGAGAGCCACTGAATTACTTGC | GGATGATGTTCAATTATTTCTTCTGCC |
| *Iapp* (human) knockin | TGAAGACTGAAGTGTGGACAC | CTTCGTATAATGTATGCTATACGAAG |
| *Iapp* (mouse) knockin | TGAAGACTGAAGTGTGGACAC | TGTGGTCTCTTAATTGAAGGC |

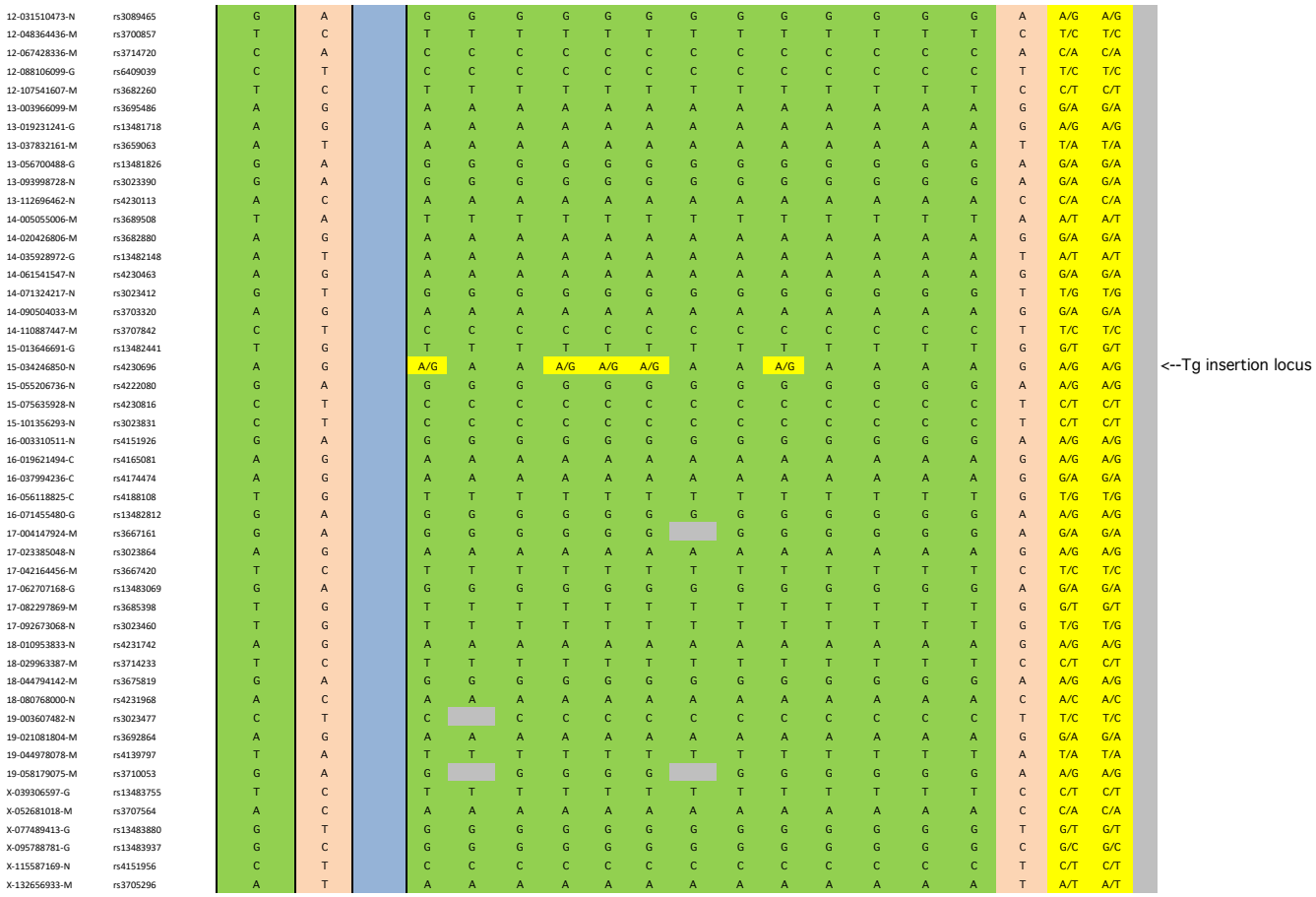
**ESM Table 2**

| ***Marker*** | ***Clone*** | ***Supplier (cat#, fluorochrome)*** | ***Dilution*** |
|---|---|---|---|
| T cell receptor beta | H57-597 | Biolegend (109212, APC) | 1:100 |
| CD3 | 17a2 | Biolegend (100237, BV605) | 1:100 |
| CD4 | RM4-5 | Biolegend (100551, BV785) | 1:100 |
| CD8a | 53-6.7 | Biolegend (100761, PE-Dazzle594) | 1:100 |
| CD11b | M1/70 | Invitrogen (12-0112-82, PE) | 1:100 |
| CD11c | N418 | Invitrogen (25-0114-82, PE/Cy7) | 1:100 |
| CD19 | eBio1D3 | eBioscience (#17-0193-82, APC) | 1:100 |
| CD45 | 30-F11 | Invitrogen (#48-0451-82, eF450) | 1:100 |
| Fc receptor block (CD16/CD32) | 93 | ThermoFisher (#14-0161-82, n/a) | 1:100 |
| Foxp3 | FJK-16s | Invitrogen (#11-5773-82, FITC) | 1:25 |
| MHCII I-A$^d$ | 39-10-08 | Biolegend (#115009, AF647) | 1:100 |
| MHCII I-A/I-E | M5/114.15.2 | Invitrogen (#17-5321-82, APC) | 1:100 |



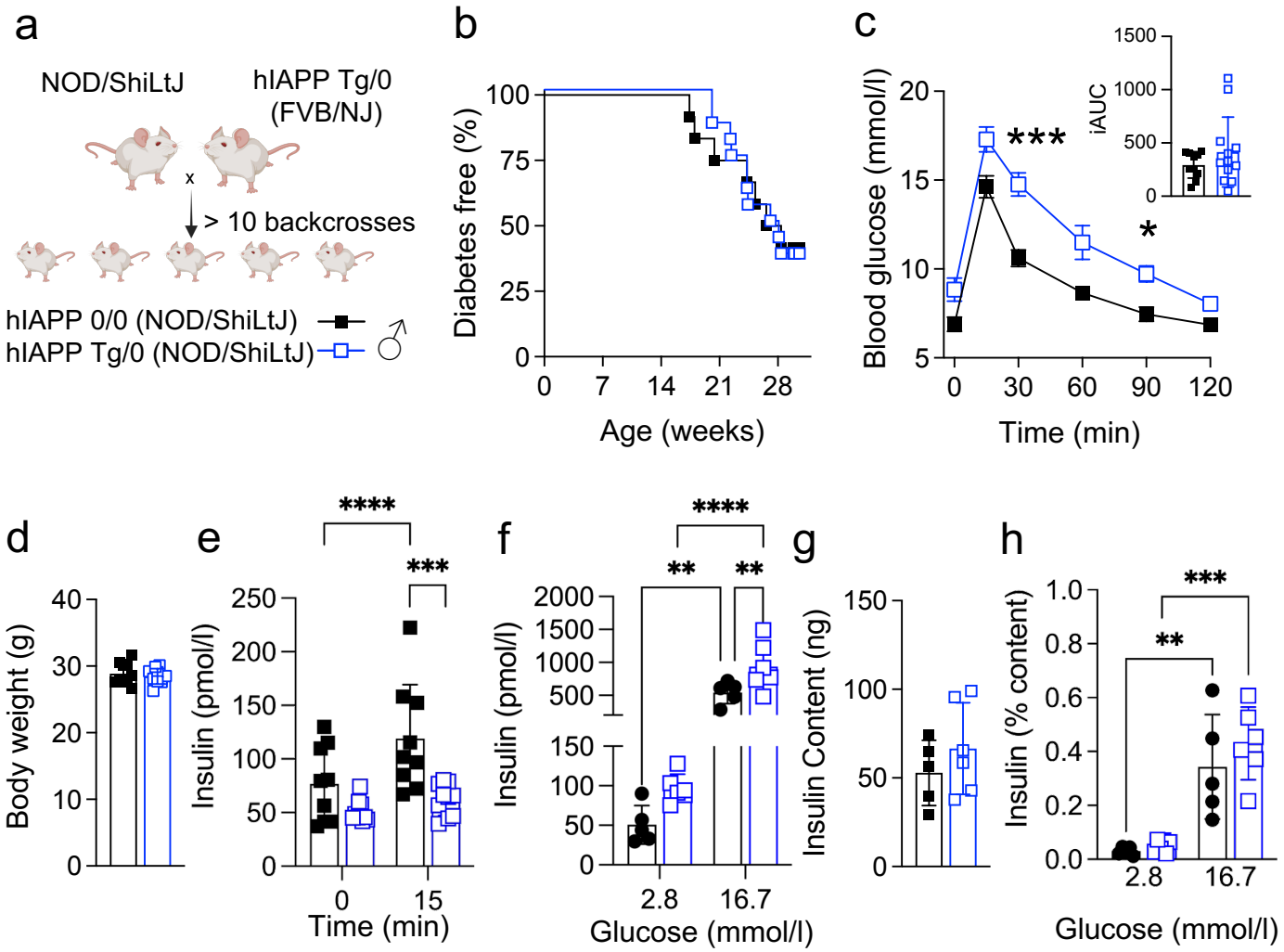

**ESM Fig. 1. Expression of endocrine and immune markers in islet cell populations.** (**a**) Feature Plots showing Chromogranin A (*ChgA*) in endocrine cells and Protein Tyrosine Phosphatase Receptor Type C (*Ptprc*, also known as CD45) expression in immune cells. (**b**) Bubble plot of MHC class I genes in myeloid clusters across samples.

| Panel Info | | | | NOD/LtJ | 257/258 | 246/246 | 254/254 | 257/258 | 257/258 | 257/258 | 248/248 | 258/258 | 257/258 | 258/258 | 258/258 | 258/258 | 258/258 | /258 | 129/258 | 129/258 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | FVB/NJ | 1/258 | /246 | /254 | 1/258 | 1/258 | 1/258 | /248 | /258 | 1/258 | /258 | /258 | /258 | /258 | 258/258 | 129/258 | 129/258 | |
| | | | | NOD/LtJ | 99.61% | 100.00% | 100.00% | 99.61% | 99.61% | 99.61% | 100.00% | 100.00% | 99.61% | 100.00% | 100.00% | 100.00% | 100.00% | 0.00% | 50.00% | 50.00% | |
| | | | | FVB/NJ | 0.39% | 0.00% | 0.00% | 0.39% | 0.39% | 0.39% | 0.00% | 0.00% | 0.39% | 0.00% | 0.00% | 0.00% | 0.00% | 100.00% | 50.00% | 50.00% | |
| | | | Sample | | hIAPP Tg/0 | hIAPP 0/0 | hIAPP 0/0 | hIAPP Tg/0 | hIAPP Tg/0 | hIAPP Tg/0 | hIAPP 0/0 | hIAPP 0/0 | hIAPP Tg/0 | hIAPP 0/0 | hIAPP 0/0 | hIAPP 0/0 | hIAPP 0/0 | FVB | NOD/FVB het 1 | NOD/FVB het 2 | Ntc |
| SNP_ID | | Expected SNPs | | | | | | | | | | | | | | | | | | | |
| Chromosome-bp | RS_ID | NOD/LtJ | FVB/NJ | | A01 | A02 | A03 | A04 | A05 | A06 | A07 | A08 | A09 | A10 | A11 | A12 | B02 | B04 | B06 | B08 | B09 |
| 01-005230167-M | rs3708040 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | T/C | T/C | |
| 01-022154835-M | rs3711079 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | T/C | T/C | |
| 01-039504168-N | rs4222284 | A | C | | A | | A | A | A | A | | A | A | A | A | A | A | C | C/A | C/A | |
| 01-059831398-M | rs3687432 | T | G | | T | T | T | T | T | T | T | T | T | T | T | T | T | G | T/G | T/G | |
| 01-079289860-N | rs4222476 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | G/A | G/A | |
| 01-098816823-G | rs13476006 | G | A | | G | G | G | G | G | G | G | G | G | G | G | G | G | A | A/G | A/G | |
| 01-119969798-M | rs3689749 | C | T | | C | | C | C | C | C | C | C | C | C | C | C | C | T | C/T | C/T | |
| 01-139952425-M | rs3677464 | A | T | | A | A | A | A | A | A | A | A | A | A | A | A | A | T | T/A | T/A | |
| 01-150718101-M | rs3680033 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | C/T | C/T | |
| 01-172244784-N | rs3022854 | C | A | | C | C | C | C | C | C | C | C | C | C | C | C | C | A | A/C | A/C | |
| 01-191466000-P | | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 02-011117260-M | rs3698941 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | C/G | C/G | |
| 02-023691071-G | rs13476383 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | G/A | G/A | |
| 02-042953536-M | rs3670748 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | A/G | A/G | |
| 02-076977189-M | rs3699089 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | C/T | C/T | |
| 02-087029735-M | rs3711897 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | C/T | C/T | |
| 02-108953011-M | rs3657882 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | C/G | C/G | |
| 02-138412137-G | rs13476794 | G | T | | G | G | G | G | G | G | G | G | G | G | G | G | G | T | T/G | T/G | |
| 02-154428186-N | rs4223578 | T | C | | T | | T | T | T | T | | T | T | T | T | T | T | C | T/C | T/C | |
| 02-176114999-M | rs3708892 | G | T | | G | G | G | G | G | G | G | G | G | G | G | G | G | T | T/G | T/G | |
| 03-011350737-M | rs3680834 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | C/G | C/G | |
| 03-030195187-M | rs3685884 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | T/C | T/C | |
| 03-052127658-M | rs3709395 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | T/C | T/C | |
| 03-073214161-M | rs3681493 | A | T | | A | A | A | A | A | A | A | A | A | A | A | A | A | T | T/A | T/A | |
| 03-091071226-M | rs3674470 | C | G | | C | C | C | C | C | C | C | C | C | C | C | C | C | G | C/G | C/G | |
| 03-115468851-N | rs4224164 | C | A | | C | C | C | C | C | C | C | C | C | C | C | C | C | A | A/C | A/C | |
| 03-142288777-N | rs3718489 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | G/C | G/C | |
| 04-009404597-G | rs13477554 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | G/A | G/A | |
| 04-019063943-M | rs3708738 | C | G | | C | C | C | C | C | C | C | C | C | C | C | C | C | G | G/C | G/C | |
| 04-039199957-M | rs3723778 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | G/C | G/C | |
| 04-056969111-M | rs4138670 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | G/C | G/C | |
| 04-086758585-N | rs4224587 | G | A | | G | G | G | G | G | G | G | G | G | G | G | G | G | A | G/A | G/A | |
| 04-107204545-N | rs4221960 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | T/C | T/C | |
| 04-128694339-G | rs13477980 | T | G | | T | T | T | T | T | T | T | T | T | T | T | T | T | G | T/G | T/G | |
| 04-145455916-G | rs13478042 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | G/A | G/A | |
| 05-008305854-N | rs4225021 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | T/C | T/C | |
| 05-030544560-G | rs6234655 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 05-050882266-M | rs3655838 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | G/C | G/C | |
| 05-070956183-G | rs13478321 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | T/C | T/C | |
| 05-091299403-M | rs3676700 | T | G | | T | T | T | T | T | T | T | T | T | T | T | T | T | G | G/T | G/T | |
| 05-111119638-M | rs3659110 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | C/G | C/G | |
| 05-128944450-M | rs3668978 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | C/T | C/T | |
| 05-146927661-M | rs3694100 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | G/A | G/A | |
| 06-006170915-M | rs3700900 | T | A | | T | T | T | T | T | T | T | T | T | T | T | T | T | A | A/T | A/T | |
| 06-026880118-G | rs13478673 | A | C | | A | A | A | A | A | A | A | A | A | A | A | A | A | C | C/A | C/A | |
| 06-043835637-G | rs13478727 | C | A | | C | C | C | C | C | C | C | C | C | C | C | C | C | A | A/C | A/C | |
| 06-053689388-N | rs3023070 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | C/T | C/T | |
| 06-095139289-M | rs3667765 | T | A | | T | T | T | T | T | T | T | T | T | T | T | T | T | A | A/T | A/T | |
| 06-117570700-G | rs13478992 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | G/A | G/A | |
| 06-138971511-M | rs3712962 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 07-006208019-M | rs3670158 | T | C | | T | T | | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 07-022997618-M | rs3662246 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 07-047745716-G | rs13479279 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | C/T | C/T | |
| 07-058987832-M | rs3693876 | A | G | | | | | | | | | | | | | | | | | | |
| 07-082090086-M | rs3685276 | G | T | | G | G | G | G | G | G | G | G | G | G | G | G | G | T | T/G | T/G | |
| 07-102009856-M | rs3681072 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 07-124000818-G | rs13479544 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 08-018678697-G | rs13479627 | C | A | | C | C | C | C | C | C | C | C | C | C | C | C | C | A | C/A | C/A | |
| 08-034010045-M | rs3726395 | C | G | | C | C | C | C | C | C | C | C | C | C | C | C | C | G | C/G | C/G | |
| 08-053200795-M | rs3717783 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | C/T | C/T | |
| 08-074679809-N | rs4227260 | A | T | | A | A | A | A | A | A | A | A | A | A | A | A | A | T | T/A | T/A | |
| 08-095444189-N | rs4227350 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 08-116218798-M | rs3656840 | A | C | | A | A | A | A | A | A | A | A | A | A | A | A | A | C | C/A | C/A | |
| 09-003938578-M | rs3694533 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | C/T | C/T | |
| 09-023643882-G | rs13480104 | G | C | | G | G | G | G | G | G | G | G | G | G | G | G | G | C | C/G | C/G | |
| 09-044089145-M | rs3653389 | C | T | | C | C | C | C | C | C | C | C | C | C | C | C | C | T | T/C | T/C | |
| 09-065027538-M | rs3664300 | T | C | | T | | T | T | T | T | | T | T | T | T | T | T | C | C/T | C/T | |
| 09-086008489-M | rs3673117 | C | A | | C | C | C | C | C | C | C | C | C | C | C | C | C | A | C/A | C/A | |
| 09-110057634-M | rs3685576 | G | A | | G | G | G | G | G | G | G | G | G | G | G | G | G | A | G/A | G/A | |
| 10-010187387-M | rs3663269 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | C/T | C/T | |
| 10-030424407-G | rs13480569 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | G/A | G/A | |
| 10-070466216-N | rs3023942 | G | A | | G | G | G | G | G | G | G | G | G | G | G | G | G | A | G/A | G/A | |
| 10-086817590-G | rs13480688 | T | A | | T | T | T | T | T | T | T | T | T | T | T | T | T | A | A/T | A/T | |
| 10-108166251-G | rs6243755 | T | C | | T | T | T | T | T | T | T | T | T | T | T | T | T | C | T/C | T/C | |
| 10-128874353-N | rs3676330 | T | A | | T | T | T | T | T | T | T | T | T | T | T | T | T | A | A/T | A/T | |
| 11-005661856-N | rs4222040 | A | T | | A | A | A | A | A | A | A | A | A | A | A | A | A | T | A/T | A/T | |
| 11-024515722-M | rs3673413 | A | G | | A | A | | A | A | A | A | A | A | A | A | A | A | G | A/G | A/G | |
| 11-044333996-M | rs3691185 | G | A | | G | G | G | G | G | G | G | G | G | G | G | G | G | A | G/A | G/A | |
| 11-066278669-N | rs3023267 | A | T | | A | A | A | A | A | A | A | A | A | A | A | A | A | T | T/A | T/A | |
| 11-080480306-M | rs3700839 | T | G | | T | T | T | T | T | T | T | T | T | T | T | T | T | G | G/T | G/T | |
| 11-102928307-N | rs4229101 | A | G | | A | A | A | A | A | A | A | A | A | A | A | A | A | G | A/G | A/G | |
| 12-011234798-M | rs4140017 | G | A | | G | G | G | G | G | G | G | G | G | G | G | G | G | A | G/A | G/A | |

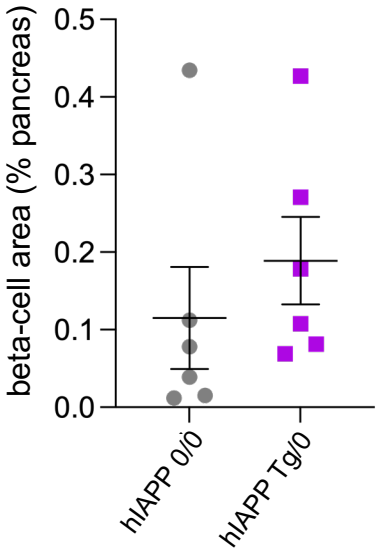



ESM Figure 2. Congenicity of NOD.hIAPP Tg/0 strain.

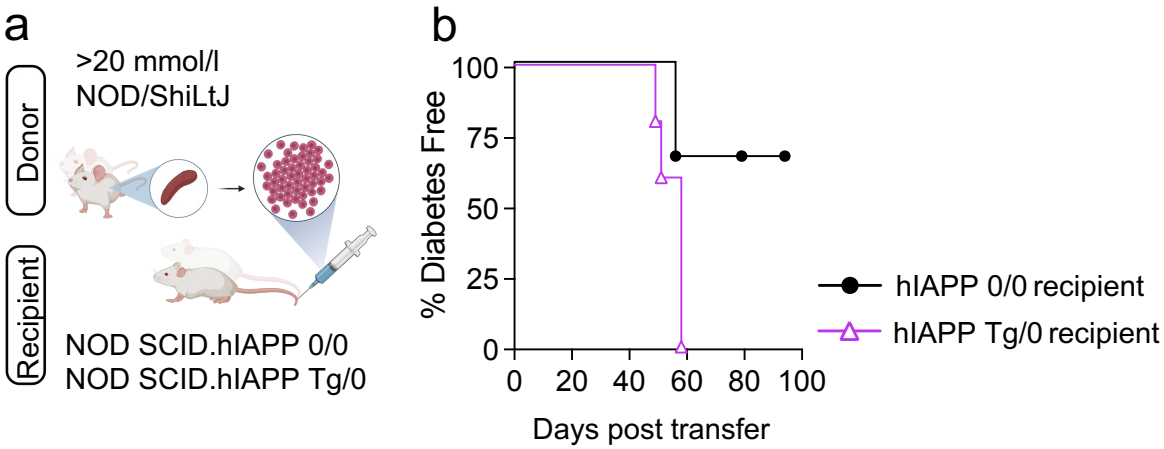
Single nucleotide polymorphism (SNP) analysis of extracted DNA from ear notches of hIAPP Tg/0 and hIAPP 0/0 female littermates following >10 back-crosses from FVB/N-Tg(Ins2-IAPP)RHFSoel/J donor strain to NOD/ShiLtJ background. Expected NOD SNPs are in green, FVB/NJ SNPs are in beige, and heterozygous SNPs are in yellow. Note that all mice are >99% NOD with the only heterozygous SNP remaining at the hIAPP transgene insertion locus on chromosome 15 of hIAPP Tg/0 mice. SNP analysis was performed by Jackson Laboratories.




**ESM Fig. 3. NOD.hIAPP Tg/0 male mice have the expected islet amyloid-induced beta cell phenotype.** (**a-h**) Data from male control (black, solid square) and hIAPP Tg/0 (blue, open square) transgenic mice on a NOD/ShiLtJ background. (**a**) Overview of hIAPP *transgenic* NOD/ShiLtJ animal model breeding strategy (Created with BioRender.com). hIAPP Tg/0 mice were fully backcrossed from an FVB/NJ background to a NOD ShiLtJ background (> 10 backcrosses). (**b**) Diabetes incidence of male NOD.hIAPP Tg/0 (n= 16) and NOD.hIAPP 0/0 control (n=12) mice. Data were analyzed via a logrank test. (**c**) Glucose tolerance (dose, i.p.) of 12-week-old male NOD.hIAPP Tg/0 (n= 12) and control NOD.hIAPP 0/0 (n=10) mice. Data were analysed using a repeated measures mixed effects analysis. Individual incremental AUC (iAUC) from experimental and control mice were analysed with the unpaired t-test. (**d**) Body weights at 12-week-old hIAPP Tg/0 (n= 12) and hIAPP 0/0 (n=10) mice. Data were analyzed using the Mann-Whitney test. (**e**) *In vivo* glucose-stimulated (1 g/kg, i.p.) plasma insulin levels from 12-week-old hIAPP Tg/0 (n= 10) and hIAPP 0/0 control (n=9) mice. Data were analyzed using a repeated measures mixed effects analysis. (**f**) In vitro glucose-stimulated insulin secretion (GSIS) from islets isolated from 12-week-old hIAPP Tg/0 (n= 6) and control hIAPP 0/0 (n=5) mice. Data were analyzed using a mixed effects analysis. (**g**) Insulin content from islets isolated from 12-week-old hIAPP Tg/0 (n= 6) and control hIAPP 0/0 (n=5) mice. (**h**) *In vitro* GSIS data normalized to insulin content from islets isolated hIAPP Tg/0 (n= 6) and control hIAPP 0/0 (n=5) mice. Data are shown as mean ± SD. $p < 0.05$ (*), $p < 0.01$ (**),$p < 0.001$ (***). (**a**) *Created in BioRender. Skovsoe, S. (2025) https://BioRender.com/ e34p682*




**ESM Fig. 4. Beta cell area in young female NOD mice.** Beta cell area as a percent of total pancreas area in 8 week old female NOD mice. Data are presented as mean ±SE, n=6 per group.




**ESM Fig. 5. hIAPP Tg/0 islets do not evade autoimmune destruction.** (**a**) Schematic overview of adoptive transfer of splenocytes from diabetic NOD donor mice into NOD SCID.hIAPP 0/0 or NOD SCID.hIAPP T/0 recipient mice (*Created in BioRender. Skovsoe, S. (2025) https://BioRender.com/u36v131*). (**b**)Diabetes incidence curve of NOD SCID.hIAPP 0/0 (black solid circles, n=3) or NOD SCID.hIAPP T/0 (pink open triangle, n=5) recipient mice that have received splenocytes from diabetic NOD donor mice. Data were analyzed via logrank test.