A37 (P52) | A type 2 diabetes polygenic risk score enhances prediction of incident diabetes compared to QDiabetes alone in British Pakistani and Bangladeshis: Results from the Genes and Health study

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Aims: To assess the utility of a polygenic risk score (PRS) in clinical risk prediction of type 2 diabetes in British Pakistani and Bangladeshi (BPB) individuals in a population disproportionately affected by the condition but underrepresented in research.
Methods: Genes & Health is a large (49,000 volunteers) population-based study of BPB, comprising linked genetic data and electronic medical records. A type 2 diabetes PRS using the largest multi-ancestry genome-wide association study available was constructed. The PRS was combined with a clinical risk instrument (QDiabetes) to create a novel integrated risk tool (IRT). IRT performance was compared to QDiabetes alone in 10-year prediction of incident diabetes in 13,468 individuals free from type 2 diabetes at study onset. In 302 women with a history of gestational diabetes (GDM), the association between PRS and progression to type 2 diabetes (n = 127/302) was assessed using adjusted Cox proportional hazard models.
Results: The PRS had an odds ratio per standard deviation of 1.57 (95% CI 1.50-165) and was not correlated with QDiabetes score ($R^2 = 0.03$). 10-year prediction of incident diabetes was improved by IRT versus QDiabetes alone (net reclassification index = 3.2%, 95% CI 2.0 – 4.4%). IRT enhanced prediction most in low-risk individuals aged under 40 years, who tended to be slim and healthy. PRS was also independently associated with progression from GDM to type 2 diabetes (hazard ratio per standard deviation 1.23, 95% CI 1.05 – 1.42).
Conclusions: In BPB individuals, a PRS enhances prediction of incident type 2 diabetes, particularly in the young.
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A38 (P65) D | Connexin-43 hemichannel mediated ATP release stimulates fibroblast activation in an *in vitro* model of diabetic kidney disease

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Aims: Tubulointerstitial fibrosis is the underlying pathology of diabetic nephropathy and develops in response to aberrant activation of multiple cell types within and around the proximal tubule of the kidney, including extracellular matrix (ECM) producing fibroblasts. Whilst we previously reported a role for connexin-43 (Cx43) hemichannel activity in tubule inflammation, the function and extent to which fibroblast hemichannels contribute to this damage, remains to be determined.
Methods: Human kidney fibroblasts (TK173) were cultured in the glucose-evoked cytokine transforming growth factor-beta1 (TGFb1) ± Cx43 hemichannel blocker Tonabersat, for 48hrs. Immunoblotting determined protein expression, whilst carboxyfluorescein dye uptake and an ATP lite assay assessed hemichannel-mediated ATP release.
Results: TGFb1 significantly increased hemichannel-mediated dye uptake by 73.6±3.9%, ($P < 0.001$, n = 4) in TK173 cells compared to control, an effect reduced when co-incubated with Tonabersat ($P < 0.01$, n = 4). The profibrotic cytokine TGFb1 increased ATP release by 92.8±13.9%, with Tonabersat decreasing ATP release by 90.8±25.8% ($P < 0.05$, n = 4). Immunoblotting determined that TGFb1 increased expression of the ECM proteins, fibronectin (330.8±16.4%, $P < 0.001$, n = 5) and collagen I (42.9±4.6%, $P < 0.001$, n = 5), and the principal Wnt signalling mediator b-catenin (91.8±6.6%, $P < 0.001$, n = 5) compared to control. Tonabersat restored expression of fibronectin, collagen I and b-catenin by 98±29.6%, ($P < 0.01$, n = 5), 20±6.8%, ($P < 0.05$, n = 5), and 56.9±26.7%, ($P < 0.05$, n = 5) respectively.
Conclusion: These data suggest that glucose-evoked changes in TGFb1, increase hemichannel-mediated ATP release and downstream expression of fibrotic candidates in human renal fibroblasts. The study indicates that Cx43

hemichannels may represent a future therapeutic target for alleviating tubulointerstitial fibrosis in people with diabetic kidney disease.

A39 (P12) | Exploring the distribution of endocrine tissue in human pancreas using state-of-the-art Artificial Intelligence (AI) imaging software

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Aim: The distribution of endocrine cells across the human pancreas can be difficult to assess using traditional methods due to potential sampling bias. In this study, state-of-the-art AI imaging software was used to analyse multiple samples from across the organ to provide a picture of normal pancreatic morphology.
Methods: Endocrine cell area, islet size and density (per unit of tissue area) were examined for 24 deceased donor pancreases from individuals without diabetes from the MRC Quality in Organ Donation (QUOD) biobank. Each organ was sectioned into eight regions to provide samples from along its length, as well as from the anterior and posterior aspects. In total, 384 sections were analysed, including more than 87,000 islets.
Results: The endocrine cell area was highest in the tail of the pancreas being approximately twice that found in the head region (median values: 4.43 vs 2.46 %, $p < 0.0001$). The endocrine cell area of the body was further reduced from that found in the head (1.65 %, $p = 0.03$). Along its length, the anterior aspect of the pancreas contained less endocrine tissue than the equivalent posterior regions (2.39 vs 2.68 %, $p = 0.04$). Islet density was highest in the tail region (4.81 islets/mm^2, $p = 0.03$ vs head) and greater in the head than the body (3.70 vs 2.58 islets/mm^2, $p = 0.03$).
Conclusions: The variable distribution of endocrine tissue throughout the pancreas demonstrates the importance of systematically sampling and assessing all anatomical regions for accurate interpretation. The AI pipeline developed in this study enables rapid and robust quantitative tissue analysis.

A40 (P16) | Spatiotemporal landscape analysis of developing human fetal pancreas reveals the role of non-endocrine cells in beta cell specification

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Aims: We sought to identify human pancreas developmental trajectories which will provide essential information for generating functional beta cells from stem cells for transplantation therapy of type 1 diabetes.
Methods: Human fetal pancreases at multiple developmental time points were processed by single-cell RNA sequencing (scRNAseq) and spatial transcriptomics to profile differentiation transitions occurring in temporal and spatial contexts.
Results: scRNAseq of 27,227 cells from 12 pancreases spanning 7 developmental timepoints (12-20 weeks post-conception) revealed distinct clusters of acinar, ductal, endocrine progenitors, alpha, beta, delta, immune, endothelial, Schwann and mesenchymal cells. Spatial transcriptomics of 8 pancreas sections at 12,15,18 and 20 gestational weeks covering 10,386 barcoded spots revealed distinct anatomical regions with spatially correlated genes. Cell trajectory inference identified three endocrine progenitor populations and novel branch-specific genes as the endocrine progenitors differentiate towards alpha, beta or delta cells, indicating that transcriptional maturation occurred over this developmental timeframe. By integrating scRNAseq with spatial transcriptomics, we showed that mesenchymal cells undergo transition in the presence of immune cells to form acinar cells, with upregulation of CTRB2, SYCN, CEL and CPA1 ($p < 2.8\text{x}10\text{e-}4$) and downregulation of COL3A1, EEF1A1, SNX3, COL1A2, RPL9 ($p < 3.9\ \text{x}10\text{e-}5$). Spatial differentiation trajectories *in situ* indicated that Schwann precursor cells are spatially co-located with endocrine progenitors and contribute to beta cell maturation via the L1CAM-EPHB2 pathway.
Conclusion: We have characterised and spatially resolved multiple human pancreatic cell populations at different developmental stages. Our data identified the roles of mesenchymal and Schwann precursor cells in the differentiation of acinar and endocrine progenitors respectively.