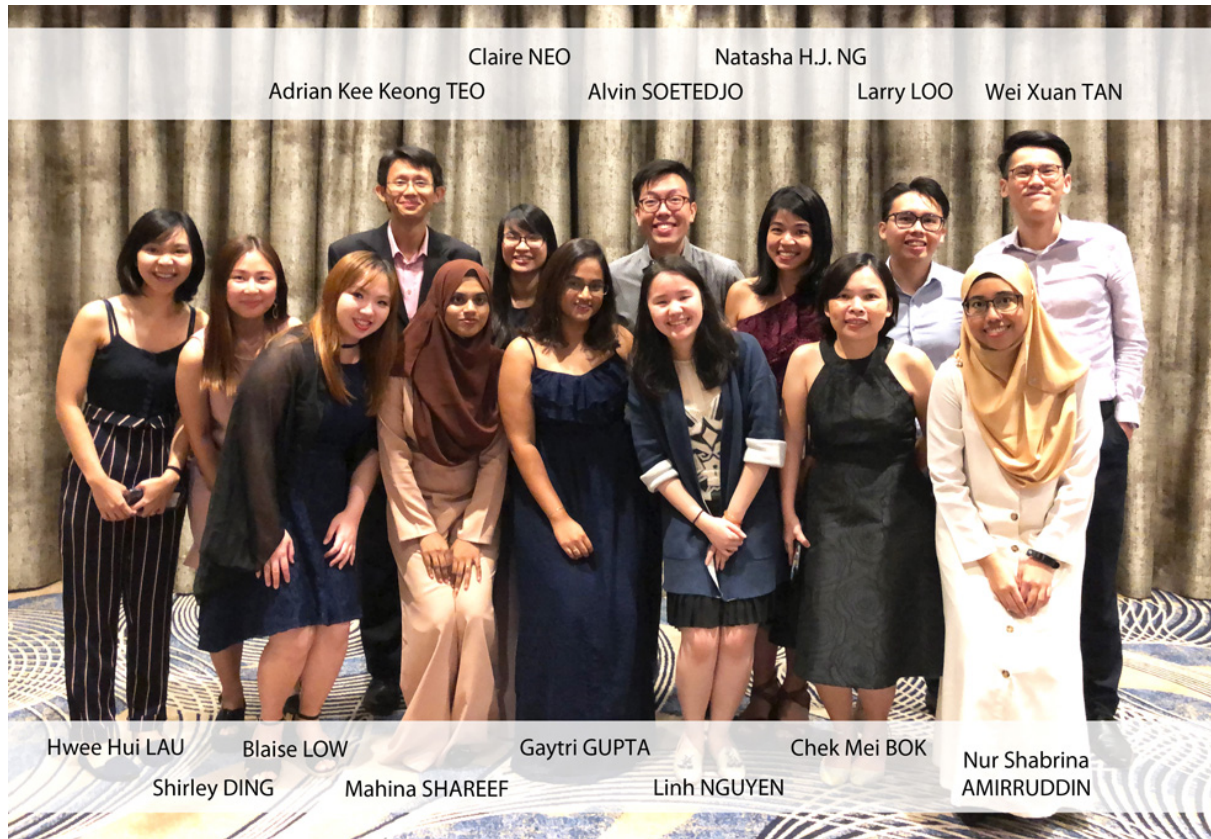


## HNF4A haploinsufficiency in MODY1 abrogates liver and pancreas differentiation from patient-derived iPSCs

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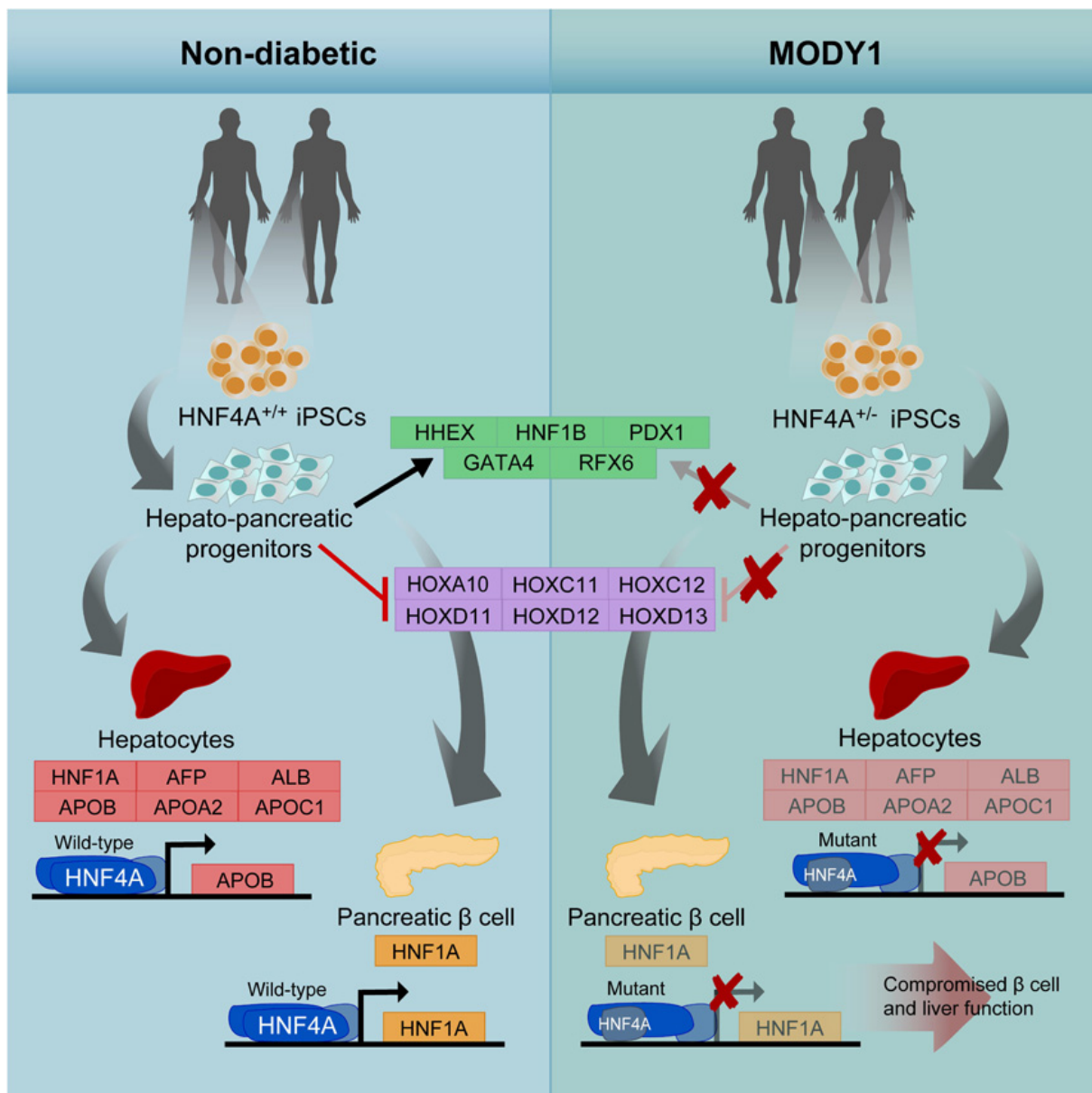
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## Abstract

Maturity onset diabetes of the young 1 (MODY1) is a monogenic diabetes condition caused by heterozygous HNF4A mutations. We investigate how HNF4A haploinsufficiency from a MODY1/HNF4A mutation influences the development of foregut-derived liver and pancreatic cells through differentiation of human induced pluripotent stem cells (hiPSCs) from a MODY1 family down the foregut lineage. In MODY1-derived hepato-pancreatic progenitors, which expressed reduced HNF4A levels and mis-localized HNF4A, foregut genes were downregulated whereas hindgut-specifying HOX genes were upregulated. MODY1-derived hepatocyte-like cells were found to exhibit altered morphology. Hepatic and  $\beta$  cell gene signatures were also perturbed in MODY1-derived hepatocyte-like and  $\beta$ -like cells respectively. As mutant HNF4A (p.Ile271fs) did not undergo complete nonsense-mediated decay or exert dominant negativity, HNF4A-mediated loss-of-function is likely due to impaired transcriptional activation of target genes. Our results suggest that in MODY1, liver and pancreas development is perturbed early on, contributing to altered hepatic proteins and  $\beta$  cell defects in patients.

Figure



**Figure legend:** Human induced pluripotent stem cells (hiPSCs) were reprogrammed from skin fibroblasts obtained from MODY1 patients and family controls. The hiPSCs were differentiated down the foregut endoderm lineage into hepato-pancreatic progenitors (HPPs), hepatocytes and pancreatic  $\beta$  cells using directed differentiation protocols. Foregut markers, hepatic and pancreatic genes were shown to be downregulated in MODY1-HPPs, whereas hindgut HOX genes were found to be upregulated. The MODY1-causing HNF4A mutation (p.Ile271fs) resulted in loss of activation of target genes in both hepatic and pancreatic  $\beta$  cells.