

P033 A potential role for *HNF4A* P1 transcripts in the development of normal beta-cell function?

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The *HNF4A* gene produces nine isoforms (*HNF4A1* to *HNF4A9*) from two promoters P1 and P2. Their spatial and temporal expression and their role in maintaining normal insulin secretion is currently unclear.

We determined the expression patterns of *HNF4A* P1 and P2 transcripts in adult and fetal pancreas by isoform-specific real-time PCR. We then investigated the impact of mutations affecting different subsets of isoforms on diabetes phenotype by correlating the age at diagnosis with mutation position, relative to isoform structure, in 164 patients with *HNF4A*-MODY.

In adult pancreas, only isoforms from the P2 promoter (*HNF4A7*, *HNF4A8* and *HNF4A9*) were detected. In fetal pancreas, transcripts from both the P1 promoter (*HNF4A1*-*HNF4A3*) and the P2 promoter (*HNF4A7*-*HNF4A9*) were identified, at 23% and 77% of total *HNF4A* expression respectively. The position of the mutation relative to the isomer structure altered the age of diagnosis.

Mutations in exons 2 to 8, which affect all 9 isoforms, caused diabetes at 24 years (median). Mutations in the P2 promoter or exon 1D affecting only P2 isoforms caused diabetes at 34 years ($p=0.005$). We conclude *HNF4A* P1 isoforms are expressed in the fetal, but not the adult pancreas, and may play a role in the development of normal beta cell function.