# ORIGINAL ARTICLES

## Obesity and hyperinsulinemia in a family with pancreatic agenesis and MODY caused by the *IPF1* mutation Pro63fsX60

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**We studied the genetic and clinical features of diabetic subjects in a 5-generation Michigan–Kentucky pedigree ascertained through a proband with pancreatic agenesis and homozygous for the *IPF1* mutation Pro63fsx60. Diabetic and nondiabetic family members were genotyped and phenotyped. We also carried out genetic studies to determine the history of the *IPF1* mutation in the Michigan–Kentucky family and a Virginia family with the same mutation. We identified 110 individuals; 34 are currently being treated for diabetes and 10 of these are Pro63fsX60 carriers (ie, MODY4). Subjects with MODY as well as those with type 2 diabetes are characterized by obesity and hyperinsulinemia. Genetic studies suggest that the *IPF1* mutation was inherited from an ancestor common to both the Michigan–Kentucky and Virginia families. MODY4 and type 2 diabetes in the Michigan–Kentucky pedigree are associated with obesity and hyperinsulinemia. Obesity and hyperinsulinemia have been observed occasionally in other subtypes of MODY, which suggests that hyperinsulinemia may be a general phenomenon when obesity occurs in MODY subjects. Hypoinsulinemia in nonobese MODY subjects seems to be caused by a functional defect in the beta cell. Genetic testing should be considered in multigenerational obese diabetic subjects, particularly when such families contain young diabetic members. (Translational Research 2010;156:7–14)**

**Abbreviations:** BMI = body mass index; Hb = hemoglobin; HbA1c = hemoglobin A1c; HNF = hepatocyte nuclear factor; IBD = identity by descent; *IPF1* = insulin promoter factor-1; MODY = maturity-onset diabetes of the young; PCR = polymerase chain reaction; SNP = single nucleotide polymorphism

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## AT A GLANCE COMMENTARY

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### Background

The *IPF1* gene is a transcription factor that plays a critical role in pancreatic and beta-cell development and function. Heterozygous mutations of this gene lead to a mild form of diabetes (maturity-onset diabetes of the young [MODY4]), and when homozygous to permanent neonatal diabetes caused by pancreatic agenesis.

### Translational Significance

We genotyped and phenotyped diabetic and nondiabetic members of a 5-generation family, some of whom carry an *IPF1* mutation and others seem to have type 2 diabetes. In contrast to most MODY diabetic subjects who are nonobese and hypoinsulinemic, the MODY4 members of this family are obese and hyperinsulinemic. Hypoinsulinemia in nonobese MODY subjects seems to be caused by a functional defect in the beta cells.

Maturity-onset diabetes of the young (MODY) is a heterogeneous group of disorders characterized by diabetes mellitus, an autosomal dominant mode of inheritance, diagnosis usually before the age of 25 years and frequently in childhood or adolescence, and a primary defect in beta-cell function. In contrast to subjects with type 2 diabetes, obesity occurs infrequently in MODY subjects.[1] MODY can result from mutations in any 1 of at least 8 different genes, as follows: glucokinase (MODY2),[2,3] hepatocyte nuclear factor (HNF)-4$\alpha$ (MODY1),[4] HNF-1$\alpha$ (MODY3),[5] insulin promoter factor-1 (*IPF1*, MODY4),[6,7] HNF-1$\beta$ (MODY5),[8] neurogenic differentiation factor 1 (MODY6),[9] carboxylester lipase (MODY7),[10] and insulin (MODY8).[11]

MODY4 is a rare form of MODY that results from mutations in *IPF1*, which is a transcription factor that plays a critical role in pancreatic and beta-cell development and function.[12,13] The largest and best described MODY4 family is a 5-generation pedigree with the *IPF1* mutation Pro63fsdelC (Pro63fsX60; c.188delC).[6,7] This Virginia family was ascertained through a female infant with permanent neonatal diabetes and severe exocrine pancreatic insufficiency caused by pancreatic agenesis.[6,7,14] The infant was homozygous for the mutation Pro63fsX60.[6,7] The parents were heterozygous carriers. The father had diabetes, whereas the mother did not. A consanguineous loop was observed in generation I that linked the 2 families.[6,7] Eight diabetic members were heterozygous carriers. Nonobese diabetic carriers in this pedigree had a greatly decreased insulin response to glucose.[15] A second subject with permanent neonatal diabetes, exocrine pancreatic insufficiency, and pancreatic agenesis was described in Switzerland.[16] This subject was a compound heterozygote, with *IPF1*, Glu164Asp, and Glu178Lys. The infant's mother carried the Glu164Asp mutation and the father carried the Glu178Lys mutation. Both parents had normal oral glucose tolerance tests but were noted to have high normal fasting plasma glucose levels (101 and 102 mg/dL, respectively). The mother had a history of gestational diabetes. There was a 2-generation family history of diabetes in each parent. The studies, to date, of heterozygous carriers of *IPF1* mutations suggest that MODY4 is a relatively mild disorder of glucose intolerance characterized by diminished insulin secretion.

Recently, we described a third case of permanent neonatal diabetes, exocrine pancreatic insufficiency, and pancreatic agenesis caused by an *IPF1* mutation.[17] Interestingly, this infant was homozygous for the same mutation (Pro63fsX60) as the first case from Virginia described previously.[6,7] Presentation of this infant initiated a study of the second extended 5-generation pedigree (Michigan–Kentucky; R-T); this pedigree has permanent neonatal diabetes, obese MODY4, and obese type 2 diabetes.

## METHODS

**Proband and family.** The details of the presentation, diagnosis, treatment, and course of the male proband with permanent neonatal diabetes, exocrine pancreatic insufficiency, and pancreatic agenesis have been presented.[17] Genetic testing showed that he was homozygous for the *IPF1* mutation Pro63fsX60.

The families of the proband's father and mother came to Michigan independently from the same town in eastern Kentucky in the early 1980s. The families were not known to be related. Other family members remain in Kentucky. Most of those who came to Michigan have subsequently moved to Florida, Kentucky, and Tennessee. We constructed a 5-generation pedigree through interviews. The Michigan–Kentucky pedigree includes 110 individuals and 34 diabetic subjects (Fig 1 and Fig 2). Subjects II-8 and II-9 were reported to be third cousins and subsequent consanguinity is possible as both families came from the same town. The surnames of members of the Michigan–Kentucky pedigree were different from those of the Virginia pedigree with the same *IPF1* mutation (W.L. Clarke, personal communication). This study was approved by the University of Michigan Medical Center Institutional Review Board. All subjects or their parents provided written informed consent. The research was carried out according to the principles of the Declarations of Helsinki.