Brief Genetics Report

Frameshift Mutation, A263fsinsGG, in the Hepatocyte Nuclear Factor-1β Gene Associated With Diabetes and Renal Dysfunction

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Recent studies have revealed mutations in the gene encoding the transcription factor hepatocyte nuclear factor (HNF)-1α to be the cause of one form of maturity-onset diabetes of the young (MODY), a monogenic form of diabetes (1–6). HNF-1α functions as a homodimer or a heterodimer with the structurally related HNF-1β (7–9), both of which are expressed in pancreatic islets, suggesting that they function together in this tissue to regulate gene expression. In this context, the HNF-1β gene was screened for mutations in families with MODY, and a nonsense mutation R177X was identified in one family (10). To gain a better understanding of HNF-1β diabetes, including the prevalence and phenotypic features, we screened the HNF-1β gene for mutations in Japanese subjects with early-onset type 2 diabetes.

A group of 40 subjects residing in Gunma prefecture who had presented with type 2 diabetes before 35 years of age and had a first-degree relative with diabetes were studied. Diabetes was diagnosed by a 75-g or 1.75-g/kg oral glucose tolerance test. Of these, 12 subjects were being treated with diet and exercise, 3 with oral hypoglycemic agents, and 25 with insulin; none were obese (BMI 20.3 ± 3.1 kg/m^2). The nine exons and flanking introns of the HNF-1β gene of the subjects were screened for mutations by direct sequencing of the amplified polymerase chain reaction products using specific primers (2) and an ABI PRISM dRhodamine terminator cycle sequencing kit (Perkin-Elmer, Foster City, CA). The sequencing reactions were analyzed using an Applied Biosystems DNA sequencer (models 373S and 377; ABI, Foster City, CA).

There was insertion of a GG dinucleotide in exon 3 of the codon for Ala263, designated A263fsinsGG, in one subject who had been diagnosed with diabetes at 19 years of age (BMI 18.3 kg/m^2) (Fig. 1*A*). This mutation causes a frameshift and the generation of a mutant truncated protein of 264 amino acids that lacks the transcription activation domain. Screening other family members showed that the mutation was also present in the proband's sister (IV-3), who had been diagnosed with glycosuria at 14 years of age during the course of an annual school physical examination. The mutation was also found in the proband's father (III-2), who had been diagnosed with diabetes at 61 years of age. The two affected sisters (IV-2 and IV-3) are currently being treated with 10–20 U of insulin, and their father with diet. Medical records indicate that the paternal grandmother (II-2) had early-onset diabetes, and so also may have inherited the mutation.

The frequency of HNF-1β gene mutations in our study population of Japanese subjects who have early-onset type 2 diabetes with a first-degree relative with diabetes is 2.5%. Together with the previous observation by Horikawa et al. (10), our results indicate that mutations in the HNF-1β gene are not a major cause of early-onset type 2 diabetes in Japanese, although the results apply only to the coding region of the HNF-1β gene.

The proband and her sister had decreased renal function (creatinine clearance <50 ml/min) and multiple bilateral renal cysts with three to five cysts per kidney (0.3–1.2 cm in diameter) (Fig. 1*B*). Their father also had chronic renal failure with renal cysts, which is now being treated by hemodialysis. While the two affected sisters showed no evidence of proteinuria, the father had persistent mild proteinuria (<300 mg/day), which was first noticed during the course of an annual health examination 20 years before the diagnosis of diabetes. The A263fsinsGG mutation was also found in the nondiabetic 2-year-old son (V-1) of the proband and the 5-year-old daughter (V-2) of the affected sister, who also had elevated levels of serum creatinine (1.3–1.8 mg/dl; normal 0.6–1.0 mg/dl) at birth. Moreover, subject V-1 was found at birth to have bilateral renal cysts measuring several millimeters in diameter, and fetal ultrasound examination at 27 weeks of gestation revealed renal abnormalities, including bilateral enlarged kidney mass and multiple parenchymal hyperechoic nodules (Fig. 1*B*).

These observations suggest that the A263fsinsGG mutation in the HNF-1β gene might be associated with diabetes and renal dysfunction in this family. Renal dysfunction described in this report is defined broadly, including proteinuria, decreased renal function, and renal cysts. Moreover, these abnormalities appear to precede the onset of dia-

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HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of the young.

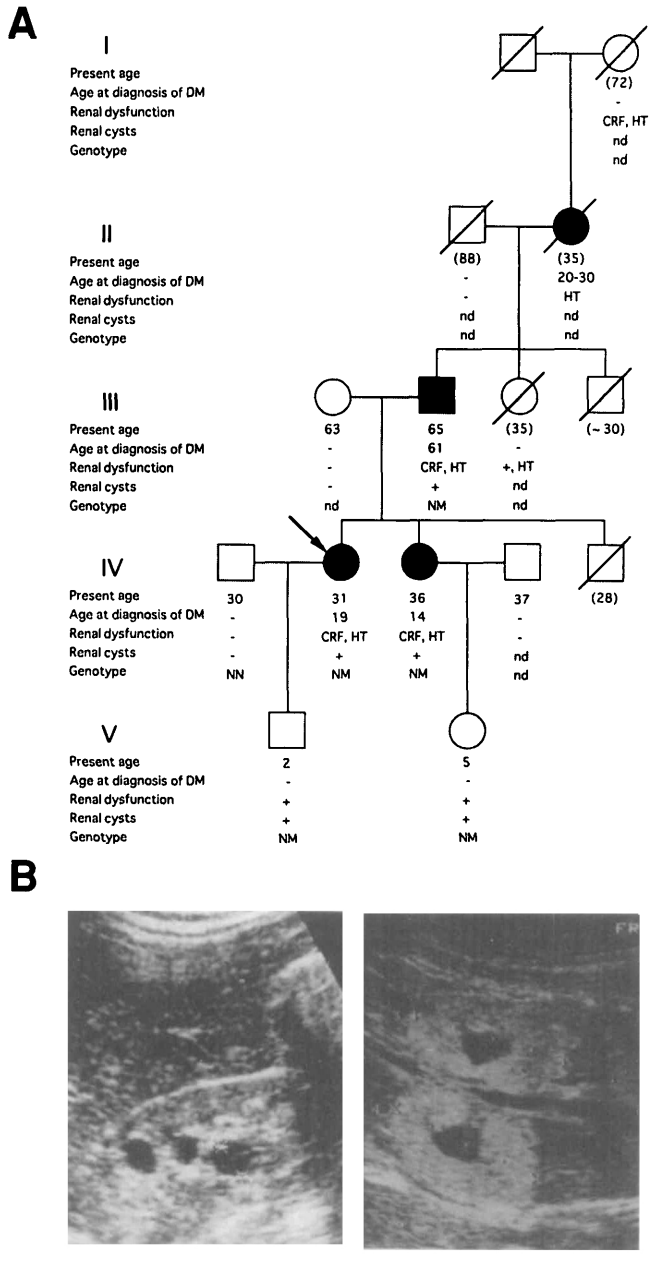

FIG. 1. *A:* **Pedigree of a Japanese family with the A263fsinsGG mutation in the HNF-1β gene. Subjects with diabetes (DM) are noted by filled symbols. The proband (IV-2) is indicated by the arrow. The genotype of each subject is indicated below the symbol: N, normal allele; M, A263fsinsGG allele; nd, not determined. The subject's present age (years) and age at diagnosis of diabetes (years) are indicated, as is the nature of the renal dysfunction. The paternal great-grandmother (I-2) died of renal failure and apoplexy at 70 years of age; it is unknown whether she also had diabetes. The paternal aunt (III-3), who was not known to be diabetic, had pregnancy-induced hypertension and died of renal failure at 30 years of age. The proband and her sister also had pregnancy-induced mild hypertension (systolic pressure 140–160 mmHg). Retinopathy of Scott I is observed only in subject IV-3. CRF, chronic renal failure/decreased renal function; HT, hypertension/pregnancy-induced hypertension.** *B:* **Renal ultrasonography. Cysts in the right kidney in subject IV-2 are shown in the left panel. Similar cysts were observed in both kidneys in subjects III-2 and IV-3. Renal ultrasonography at 27 weeks of gestation in subject V-1 is shown in the right panel. The imaging shows that both kidneys are diffusely enlarged (longitudinal length 5.3 cm in the right panel, normal length at 27 weeks gestation 1.6–3.8 cm) and contain multiple parenchymal hyperechoic nodules. Similar parenchymal hyperechoic nodules that suggest the presence of tiny cysts were also observed in subject V-2. Renal cysts were not observed in nondiabetic subjects III-1 and IV-1.**

betes. Interestingly, renal dysfunction of unknown origin was also a feature of the HNF-1β–related diabetic family studied by Horikawa et al. (10). Since HNF-1β transcripts can be detected in mesoderm-derived cells differentiating into the polarized epithelium during organogenesis of rat kidney (11), the renal abnormalities found in the affected subjects might arise at the earliest stages of renal development.

The present study suggests that mutations in the HNF-1β gene might be associated with diabetes and renal dysfunction, and subjects presenting with these features, especially those who have early-onset renal dysfunction with subsequent development of diabetes, should be screened for mutations in this gene.

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