

# Clinical Spectrum Associated with Hepatocyte Nuclear Factor-1 $\beta$ Mutations

Christine Bellanné-Chantelot, PharmD, PhD; Dominique Chauveau, MD; Jean-François Gautier, MD, PhD; Danièle Dubois-Laforgue, MD, PhD; Séverine Clauin; Sandrine Beaufils; Jean-Marie Wilhelm, MD; Christian Boitard, MD; Laure-Hélène Noël, MD; Gilberto Velho, MD, PhD; and José Timsit, MD

**Background:** Maturity-onset diabetes of the young type 5 (MODY5), a type of dominantly inherited diabetes mellitus and nephropathy, has been associated with mutations of the hepatocyte nuclear factor-1 $\beta$  (*HNF-1 $\beta$* ) gene, mostly generating truncated protein. Various phenotypes, including urogenital malformations, are related to *HNF-1 $\beta$*  mutations.

**Objective:** To describe clinical and genetic findings in 13 patients with 8 novel *HNF-1 $\beta$*  mutations.

**Design:** Multicenter, descriptive study.

**Setting:** 2 departments of diabetes, 1 department of internal medicine, and 1 department of nephrology.

**Participants:** 8 probands with diabetes diagnosed before 40 years of age and nondiabetic kidney disease who were selected independent of their family history of diabetes, and 5 offspring.

**Measurements:** Characteristics of diabetes, renal function and structure, genital tract abnormalities, pancreas structure, insulin secretion, exocrine pancreas function, and liver test results.

**Results:** All mutations, including 5 missense changes, were found in the DNA-binding domain. Cosegregation of the mutation and MODY5 phenotype was observed in 4 families. Occurrence of

a de novo mutation was demonstrated in 2 families. Diabetes was present in 10 of 13 mutation carriers. It was clinically overt in 5 participants and found by screening at age 19 to 38 years in 5 participants. Pancreas atrophy was observed in 5 of 6 probands, and pancreas exocrine insufficiency was observed in 6 of 7 probands. Renal involvement, consisting of structural changes and slowly progressive renal failure, was recognized in 9 patients at 18 to 41 years of age. Dysplastic kidneys were found by ultrasonography in 3 fetuses who subsequently showed transient neonatal renal failure. Genital tract abnormalities were present in 5 probands and liver enzyme levels were abnormal in 11 of 13 patients.

**Limitations:** Since the study was small and not population-based, it could not estimate the prevalence of MODY5. Other phenotypes might be associated with *HNF-1 $\beta$*  mutations.

**Conclusions:** Maturity-onset diabetes of the young type 5 encompasses a wide clinical spectrum. Analysis for mutations of *HNF-1 $\beta$*  is warranted, even without a family history of diabetes, in nonobese patients with diabetes and slowly progressive nondiabetic nephropathy, particularly when pancreatic atrophy or genital abnormalities are present.

*Ann Intern Med.* 2004;140:510-517.

www.annals.org

For author affiliations, see end of text.

The prevalence of diabetes mellitus is estimated to be 6% to 7% in western industrialized countries; type 2 diabetes mellitus accounts for 90% of the cases (1). Maturity-onset diabetes of the young (MODY) is defined by the occurrence, typically before age 25 years, of nonketotic diabetes mellitus due to a primary defect of insulin secretion, along with autosomal dominant inheritance. With the exception of MODY2, which is due to mutations in the glucokinase gene, the identified MODY subtypes are related to mutations of transcription factor genes: hepatocyte nuclear factor-4 $\alpha$  (*HNF-4 $\alpha$* ) for MODY1, *HNF-1 $\alpha$*  for MODY3, insulin promoter factor-1 for MODY4, *HNF-1 $\beta$*  for MODY5, and neurogenic differentiation factor-1 for MODY6. The subtypes of MODY may account for 2% to 5% cases of type 2 diabetes, with types 3 and 2 representing 65% and 15% of these cases, respectively. The other subtypes of MODY are thought to be rare (2).

Maturity-onset diabetes of the young type 5 was initially described in a Japanese family as the association of early-onset diabetes and nephropathy (3). Heterogeneous phenotypes, including diabetes, renal abnormalities, and genital malformations, were subsequently described through isolated case reports in white and Japanese populations (3–16). Currently, all but 2 families (6, 16) with

MODY5 demonstrated autosomal dominant inheritance of private mutations.

In our report, using a standardized evaluation, we describe clinical and genetic findings in 13 patients from 8 unrelated families with novel *HNF-1 $\beta$*  mutations. Detailed phenotypic analysis underlines the systemic spectrum of the disease and its wide variability, leading to different modes of presentation. We also confirm that MODY5 may occur because of de novo mutation in *HNF-1 $\beta$* . These findings may help to define criteria for *HNF-1 $\beta$*  gene testing.

## METHODS

### Patients

Participants were recruited from the patients of 2 departments of diabetes, 1 internal medicine department, and 1 nephrology department, on the basis of the following clinical characteristics: 1) diabetes (fasting plasma glucose level  $\geq$  7.0 mmol/L [126 mg/dL]), suggesting a MODY phenotype if diabetes occurred before 40 years of age, if the patient was not obese (body mass index  $<$  30 kg/m<sup>2</sup>), and the patient did not have islet-cell antibodies and glutamic acid decarboxylase autoantibodies; 2) impaired renal function (creatinine clearance  $<$  1.34 mL/s

[<80 mL/min]) without diabetic retinopathy and albumin excretion greater than 0.5 g/d (17); and 3) kidney structural abnormalities (reduced kidney size, presence of cysts, or both). A family history of diabetes was not a criterion. A total of 20 unrelated white patients were identified from clinic lists and screened for *HNF-1 $\beta$*  mutation: 13 men and 7 women with a mean ( $\pm$ SD) age of  $26 \pm 8$  years, a mean body mass index of  $23.4 \pm 2.7$  kg/m<sup>2</sup> at onset of diabetes, and functional and structural renal abnormalities at presentation. The Ethics Committee of Necker Hospital, Paris, France, approved the study, and all participants gave written informed consent.

### Clinical Evaluation

Clinical history of diabetes mellitus and renal involvement were recorded by using a standardized examination of the patients and their relatives. Creatinine clearance was calculated according to the Cockcroft–Gault formula (18). Imaging studies of the kidneys, consisting of ultrasonography and intravenous urography or computed tomography, and renal biopsy specimens were reviewed by a nephrologist and a renal pathologist. Genital tract abnormalities were assessed by ultrasonography. Endogenous insulin secretion was assessed by measuring C-peptide plasma concentration (Bio-Rad Specific C-Peptide, Bio-Rad, Marne la Coquette, France) before and 6, 10, and 15 minutes after intravenous injection of 1 mg of glucagon (19). Pancreas structure was assessed by computed tomography. Pancreas exocrine function was evaluated by measuring fecal fat excretion and elastase concentration (Schebo-Biotech, Gießen, Germany). Liver biopsy was performed in 3 patients whose liver test results were persistently abnormal.

### Mutation Analysis of the *HNF-1 $\beta$* Gene

Genomic DNA was extracted from peripheral blood samples by standard procedures. The minimal promoter, the coding region of the 9 exons, and exon–intron boundaries of the *HNF-1 $\beta$*  gene were screened for mutations by direct sequencing as previously described (3). Direct diagnosis of the mutations identified in probands was offered to first-degree relatives (parents, siblings, and offspring) regardless of their clinical status.

## RESULTS

### Molecular Analysis

A mutation of *HNF-1 $\beta$*  was found in 8 of the 20 unrelated patients. Among 19 of 35 first-degree relatives from 6 unrelated families tested, 5 of 8 offspring had inherited a mutation. None of the 8 mutations have been reported to date. All are located in the DNA-binding domain (20). Five are point mutations resulting in amino acid substitutions (also called missense mutations) that affect residues conserved in *HNF-1 $\beta$*  human, pig, mouse, rat, xenopus, and salmon sequences. Two other mutations are nonsense mutations resulting in a truncated protein lacking the 3'-part of the DNA-binding domain and the

### Context

Maturity-onset diabetes of the young type 5 (MODY5) is an uncommon variant of a dominantly inherited disease associated with mutations in the hepatocyte nuclear factor-1 $\beta$  (*HNF-1 $\beta$* ) gene. We know little about its spectrum except that it may include urogenital abnormalities.

### Contribution

This multicenter study describes 8 probands with MODY5 and known nondiabetic kidney disease and 5 offspring. Each proband had a different mutation in the *HNF-1 $\beta$*  gene. Probands and offspring had various renal abnormalities, including dysplastic kidneys and renal cysts. Some also had genital tract abnormalities, pancreatic atrophy, and abnormal liver enzyme levels.

### Implications

Maturity-onset diabetes of the young type 5 is genetically and phenotypically heterogeneous.

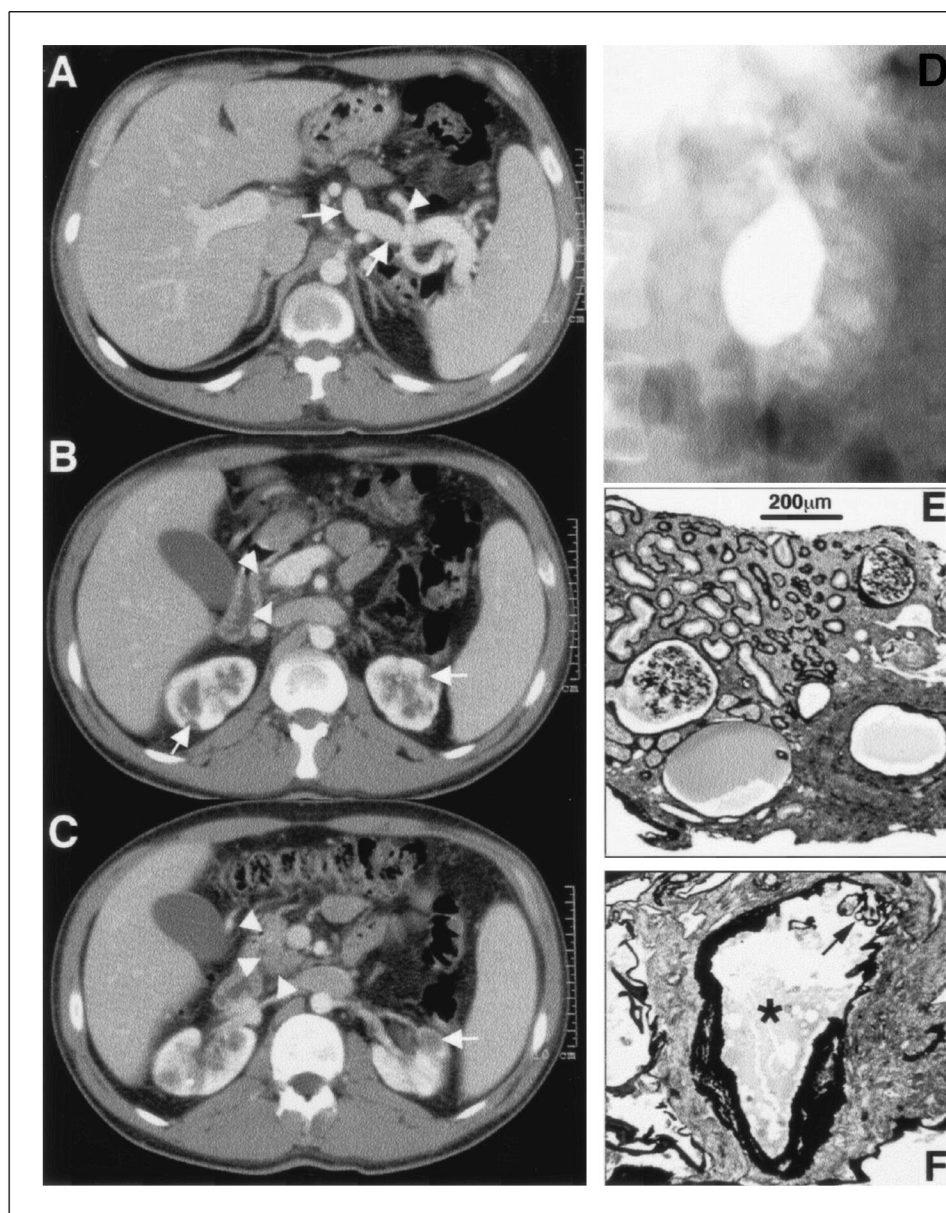
—The Editors

C-terminal transactivation domain. The last mutation is localized in the splice donor site of intron 2 at the highly conserved +1 position. Another base change (G→A) at the same position was described in a Japanese family with MODY5 (8). No nucleotide variant was detected in 212 control chromosomes of unrelated nondiabetic white participants and in 170 chromosomes of patients with classic type 2 diabetes.

In 4 families (families 1, 5, 6, and 8), cosegregation of a *HNF-1 $\beta$*  mutation and MODY5 phenotype was consistent with dominant inheritance because 5 affected offspring inherited the mutation detected in the proband. A de novo mutation was demonstrated in 2 probands (patient II-1, family 6, and patient II-1, family 7). In each case, the proband's parents were not carriers of the mutation. Parental relationships were confirmed by using microsatellite markers (data not shown). Two relatives in family 3 (patients I-2 and II-1) and 2 relatives in family 6 (patients I-1 and I-2) had diabetes mellitus but did not exhibit the corresponding mutation of *HNF-1 $\beta$* .

### Clinical Phenotype

Diabetes was present in all probands and in 2 offspring (patient III-1, family 1, and patient II-1, family 8) with a mutation. Five patients presented with clinical symptoms, including severe metabolic decompensation in 2 patients, at age 1 year (patient II-1, family 8) and 13 (patient II-1, family 6) years, respectively. In the 5 other patients, diabetes was found by routine plasma glucose measurement. Clinical characteristics were consistent with a defect of insulin secretion: All patients were lean at diagnosis, ketosis was observed in 2 patients, and progression of the disease was observed in 3 patients who ultimately required insulin therapy. Endogenous insulin response to intravenous glu-

**Figure.** Pancreas and kidney abnormalities in patients with hepatocyte nuclear factor-1 $\beta$  (*HNF-1 $\beta$* ) mutation.

A, B, and C. Pancreas atrophy and kidney malformations evidenced by computed tomography in a 33-year-old man (patient II-2, family 2) with diabetes and mild renal failure. A. No pancreatic tissue was detected close to the splenic artery (*arrow*) and the splenic vein (*arrowheads*). B and C. The body and tail of the pancreas were not visible on serial axial slices. Only the head of the pancreas (*arrowheads*) was present. Bilateral renal cysts were also detected (*arrows*). D. Excretory urogram in the same patient shows caliceal clubbing and blunting. Some cysts communicate with the dilated calices and may be regarded as diverticula. E and F. Glomerulocystic disease on kidney biopsy specimen in a 24-year-old man (patient II-1, family 7) with diabetes, mild renal failure, and a mutation of *HNF-1 $\beta$* . E. Two microcysts are visible in the renal cortex, close to unaffected glomeruli (Jones staining). F. The presence of capillary loops (*arrow*) in the cyst (\*) demonstrates its glomerular origin (Jones staining; magnification  $\times 4$  as compared with panel E).

cagon, assessed in 7 of the 8 probands, disclosed heterogeneous degrees of impairment, but residual insulin secretion was detectable in all probands. In patient II-1, family 6, endogenous insulin secretion was measurable 22 years after diabetes was revealed by severe ketoacidosis. No patient had diabetic retinopathy or neuropathy. Pancreas atrophy was found in 5 of the 6 patients assessed by abdominal computed tomography (Table 1 and Figure). No pancreas calcification or cyst was noticed. No patient exhibited

symptoms of overt pancreatic exocrine deficiency. However, of the 7 probands tested, 6 had a subclinical defect of pancreas exocrine function (Table 1 and Figure).

Renal involvement was found in all probands (Table 2) and 4 offspring. In the probands, age at recognition of kidney disease ranged from 18 to 41 years. All exhibited structural kidney abnormalities, including decreased kidney size, ranging from 85 to 105 mm in height with global cortical loss, and a cystic pattern (Figure). Pelviccaliceal ab-

**Table 1. Characteristics of Mutations, Diabetes, Pancreas Exocrine Function, and Liver Tests in 8 Probands with Hepatocyte Nuclear Factor-1 $\beta$  Mutations\***

Characteristic	Probands with <i>HNF-1<math>\beta</math></i> Mutations							
	II-1, Family 1	II-2, Family 2	II-2, Family 3	II-1, Family 4	I-1, Family 5	II-1, Family 6	II-1, Family 7	I-1, Family 8
<b>Mutation</b>	R112P	Q136E	K164Q	R165H	R181ter	R182ter	IVS2+1G→T	R295H
<b>Diabetes</b>								
Age at diagnosis, y	38	30	27	20	33	13	19	24
Symptoms at presentation	None	None	Polyuria, no ketosis	None	Polyuria, ketosis	Ketoacidosis	None	Polyuria, no ketosis
BMI at diagnosis, kg/m <sup>2</sup>	23	22.5	22	23.2	26	NA	22.8	25.6
First abnormal fasting plasma glucose level, mmol/L (mg/dL) <sup>†</sup>	6.9 (124)	7.2 (130)	24 (432)	6.5 (118)	20 (360)	65 (1171)	6.9 (124)	22 (396)
Daily insulin requirement, IU/kg	0.75	0.28	0 (diet)	0 (acarbose)	0.25	0.64	0.09	0.44
<b>C-peptide concentration, nmol/L<sup>‡</sup></b>								
Basal	ND	1.10	1.97	0.80	0.09	0.24	0.25	0.29
Stimulated	ND	1.40	1.95	1.30	0.23	0.38	0.52	0.90
<b>Exocrine pancreas evaluation</b>								
Pancreas structure found on CT scan	Diffuse atrophy	Diffuse atrophy	Diffuse atrophy	Atrophy of body	Normal	ND	ND	Diffuse atrophy
Fecal fat excretion, g/d <sup>§</sup>	ND	8.2	3.7	4.7	5.2	5	ND	6
Fecal elastase concentration, mg/g	119	23	88	82	135	396	ND	184
<b>Liver enzyme levels<sup>  </sup></b>								
Aspartate aminotransferase	Normal	Normal	1.3	Normal	Normal	Normal	2.8	Normal
Alanine aminotransferase	Normal	1.7	3.2	2.0	1.3	Normal	6.0	Normal
$\gamma$ -glutamyltranspeptidase	3.0	3.4	4.3	2.0	2.3	Normal	8.8	1.5
<b>Liver biopsy results</b>	ND	Mild cholestasis	Normal	ND	ND	ND	Normal	ND

\* Mutations are described at protein level by the amino acid (for example, R112P denotes that at amino acid 112, arginine [R] is changed to a proline [P]). BMI = body mass index (normal value < 25 kg/m<sup>2</sup>); CT = computed tomography; *HNF-1 $\beta$*  = hepatocyte nuclear factor-1 $\beta$ ; NA = not available; ND = not done.

<sup>†</sup> Normal values, 3.9–5.8 mmol/L (70–104 mg/dL).

<sup>‡</sup> Peak C-peptide plasma concentration measured after intravenous glucagon. Mean ( $\pm$ SD) normal values: basal, 0.74  $\pm$  0.15 nmol/L (2.23  $\pm$  0.45 ng/mL); stimulated, 2.30  $\pm$  0.48 nmol/L (6.95  $\pm$  1.45 ng/mL).

<sup>§</sup> Exocrine pancreas function was assessed by fecal fat excretion (normal value < 6 g/d) and fecal elastase concentration (normal value > 200 mg/g).

<sup>||</sup> Values for liver enzyme levels are given as x times the upper limit of normal range.

normalities were observed in 6 of the 7 patients who were tested and consisted of clubbing or tiny diverticulae of the calices or mild pelvic dilatation without obstructive uropathy (Figure). All probands also had mild to moderate renal failure with creatinine clearance ranging from 0.48 to 1.28 mL/s (29 to 77 mL/min). On follow-up, the mean

annual decrease of creatinine clearance ranged from 0 to 0.03 mL/s (0 to 2 mL/min). It averaged 0.02 mL/s per year (1.1 mL/min per year) in the 4 patients who were followed for 14 to 16 years (Table 2). Since the clinical, biological, and radiologic characteristics of renal disease made the diagnosis of diabetic glomerulopathy very unlikely, a kidney

**Table 2. Renal and Genital Abnormalities in 8 Probands with Hepatocyte Nuclear Factor-1 $\beta$  Mutations\***

Characteristic	Probands with <i>HNF-1<math>\beta</math></i> Mutations							
	II-1, Family 1	II-2, Family 2	II-2, Family 3	II-1, Family 4	I-1, Family 5	II-1, Family 6	II-1, Family 7	I-1, Family 8
<b>Kidney function</b>								
Age at first recorded renal abnormality, y	41	30	36	20	33	18	19	28
Duration of follow-up, y	16	3	2	14	1	14	16	5
Creatinine clearance, mL/s (mL/min)								
Initial	0.67 (40)	0.87 (52)	0.63 (38)	0.48 (29)	1.23 (74)	1.25 (75)	1.28 (77)	1.13 (68)
Follow-up	0.32 (19)	0.87 (52)	0.57 (34)	0.33 (20)	1.12 (67)	1 (60)	0.92 (55)	0.95 (57)
Mean annual decrease	0.022 (1.3)	0	0.03 (2)	0.011 (0.6)	0.11 (7)	0.018 (1.10)	0.023 (1.4)	0.036 (2.2)
Blood pressure at follow-up, mm Hg	120/70	124/72 <sup>†</sup>	111/77	120/65 <sup>†</sup>	120/70	114/80	133/75	115/70 <sup>†</sup>
Urinary albumin excretion, mg/d	180	14	1140	<30	<30	14	22	60
<b>Kidney abnormality<sup>‡</sup></b>	ND	Cortical atrophy, interstitial fibrosis, oligomeganephronia	Enlarged glomeruli, mild interstitial fibrosis	Mild interstitial fibrosis	Enlarged glomeruli, mild interstitial fibrosis	ND	Glomerular cysts, mild interstitial fibrosis	1 glomerular cyst, mild interstitial fibrosis
<b>Genital abnormalities</b>	None	Asthenospermia	Bilateral epididymal cysts	Bicornuate uterus	ND	None	Atresia of vas deferens	Bilateral epididymal cysts

\* *HNF-1 $\beta$*  = hepatocyte nuclear factor-1 $\beta$ ; ND = not done.

<sup>†</sup> While receiving antihypertensive therapy.

<sup>‡</sup> All patients had kidney structural abnormalities consisting of reduced kidney size, presence of cysts, or pelvic/renal abnormalities.

**Table 3. Main Characteristics of 5 Offspring Who Inherited a Mutation of Hepatocyte Nuclear Factor-1 $\beta$** 

Characteristic	Offspring				
	III-1, Family 1	II-1, Family 5	III-2, Family 6	II-1, Family 8	II-2, Family 8
Age at first manifestation, y	34	Fetal life	Fetal life	Fetal life	5
<b>Renal abnormalities</b>					
At diagnosis					
Kidney structure	Right kidney: agenesis Left kidney: pelvicaliceal dilatation	Right kidney: dysplastic, multicystic Left kidney: diffuse hyper-echogenicity	Right kidney: dysplastic, multicystic Left kidney: diffuse hyper-echogenicity	Both kidneys: Diffuse hyper-echogenicity, mild dilatation	Normal
Serum creatinine level, mmol/L (mg/dL)	186 (2.1) at age 34 y	97 (1.1) at birth	110 (1.2) at birth	91 (1.0) at birth	44 (0.50) at age 5 y
At follow-up					
Duration of follow-up, y	0	7	1	11	0
Kidney structure	—	Right kidney: dysplastic, multicystic Left kidney: normal	—	Right kidney: normal Left kidney: 1 cyst	—
Serum creatinine level, mmol/L (mg/dL)	—	71 (0.80)	95 (1.1)	61 (0.7)	—
<b>Diabetes</b>	Discovered by screening at age 34 y	No diabetes at age 6 y	No diabetes at age 1 y	Acute onset at age 1 y	No diabetes at age 5 y
<b>Liver enzyme levels*</b>					
Aspartate aminotransferase	Normal	1.2	Normal	Normal	2.0
Alanine aminotransferase	1.8	1.2	Normal	Normal	1.9
$\gamma$ -glutamyltranspeptidase	Normal	Normal	Normal	10.0 at birth, then normal	Normal

\* Values for liver enzyme levels are given as  $x$  times the upper limit of normal range.

biopsy was performed in 6 probands. No proband exhibited diabetic glomerulosclerosis. Interstitial fibrosis was observed in all biopsy specimens. Enlarged glomeruli were observed in 4 cases, associated with glomerular cysts in 2 cases (Figure) and oligomeganephronia in 1 case.

Of 5 offspring who inherited a mutation, 4 had renal involvement (Table 3). One of these 4 patients (patient III-1, family 1) had moderate renal failure (creatinine clearance, 0.63 mL/s [38 mL/min]) detected at 34 years of age, with right kidney agenesis and mild caliceal dilatation of the left kidney. In the other 3 patients, renal disease was found by fetal ultrasonography. Two fetuses had asymmetric lesions consisting of 1 multicystic dysplastic kidney and contralateral hyperechogenicity. In the third fetus, bilateral hyperechogenicity was associated with mild caliceal dilatation. Renal failure and mild metabolic acidosis were observed in the 3 neonates, associated with renal salt-wasting in 1 neonate. Renal function improved within 3 months and was sustained in all neonates (Table 3).

Genital tract abnormalities were present in 5 probands (Table 2). One woman had a bicornuate uterus. In 1 patient, infertility due to azoospermia led to recognition of bilateral atresia of vas deferens. Screening found no mutation in the cystic fibrosis transmembrane conductance regulator gene. In another patient, infertility was due to asthenospermia but no definite cause was identified. Finally, 2 patients had bilateral epididymal cysts that were detected by ultrasonography.

In 7 probands and 4 offspring, liver enzyme levels fluctuated up to 10 times the upper range of normal. In all patients, coagulation test results and serum albumin levels

were normal. Liver and biliary tract ultrasonogram, computed tomography scan, or both were normal in all patients. A liver biopsy was performed in 3 cases and specimens were normal except for mild cholestasis in patient II-2, family 2. In 1 offspring (patient II-2, family 8), a mild increase in liver enzyme level was the only abnormality. At 5 years of age, the patient's kidney ultrasonogram, serum creatinine level, and fasting blood glucose concentration are currently normal.

One patient (II-1, family 4) developed 2 types of cancer. Left ovarian carcinoma was diagnosed at 48 years of age. While in remission, she developed chromophobe-cell cancer in the left kidney at 54 years of age.

## DISCUSSION

In this report, we describe the phenotype related to *HNF-1 $\beta$*  mutations in 13 patients belonging to 8 families. Our data show that molecular abnormalities of *HNF-1 $\beta$* , including missense mutations, are responsible for multi-organ involvement and that the diagnosis of MODY5 should be considered in various clinical circumstances.

A different molecular abnormality in *HNF-1 $\beta$*  gene was identified in each proband, leading to the description of 8 novel mutations. All mutations are located in the DNA-binding domain, as reported for 10 of the 14 mutations previously described (3–16). Among these 14 mutations, 10 mutations lead to truncated protein. By contrast, in our series, 5 of 8 are missense mutations. Converging evidence supports the pathogenicity of these mutations. First, all amino acid changes affect residues conserved in

*HNF-1 $\beta$*  sequences of different species, and, with the exception of the R112P mutation, they involve amino acids that are also conserved in the structurally related gene *HNF-1 $\alpha$* . Some missense mutations result in alterations of the charge, polarity of the corresponding amino acid (R112P, K164Q, and Q136E), or both. Several mutations locate in conformational motifs, thus predicting alterations of protein structure (R112P, K164Q, R165H, and R295H). Two of the novel *HNF-1 $\beta$*  mutations (K164Q and R165H) involve residues for which corresponding mutants with reduced transcriptional activity were described in *HNF-1 $\alpha$*  (K158N and R159Q) (21, 22). Second, the 5 missense mutations were absent from 212 control chromosomes and 170 chromosomes of patients with type 2 diabetes, thus excluding that they may be rare polymorphisms. Third, a cosegregation of the MODY5 phenotype and the mutation was obtained in 4 families, including 2 families with missense mutations.

Our data show that MODY5 encompasses a wide clinical spectrum. Renal disease was present in 12 mutation carriers. Renal involvement is a constant finding in patients with MODY5 (3–16). Various phenotypes were reported as distinct entities, including dysplastic kidneys discovered during fetal life (6, 7, 9, 12), association of diabetes with renal cysts (7, 23, 24), familial glomerulocystic kidney disease (7, 12, 16), and oligomeganephronia (5). We think that all renal phenotypes described so far through isolated case reports exemplify the clinical heterogeneity of a unique disorder. In our series, dysplastic cystic kidneys were diagnosed by ultrasonography in 3 fetuses. Renal failure was present at birth in 2 children; this rapidly improved, however, and renal function remained subsequently stable. It is not known whether a milder form of the same disease may account for the renal cysts and diabetes syndrome phenotype reported in the adult. Indeed, this is a reasonable hypothesis: Structural kidney abnormalities were recognized in adulthood in the 8 probands and in 1 offspring; all patients exhibited chronic renal failure; in the 4 patients with long-term follow-up (Table 2), the decline of renal function was mild (0.02 mL/s per year [1.1 mL/min per year], on average) and may have started early in life; and finally, among these adult patients, 2 had glomerular cysts and 1 had oligomeganephronia on renal biopsy specimens.

The clinical expression of diabetes was similar to that observed in MODY3, with acute onset at a young age in some patients (25, 26) and a slowly progressive disease in others (27). Several features suggested that diabetes was due to a primary and progressive defect of insulin secretion. On average, mean ( $\pm$ SD) stimulated C-peptide concentration was  $0.95 \pm 0.63$  nmol/L (Table 1), compared with  $0.42 \pm 0.28$  nmol/L in 90 patients with recent-onset type 1 diabetes (19). One striking observation was the presence of pancreas atrophy in almost all patients with diabetes. Given the fact that islets represent only 1% of the total pancreatic mass, the presence of pancreatic atrophy

indicates that exocrine pancreas is also involved. Accordingly, some patients also demonstrated mild to moderate defects of exocrine function. A neonate carrying a homozygous mutation of insulin promoter factor-1 was born with pancreatic agenesis (28), and a non-statistically significant reduction of pancreatic volume was reported in patients with heterozygous mutation of insulin promoter factor-1 (MODY4) (29). In our series, a mutation in insulin promoter factor-1 was excluded in the 8 probands (data not shown). Given the interactions between *HNF-1 $\alpha$* , *HNF-1 $\beta$* , *HNF-4 $\alpha$* , and insulin promoter factor-1 (30), the assessment of pancreas structure and function in the various types of MODY would be of interest.

Our findings show that genital involvement is also frequent in patients with MODY5 (Table 2). One patient had a bicornuate uterus, similar to disorders of Müllerian duct development described in 3 families (5, 8, 12). We also observed genital abnormalities in 4 male patients, including large epididymal cysts, asthenospermia, and bilateral agenesis of vas deferens. This expands the spectrum of genital abnormalities in men, since only 1 case of hypospadias was reported so far (12).

Liver test alterations were reported in 2 families with MODY5 (13, 31). Liver enzyme levels increased in 11 patients from the present series. These levels may be present at birth and fluctuate over years. Because these abnormalities are not specific, their frequency may have been underestimated. By contrast, with the striking anatomic changes observed in kidneys and pancreas, minimal histologic changes, if any, were found on liver biopsy specimens in 3 patients, and no functional consequence was observed.

The clinical defects of MODY5 fit well with the expression pattern of *HNF-1 $\beta$*  during the early stages of organogenesis of urinary and genital tract, liver and biliary ducts, and pancreas as described in mice (32–34) and humans (9). The fact that the *HNF-1 $\beta$*  expression is maintained in adulthood may explain the progression of renal and pancreatic functional defects observed in patients with *HNF-1 $\beta$*  mutations.

One patient from our series developed cancer in 2 organs that were directly involved by the expression pattern of *HNF-1 $\beta$* . Although a fortuitous association cannot be excluded, further investigation of patients with *HNF-1 $\beta$*  mutation may be worthwhile. Biallelic inactivation of *HNF-1 $\beta$*  should be investigated to determine whether it promotes carcinogenesis since such defects in *HNF-1 $\alpha$*  were recently associated with hepatic tumors (35).

Maturity-onset diabetes of the young is characterized by autosomal dominant transmission. With the exception of 2 de novo mutations, all families with MODY5 reported so far fit this mode of inheritance (6, 16). By contrast, the family history of our patients did not suggest MODY, since only 5 probands in our series reported a first-degree relative with diabetes. Among them, type 2 diabetes was detected in 2 families (families 3 and 6). This is not surprising given the prevalence of diabetes mellitus in the general population.

Our study has several limitations. First, the study was not population-based and does not allow for the assessment of the true prevalence of *HNF-1 $\beta$*  mutations among patients with diabetes. Second, our selection criteria for gene testing relied on both diabetes and renal involvement. Finally, our findings are based on a small number of patients. Thus, we cannot claim that the clinical spectrum we have described represents the phenotype of most patients with *HNF-1 $\beta$*  mutations. Some patients with *HNF-1 $\beta$*  mutations may present with a less complete phenotype, since previous case reports (7, 12) and long-term follow-up of several of our patients suggest that renal disease may occur long before the onset of diabetes. Whether *HNF-1 $\beta$*  mutations may be associated with more restricted phenotypes, such as isolated dysplastic cystic kidneys in the fetus or neonate, or isolated genital abnormalities deserves further investigation. In 1 family (family 8), a 5-year-old girl carrying an *HNF-1 $\beta$*  mutation had only increased liver enzyme levels, whereas 2 relatives carrying the same mutation had multiorgan involvement. This finding suggests that pleiotropy may be wide and expressivity may be highly variable for a specific *HNF-1 $\beta$*  mutation.

In conclusion, our study shows that the clinical phenotype of MODY5 may extend far beyond diabetes and renal disease and that several defects in organogenesis account for the variable presentation. Further description of the clinical spectrum of MODY5 may benefit from recruiting new cases on the basis of restricted phenotypes. Additional studies may help to identify the various clinical situations that warrant screening for *HNF-1 $\beta$*  mutation. Furthermore, population-based studies are needed to establish the prevalence of MODY5.

From Hôpital Saint-Antoine, Hôpital Cochin, Hôpital Necker, Hôpital Saint-Louis, and Hôpital Saint-Vincent-de-Paul, Paris, France, and Hôpital Saint-Morand, Altkirch, France.

**Acknowledgements:** The authors thank the families for their participation in the study; Drs. Véronique Baudouin, Véronique Blanchetier, Guy Parlier, and Rémi Salomon for the follow-up of patients; and Dr. Pascal Hammel for helpful advice.

**Potential Financial Conflicts of Interest:** None disclosed.

**Requests for Single Reprints:** Christine Bellanné-Chantelot, PharmD, PhD, Fédération des Services de Biochimie, Laboratoire de Biologie Moléculaire, Hôpital Saint-Antoine, 184 rue du faubourg Saint-Antoine, 75012 Paris, France; e-mail, christine.bellanne@sat.ap-hop-paris.fr.

Current author addresses and author contributions are available at [www.annals.org](http://www.annals.org).

## References

- King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care*. 1998;21:1414-31. [PMID: 9727886]
- Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med*. 2001;345:

971-80. [PMID: 11575290]

- Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, et al. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY [Letter]. *Nat Genet*. 1997;17:384-5. [PMID: 9398836]
- Nishigori H, Yamada S, Kohama T, Tomura H, Sho K, Horikawa Y, et al. Frameshift mutation, A263fsinsGG, in the hepatocyte nuclear factor-1beta gene associated with diabetes and renal dysfunction. *Diabetes*. 1998;47:1354-5. [PMID: 9703339]
- Lindner TH, Njolstad PR, Horikawa Y, Bostad L, Bell GI, Sovik O. A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1beta. *Hum Mol Genet*. 1999;8:2001-8. [PMID: 10484768]
- Bingham C, Ellard S, Allen L, Bulman M, Shepherd M, Fraying T, et al. Abnormal nephron development associated with a frameshift mutation in the transcription factor hepatocyte nuclear factor-1 beta. *Kidney Int*. 2000;57:898-907. [PMID: 10720943]
- Bingham C, Bulman MP, Ellard S, Allen LI, Liplin GW, Hoff WG, et al. Mutations in the hepatocyte nuclear factor-1beta gene are associated with familial hypoplastic glomerulocystic kidney disease. *Am J Hum Genet*. 2001;68:219-24. [PMID: 11085914]
- Iwasaki N, Okabe I, Momoi MY, Ohashi H, Ogata M, Iwamoto Y. Splice site mutation in the hepatocyte nuclear factor-1 beta gene, IVS2nt + 1G > A, associated with maturity-onset diabetes of the young, renal dysplasia and bicornuate uterus [Letter]. *Diabetologia*. 2001;44:387-8. [PMID: 11317673]
- Kolatsi-Joannou M, Bingham C, Ellard S, Bulman MP, Allen LI, Hattersley AT, et al. Hepatocyte nuclear factor-1beta: a new kindred with renal cysts and diabetes and gene expression in normal human development. *J Am Soc Nephrol*. 2001;12:2175-80. [PMID: 11562418]
- Carbone I, Cotellessa M, Barella C, Minetti C, Ghiggeri GM, Caridi G, et al. A novel hepatocyte nuclear factor-1beta (MODY-5) gene mutation in an Italian family with renal dysfunctions and early-onset diabetes. *Diabetologia*. 2002;45:153-4. [PMID: 11845237]
- Yoshiuchi I, Yamagata K, Zhu Q, Tamada I, Takahashi Y, Onigata K, et al. Identification of a gain-of-function mutation in the HNF-1beta gene in a Japanese family with MODY. *Diabetologia*. 2002;45:154-5. [PMID: 11845238]
- Bingham C, Ellard S, Cole TR, Jones KE, Allen LI, Goodship JA, et al. Solitary functioning kidney and diverse genital tract malformations associated with hepatocyte nuclear factor-1beta mutations. *Kidney Int*. 2002;61:1243-51. [PMID: 11918730]
- Montoli A, Colussi G, Massa O, Caccia R, Rizzoni G, Civati G, et al. Renal cysts and diabetes syndrome linked to mutations of the hepatocyte nuclear factor-1 beta gene: description of a new family with associated liver involvement. *Am J Kidney Dis*. 2002;40:397-402. [PMID: 12148114]
- Furuta H, Furuta M, Sanke T, Ekawa K, Hanabusa T, Nishi M, et al. Nonsense and missense mutations in the human hepatocyte nuclear factor-1 beta gene (TCF2) and their relation to type 2 diabetes in Japanese. *J Clin Endocrinol Metab*. 2002;87:3859-63. [PMID: 12161522]
- Waller SC, Rees L, Woolf AS, Ellard S, Pearson ER, Hattersley AT, et al. Severe hyperglycemia after renal transplantation in a pediatric patient with a mutation of the hepatocyte nuclear factor-1beta gene. *Am J Kidney Dis*. 2002;40:1325-30. [PMID: 12460054]
- Mache CJ, Preisegger KH, Kopp S, Ratschek M, Ring E. De novo HNF-1 beta gene mutation in familial hypoplastic glomerulocystic kidney disease. *Pediatr Nephrol*. 2002;17:1021-6. [PMID: 12478351]
- Barnes DJ, Pinto JR, Viberti GC. The patient with diabetes mellitus. In: Davison AM, Cameron JS, Grünfeld JP, Kerr DNS, Ritz E, Winearls CG, eds. *Textbook of Clinical Nephrology*. 2nd ed. Oxford: Oxford Univ Pr; 1998:723-76.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41. [PMID: 1244564]
- Assan R, Feutren G, Sirmaj J, Laborie C, Boitard C, Vexiau P, et al. Plasma C-peptide levels and clinical remissions in recent-onset type I diabetic patients treated with cyclosporin A and insulin. *Diabetes*. 1990;39:768-74. [PMID: 2191883]
- Mendel DB, Hansen LP, Graves MK, Conley PB, Crabtree GR. HNF-1 alpha and HNF-1 beta (vHNF-1) share dimerization and homeo domains, but not activation domains, and form heterodimers in vitro. *Genes Dev*. 1991;5:

1042-56. [PMID: 2044952]

21. Vaxillaire M, Abderrahmani A, Boutin P, Bailleul B, Froguel P, Yaniv M, et al. Anatomy of a homeoprotein revealed by the analysis of human MODY3 mutations. *J Biol Chem*. 1999;274:35639-46. [PMID: 10585442]

22. Yamada S, Tomura H, Nishigori H, Sho K, Mabe H, Iwatani N, et al. Identification of mutations in the hepatocyte nuclear factor-1alpha gene in Japanese subjects with early-onset NIDDM and functional analysis of the mutant proteins. *Diabetes*. 1999;48:645-8. [PMID: 10078571]

23. Rizzoni G, Loirat C, Levy M, Milanesi C, Zachello G, Mathieu H. Familial hypoplastic glomerulocystic kidney. A new entity? *Clin Nephrol*. 1982;18:263-8. [PMID: 7151342]

24. Kaplan BS, Gordon I, Pincott J, Barratt TM. Familial hypoplastic glomerulocystic kidney disease: a definite entity with dominant inheritance. *Am J Med Genet*. 1989;34:569-73. [PMID: 2624270]

25. Yamada S, Nishigori H, Onda H, Utsugi T, Yanagawa T, Maruyama T, et al. Identification of mutations in the hepatocyte nuclear factor (HNF)-1 alpha gene in Japanese subjects with IDDM. *Diabetes*. 1997;46:1643-7. [PMID: 9313763]

26. Moller AM, Dalgaard LT, Pociot F, Nerup J, Hansen T, Pedersen O. Mutations in the hepatocyte nuclear factor-1alpha gene in Caucasian families originally classified as having Type I diabetes. *Diabetologia*. 1998;41:1528-31. [PMID: 9867222]

27. Lehto M, Tuomi T, Mahtani MM, Widen E, Forsblom C, Sarelin L, et al. Characterization of the MODY3 phenotype. Early-onset diabetes caused by an insulin secretion defect. *J Clin Invest*. 1997;99:582-91. [PMID: 9045858]

28. Stoffers DA, Ferrer J, Clarke WL, Habener JF. Early-onset type-II diabetes mellitus (MODY4) linked to IPF1 [Letter]. *Nat Genet*. 1997;17:138-9. [PMID: 9326926]

29. Cloquet AR, Egan JM, Stoffers DA, Muller DC, Wideman L, Chin GA, et al. Impaired insulin secretion and increased insulin sensitivity in familial maturity-onset diabetes of the young 4 (insulin promoter factor 1 gene). *Diabetes*. 2000;49:1856-64. [PMID: 11078452]

30. Shih DQ, Stoffel M. Dissecting the transcriptional network of pancreatic islets during development and differentiation. *Proc Natl Acad Sci U S A*. 2001;98:14189-91. [PMID: 11734636]

31. Iwasaki N, Ogata M, Tomonaga O, Kuroki H, Kasahara T, Yano N, et al. Liver and kidney function in Japanese patients with maturity-onset diabetes of the young. *Diabetes Care*. 1998;21:2144-8. [PMID: 9839108]

32. Coffinier C, Barra J, Babinet C, Yaniv M. Expression of the vHNF1/HNF1beta homeoprotein gene during mouse organogenesis. *Mech Dev*. 1999;89:211-3. [PMID: 10559500]

33. Reber M, Cereghini S. Variant hepatocyte nuclear factor 1 expression in the mouse genital tract. *Mech Dev*. 2001;100:75-8. [PMID: 11118887]

34. Coffinier C, Gresh L, Fiette L, Tronche F, Schutz G, Babinet C, et al. Bile system morphogenesis defects and liver dysfunction upon targeted deletion of HNF1beta. *Development*. 2002;129:1829-38. [PMID: 11934849]

35. Bluteau O, Jeannot E, Bioulac-Sage P, Marques JM, Blanc JF, Bui H, et al. Bi-allelic inactivation of TCF1 in hepatic adenomas. *Nat Genet*. 2002;32:312-5. [PMID: 12355088]

**Current Author Addresses:** Dr. Bellanné-Chantelot, Ms. Clauin, and Ms. Beaufls: Fédération des Services de Biochimie, Laboratoire de Biologie Moléculaire, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, 75012 Paris, France.

Drs. Chauveau and Noël: Service de Néphrologie, Hôpital Necker, 161 rue de Sèvres, 75015 Paris, France.

Dr. Gautier: Service d'Endocrinologie, Hôpital Saint-Louis, 1 Avenue Claude Vellefaux, 75010 Paris, France.

Drs. Dubois-Laforgue, Boitard, and Timsit: Service d'Immuno-Diabétologie, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France.

Dr. Wilhelm: Centre Hospitalier Saint-Morand, BP 1022, 68134 Altkirch Cedex, France.

Dr. Velho: INSERM U561, Hôpital Saint-Vincent-de-Paul, 74 Avenue Denfert Rochereau, 75014, Paris, France.

**Author Contributions:** Conception and design: C. Bellanné-Chantelot, D. Chauveau, G. Velho, J. Timsit.

Analysis and interpretation of the data: C. Bellanné-Chantelot, D. Chauveau, J.-F. Gautier, D. Dubois-Laforgue, S. Clauin, S. Beaufls, J.-M. Wilhelm, C. Boitard, L.-H. Noël, G. Velho, J. Timsit.

Drafting of the article: C. Bellanné-Chantelot, D. Chauveau, G. Velho, J. Timsit.

Critical revision of the article for important intellectual content: C. Bellanné-Chantelot, D. Chauveau, J.-F. Gautier, D. Dubois-Laforgue, C. Boitard, G. Velho, J. Timsit.

Final approval of the article: C. Bellanné-Chantelot, D. Chauveau, J.-F. Gautier, D. Dubois-Laforgue, S. Clauin, S. Beaufls, J.-M. Wilhelm, C. Boitard, L.-H. Noël, G. Velho, J. Timsit.

Provision of study materials or patients: D. Chauveau, J.-F. Gautier, D. Dubois-Laforgue, J.-M. Wilhelm, C. Boitard, J. Timsit.

Administrative, technical, or logistic support: S. Clauin, S. Beaufls.

Collection and assembly of data: C. Bellanné-Chantelot, D. Chauveau, J. Timsit.