Diabetes, Associated Clinical Spectrum, Long-term Prognosis, and Genotype/Phenotype Correlations in 201 Adult Patients With Hepatocyte Nuclear Factor 1B (*HNF1B*) Molecular Defects

*Danièle Dubois-Laforgue,[1,2] Erika Cornu,[1] Cécile Saint-Martin,[3] Joël Coste,[4] Christine Bellanné-Chantelot,[3] and José Timsit,[1] for the Monogenic Diabetes Study Group of the Société Francophone du Diabète**

Diabetes Care 2017;40:1436–1443 | https://doi.org/10.2337/dc16-2462

OBJECTIVE

Molecular defects of hepatocyte nuclear factor 1B (*HNF1B*) are associated with a multiorgan disease, including diabetes (maturity-onset diabetes of the young 5) and kidney abnormalities. The HNF1B syndrome is related to *HNF1B* mutations or to a 17q12 deletion spanning 15 genes, including *HNF1B*. Here, we described HNF1B-related diabetes and associated phenotypes and assessed genotype/phenotype correlations at diagnosis and in the long-term.

RESEARCH DESIGN AND METHODS

This multicenter retrospective cohort study included 201 patients, aged 18 years or older at follow-up, with *HNF1B* mutations (n = 101) or deletion (n = 100).

RESULTS

Diabetes was present in 159 patients. At diagnosis, clinical symptoms of diabetes were present in 67 of 144 patients and HNF1B renal disease in 64 of 102. Although responsiveness to sulfonylureas/repaglinide was observed in 29 of the 51 tested, 111 of 140 patients (79%) were treated with insulin at follow-up. Diabetic retinopathy and/or neuropathy were present in 46 of 114 patients. Renal cysts were present in 122 of 166 patients, chronic kidney disease stages 3–4 (CKD3–4) in 75 of 169 (44%), and end-stage renal disease (ESRD) in 36 of 169 (21%). Compared with the patients with mutations, those with *HNF1B* deletion less often had CKD3–4/ESRD at diagnosis (11 of 43 vs. 27 of 35, $P < 10^{-4}$) and in the long term (40 of 78 vs. 71 of 91, $P = 0.0003$). They were leaner and more frequently treated with insulin.

CONCLUSIONS

In patients with HNF1B syndrome, diabetes complications, cardiovascular risk factors, CKD3–4, and ESRD are highly prevalent. At diabetes diagnosis, the presence of morphological and/or functional kidney disease may help etiological diagnosis. Genotype/phenotype correlations may have implications for the care and the prognosis of these patients.

[1]Department of Diabetology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, and Paris Descartes University, DHU AUTHORS, Paris, France
[2]INSERM U1016, Cochin Hospital, Paris, France
[3]Department of Genetics, Pitié-Salpétrière Hospital, Assistance Publique-Hôpitaux de Paris, and Pierre et Marie Curie University, Paris, France
[4]Department of Biostatistics and Epidemiology, Hôtel-Dieu Hospital, Assistance Publique-Hôpitaux de Paris, and Paris Descartes University, Paris, France

Corresponding author: Danièle Dubois-Laforgue, daniele.dubois@aphp.fr.

Received 18 November 2016 and accepted 21 March 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-2462/-/DC1.

C.B.-C. and J.T. contributed equally to this study.

**A list of the participant investigators of the Monogenic Diabetes Study Group of the Société Francophone du Diabète can be found in the Supplementary Data online.*

See accompanying article, p. 1433.

Molecular alterations of hepatocyte nuclear factor 1B (*HNF1B)* are associated with a multiorgan disease (1,2), including maturity-onset diabetes of the young 5 (MODY5, HNF1B-MODY) (3–5), kidney morphological abnormalities, particularly renal cysts (6–9), decreased renal function (4–9), morphological and functional anomalies of the exocrine pancreas (4,10), liver test alterations (4,9,11), and genital tract (4,12,13) and neurocognitive defects (14–18).

The HNF1B-related syndrome is considered to be caused by *HNF1B* haploinsufficiency (2). In 40–50% of the patients, the disease is a result of *HNF1B* mutations, whereas in the others, it is associated with a heterozygous whole *HNF1B* gene deletion (7,19,20). In all cases investigated to date, *HNF1B* deletion is the result of a 17q12 deletion spanning 1.5 Mb on average encompassing 15 genes, including *HNF1B* (15–17,19). So far, except for one study showing that neurodevelopmental disorders occur only in patients with the 17q12 deletion (17), no differences have been reported in the phenotypes of the patients with this large rearrangement compared with those with *HNF1B* mutations (2).

Although the HNF1B-associated renal disease has been extensively described (1,2,4–9), the clinical characteristics and care of HNF1B-related diabetes have not been reported in large series, and no long-term studies are available. A meta-analysis of 47 articles only mentioned that diabetes occurred in 95 of 211 patients with *HNF1B* defects, at a mean age of 23.7 years, and that 77% of the patients were treated with insulin (1).

The aims of our study were, in a cohort of 201 adult patients with *HNF1B* defects, to describe the phenotype of diabetes and of the associated clinical spectrum, to report the long-term follow-up of these patients, and to reassess genotype/phenotype correlations.

RESEARCH DESIGN AND METHODS

Criteria for *HNF1B* Genetic Screening

Reasons for referring the patients for genetic testing were

1. the association of diabetes suggesting MODY (absence of islet autoantibodies in the proband, onset of diabetes before age 40 in the proband and/or in at least one family member, absence of familial obesity) and impaired renal function not ascribable to diabetes (i.e., in the absence of diabetic retinopathy and with albumin excretion $<$0.5 g/day), and/or kidney morphological abnormalities (19);
2. the association of diabetes with other organ involvement previously described in HNF1B-MODY (renal disease, pancreatic hypoplasia, unexplained elevated liver enzymes, or genital tract abnormalities) (1,2,19);
3. renal disease suggestive of an *HNF1B* defect (2,9); and
4. screening of relatives of a patient with an *HNF1B* molecular defect.

Genetic Analyses

Genetic analyses were performed in two steps: *1*) the search for genomic rearrangements of *HNF1B* (NM_000458.2) by multiplex quantitative PCR (19) and *2*) the search for sequence variants of *HNF1B* by Sanger sequencing from 2000 to 2013, and since 2014 by multiplex amplification (Kit MODY MASTR assay V1.0; Multiplicom, Antwerp, Belgium), including seven genes (*GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *ABCC8*, *KCNJ11*, and *INS*), followed by sequencing on a MiSeq system (Illumina). All patients gave informed consent for the study.

Pathogenicity of variants was assessed according to current guidelines, and all variants were classified using a five-class score (21). Truncating mutations were considered as disease causing. Interpretation of missense and splice-site mutations was based on the following criteria: mutation not present in the population database (Exome Aggregation Consortium [ExAC] Browser) (22); mutation previously reported in HNF1B deficiency, based on literature and gene-specific database (Human Genome Mutation Database [HGMD]) (23); de novo occurrence and familial cosegregation analysis; predictive algorithms of pathogenicity for missense mutations (sorting intolerant from tolerant [SIFT], PolyPhen-2, Align-GVGD [Grantham Variation, Grantham Deviation] and Combined Annotation-Dependent Depletion [CADD] score) (24) and for splice-site defects (MaxEntScan and Human Splicing Finder). The predictive algorithms, except CADD, were run with the Alamut Visual 2.7 software (Interactive Biosoftware, Rouen, France).

Study Population

Between 2000 and 2015, a molecular defect of *HNF1B* was identified in 380 patients in the Department of Genetics (Hôpital Pitié-Salpétrière, Paris, France). Because our main goal was to describe the phenotype of HNF1B diabetes, which is rarely present in children (1), 137 patients younger than age 18 years at the time of follow-up were excluded from the study. We also excluded 18 patients in whom the identified *HNF1B* molecular abnormality was considered an unlikely pathogenic variant, rather than a disease-causing mutation, and 24 patients with no available clinical data. Thus, 201 adult patients (154 families) were included in the study. Among these patients, 39 have been reported as case reports or in short series (4,19,25–28), and a further 68 were specifically assessed for intellectual disability (18).

Data Collection

Clinical and biological parameters at onset and at follow-up were recorded on standardized forms filled in by the referring clinicians and were reviewed by three of us (D.D.-L., E.C., J.T.). Arterial hypertension, dyslipidemia, and coronary artery disease were defined as previously described (29). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Chronic kidney disease stages 3 and 4 (CKD3–4) were defined as an eGFR between 59 and 15 mL/min/1.73 m^2, and end-stage renal disease (ESRD) as an eGFR $<$15 mL/min/1.73 m^2 or dialysis or kidney transplantation (30). Retinopathy and neuropathy were defined and assessed as recommended (31). Responsiveness to sulfonylureas (SUs) or repaglinide was defined as an HbA_{1c} $<$7.0% (53 mmol/mol) under treatment (31).

Statistical Analysis

Data are shown as medians and interquartile ranges (IQRs) or as numbers and percentages. Univariate analyses were performed using the Mann-Whitney *U* test and the Fisher exact test. Correlations were assessed by Spearman rank order correlation. For multivariate analyses, variables associated with genotype or with renal failure with a *P* value $<$0.10 in the univariate analyses were included in multiple logistic regression models, and manual backward elimination procedures were performed to choose the final models. In case of collinearity between two or more variables, the most clinically

pertinent was chosen. Adjusted odds ratios are reported with 95% CIs. Because the study included probands and relatives, sensitivity analyses were performed in probands, and all showed results similar to those in the total population (not shown). A P value <0.05 was considered significant. Analyses were performed with SAS 9.3 software (SAS Institute, Inc., Cary, NC).

RESULTS

Mutational Spectrum

Among the 154 probands, 87 (56%) had a whole gene deletion. The molecular defects found in the 67 other probands consisted of 37 missense mutations, 7 nonsense, 8 splice-site defects, 11 small insertion/deletion, 3 exonic deletions (exon 5, exons 1–4, exons 3–4) and one exon 5 duplication. They are subsequently referred to as "mutations." Fifty-seven of these 67 are distinct variants and, among them, 26 are novel mutations (Supplementary Table 1) (2,23).

Clinical Spectrum of the HNF1B-Related Syndrome

The frequencies of the main components of the HNF1B-related syndrome are reported in Table 1. Diabetes was present in 159 of 194 patients. A family history of diabetes was present in 78 of 110 probands (71%), suggesting MODY in 31 of 78 (40%). Clinical presentation at diabetes diagnosis was highly variable (Fig. 1 and Table 2). Age at diabetes onset was >25 years in 91 of 159 patients (57%). Clinical symptoms (polyuria and/or weight loss) were present in 67 of 144 patients (47%), but ketoacidosis was rare (7 of 144 [5%]). BMI was <25 kg/m^2 in 81 of 101 patients (80%). HbA_{1c} was <7% (53 mmol/mol) in 24 of 74 (32%) and ≥13% (119 mmol/mol) in 25 (34%). Basal and stimulated C-peptide plasma concentrations, assessed in 55 and 36 patients, respectively, after a median 9-year diabetes duration (IQR 1–18), showed residual insulin secretion in 80% of the patients (Supplementary Fig. 1) and did not correlate with diabetes duration or eGFR (not shown). At diabetes onset, 68 patients (49%) were treated with insulin. They were younger, leaner, presented more often with clinical symptoms of diabetes, had higher blood glucose and HbA_{1c} levels, and more often carried an *HNF1B* deletion than those treated with diet or oral hypoglycemic agents (OHA) (Supplementary Table 2).

At last follow-up, median age of the patients was 45 years and diabetes

Table 1—Main components of the HNF1B syndrome in 201 adult patients

Organ	Observed prevalence, *n/N* investigated (%)	Features: numbers of cases
Diabetes	159/194 (82)	
Kidney morphological abnormalities*	151/166 (91)	Cysts: 124 Renal atrophy: 37 Pelviureteric junction obstruction: 26 Solitary kidney: 20
CKD3–4†	75/169 (44)	
ESRD‡	36/169 (21)	
Hypomagnesemia	49/65 (75)	
Pancreas morphological abnormalities*	59/95 (62)	Atrophy/agenesis: 39 Calcifications: 24 Pancreas divisum: 3; ring pancreas: 1; malrotation: 1 Intraductal papillary mucinous tumor: 2
Pancreas exocrine dysfunction§	29/38 (76)	
Liver test abnormalities	101/142 (71)	ALT > upper limit of normal: 52, by 1.62 times (1.38–2.44) AST > upper limit of normal: 38, by 1.49 times (1.17–2.00) GGT > upper limit of normal: 63, by 3.00 times (2.09–4.87)
Liver imaging abnormalities*	31/97 (32)	Nonspecific abnormalities: 22 Biliary cysts: 4 Abnormal biliary ducts: 5
Liver biopsy abnormalities	13/24 (54)	Rarefaction of biliary ducts: 5 Fibrosis: 3 Steatosis: 3 Focal nodular hyperplasia: 2
Genital tract abnormalities		
In females	28/56 (50)	Bicornuate uterus: 22 Mayer-Rokitansky-Küster-Hauser syndrome: 5 Hemiuterus: 1
In males	16/20 (80)	Spermiogram abnormalities: 7 Epididymal cysts: 4; cryptorchidism: 3; varicocele: 3 Enlarged seminal vesicles: 2; absence of vas deferens: 1

Results are expressed as actual numbers and percentages or as median (IQR). ALT, alanine aminotransferase, AST, aspartate aminotransferase, GGT, γ-glutamyltransferase. *Morphological abnormalities were assessed by ultrasonography and/or computed tomography scan. †Defined as an eGFR between 59 and 15 mL/min/1.73 m^2, calculated by the CKD-EPI formula (30). ‡Defined as an eGFR <15 mL/min/1.73 m^2, dialysis, or kidney transplantation. §Defined as an elastase fecal concentration <200 μg/g and/or a fecal fat excretion >6 g/day.

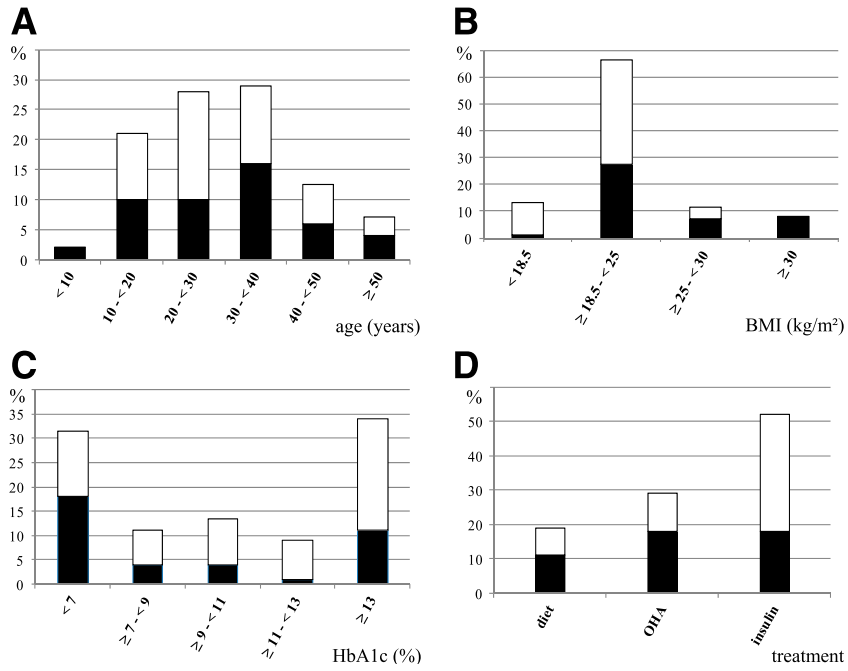

Figure 1—Distribution (%) of age (n = 153) (*A*), BMI (n = 109) (*B*), HbA_{1c} (n = 73) (*C*), and treatment of diabetes (n = 125) (*D*) in probands. Black bars, patients with *HNF1B* mutations; white bars, patients with *HNF1B* deletion.

duration was 12 years (Table 2). Median HbA_{1c} was 7.05% (54 mmol/mol). Insulin therapy was instituted in 48 of 72 patients (67%) initially on diet or OHA. Thus, the proportion of insulin-treated patients rose to 111 of 140 (79%). In these patients, insulin dosage was 0.55 IU/kg/day (IQR 0.39–0.70), and median HbA_{1c} was 7.3% (IQR 6.7–8.4) (56 mmol/mol [IQR 50–67]).

Responsiveness to SU or repaglinide was observed in 29 of 51 patients (57%) treated after a 0.75-year diabetes duration (IQR 0–5.25). HbA_{1c} decreased from 7.1% (IQR 5.5–12.1) (54 mmol/mol [IQR 37–109]) to 6.1% (IQR 4.4–7.0) (43 mmol/mol [IQR 25–53]) ($P < 10^{-4}$). Responsiveness to SU/repaglinide was associated with a better residual insulin secretion (not shown). Duration of SU/repaglinide treatment was 5 years (IQR 3–9). Switching insulin therapy for SU/repaglinide was attempted in 10 patients only and was successful in 3.

At follow-up, diabetic retinopathy was observed in 33 of 121 patients (27%) and was mild in 14, moderate to severe in 8, and proliferative in 11. Peripheral neuropathy was noticed in 29 of 112 patients (26%) (Table 2). Retinopathy and/or neuropathy, present in 46 of 114 patients (40%), were associated with older age and longer diabetes duration, higher HbA_{1c} and systolic blood pressure, more frequent insulin therapy, and the presence of CKD3–4/ESRD (Supplementary Table 3). Overt coronary artery disease was present in 11 of 111 patients (10%). Cardiovascular risk factors were present in many patients since the minimal prevalence of diabetes, CKD3–4/ESRD, body weight excess, arterial hypertension, and hyperlipidemia was 79%, 55%, 30%, 37%, and 39%, respectively, and 43% of the patients had four or more risk factors.

At the time of the study, 35 patients had no diabetes. Their main characteristics were not different from those of patients with diabetes, except for a higher proportion of relatives (Supplementary Table 4). Of note, age at follow-up in the patients without diabetes was older than the age at diabetes diagnosis in the 159 others.

HNF1B-related renal disease, defined by the presence of kidney morphological abnormalities, CKD3–4/ESRD, and/or hypomagnesemia (Table 1), was present in 173 of 176 patients. Median age at diagnosis of renal disease was 26 years (IQR 11.3–38). In the 102 patients with known ages at diabetes and renal disease diagnosis, renal disease was diagnosed first in 40 (39%). It was uncovered concomitantly with diabetes in 24 (24%) and after a median diabetes duration of 11 years (IQR 5.5–16) in 38 (37%) (Supplementary Fig. 2). In these two latter groups, renal function was already decreased in 9 of 34 patients (26%) at diabetes diagnosis, and kidney morphological abnormalities were eventually found in 49 of 56 (87%).

Kidney morphological abnormalities were found in 151 of 166 patients. They consisted of renal cysts in 81% and were the sole abnormality in 48%. Renal imaging showed no abnormalities in 15 patients (9%). Hypomagnesemia was observed in 49 of 65 patients (75%) and hyperuricemia in 50 of 85 patients (59%; 41% of those with a normal eGFR). Of note, renal imaging showed abnormalities in 30 of 34 relatives (88%), including the presence of cysts in 83%, as observed in the probands (92% and 81%, respectively).

At follow-up, 58 patients (34%) had an eGFR $\geq$60 mL/min/1.73 m^2, and 75 (44%) had CKD3–4 and 36 (21%) ESRD, including 7 patients on hemodialysis and 24 patients with a kidney transplantation. CKD3–4/ESRD was as frequent in relatives as in probands (not shown). Age at ESRD was highly variable (median 50 years [IQR 30–56.5]). Microalbuminuria was present in 40 of 125 (32%) and proteinuria in 32 of 125 patients (26%). A renal biopsy was performed in 20 patients and showed various lesions, including interstitial fibrosis in 10 and diabetic glomerular disease in 5. Factors associated with CKD3–4/ESRD at follow-up were first identified by univariate analysis (Table 3). eGFR at follow-up was strongly correlated with eGFR at diagnosis and with age at follow-up ($P < 10^{-4}$ for both correlations [data not shown]). By multivariate analysis, CKD3–4/ESRD at follow-up was associated with *HNF1B* mutation (vs. deletion), arterial hypertension, proteinuria, and age (Supplementary Table 5).

The main other components of the HNF1B-related disease are detailed in Table 1. Pancreas imaging and pancreas exocrine functional tests, performed in 95 and 38 patients, showed abnormalities in 62% and 76%, respectively. Abnormal liver test results were reported in 101 of 142 patients. No hepatic failure or portal hypertension was reported. Genital tract abnormalities were found in 28 of

Table 2—Characteristics of the patients with HNF1B-related diabetes

	At diabetes onset	At last follow-up
Age (years)	28 (20–37) [159]	45 (3–56) [144]
Duration of diabetes (years)	0	12 (5.5–22.5) [143]
BMI (kg/m^2)	23.1 (19.7–24.4)	23.9 (20.9–26.3)
BMI		
Normal	89	78
Overweight	13	39
Obese	9	15
Blood glucose concentration (mmol/L)	15.8 (7.8–27.2) [82]	NA
HbA_{1c} (%)	9.85 (6.6–14.2) [74]	7.05 (6.1–8.1) [135]
HbA_{1c} (mmol/mol)	84.5 (49–132) [74]	54 (43–65) [135]
Treatment of diabetes		
Diet	25	7
OHA	47	22
Insulin	68	111
eGFR (mL/min/1.73 m^2)*	60 (39.5–96.5) [67]	50.5 (32–89) [104]
Renal function		
Normal	40	45
CKD3–4†	31	66
ESRD‡	7	31
Increased albumin urinary excretion: yes/no	NA	65/43
Retinopathy: yes/no	NA	33/88
Neuropathy: yes/no	NA	29/83
Coronary artery disease: yes/no	NA	11/99

Results are expressed as median (IQR), with numbers of available data in brackets, or as actual numbers. NA, not available. *eGFR calculated by the CKD-EPI formula (30), excluding patients on dialysis or with kidney transplantation. †Defined as an eGFR between 59 and 15 mL/min/1.73 m^2. ‡Defined as an eGFR $<$15 mL/min/1.73 m^2, dialysis, or kidney transplantation.

56 women and in 16 of 20 men who were investigated. Rare abnormalities reported by the referring physicians are summarized in Supplementary Table 6.

Genotype/Phenotype Correlations

Among the patients with mutations, we observed no differences in the phenotypes of the patients with missense compared with those with truncating mutations (not shown). In the univariate analysis (Table 4), compared with patients with an *HNF1B* mutation, those with a whole *HNF1B* deletion were more often probands, had a lower BMI at diabetes diagnosis and at follow-up, and were more often treated with insulin at diabetes diagnosis. They also had a higher eGFR at diabetes diagnosis and at follow-up and a lower frequency of kidney transplantation. Thus, CKD3–4/ESRD was less frequent in patients with deletion than in those with mutations at diabetes diagnosis (11 of 43 [26%] vs. 27 of 35 [77%], $P < 10^{-4}$) and at follow-up (40 of 78 [51%] vs. 71 of 91 [78%], P = 0.0003). No genotype/phenotype correlations were observed for kidney morphology, pancreas morphology and exocrine function, plasma C-peptide concentrations, liver tests, and genital tract abnormalities.

Variables associated with the genotype (deletion vs. mutations) were entered into multivariate analyses (Supplementary Table 7). At diabetes diagnosis, a normal BMI and a normal renal function were strongly associated with the presence of whole gene deletion. At follow-up, a normal renal function remained associated with *HNF1B* deletion.

CONCLUSIONS

This large series first allowed us to refine the phenotype of HNF1B-related diabetes. Most probands had no family history suggestive of MODY, in keeping with the frequent de novo occurrence of *HNF1B* defects (7,20), and age at diabetes onset was $>$25 years.

At diabetes diagnosis, insulin therapy was instituted in half the patients and was associated with a young age, a low BMI, frequent clinical symptoms, and high blood glucose and HbA_{1c} values. Afterward, insulin therapy was rarely switched for OHA. This suggests that some patients might have been misdiagnosed as having type 1 diabetes, as described in other MODY subtypes (32). In this respect, early recognition of renal disease at diabetes diagnosis may help correct etiological diagnosis. As a result of the clinical latency of kidney morphological abnormalities, renal ultrasonography may orientate etiological diagnosis of nonautoimmune diabetes because renal cysts were found in most of our patients, as described in the renal cysts and diabetes (RCAD) phenotype (6). Also, the presence of a decreased renal function at diabetes onset, after initial rehydration, should alert the physician.

Patients with HNF1B diabetes have been reported to exhibit insulin resistance (33). In our series, in the patients treated with insulin, a good diabetes control was achieved with insulin dosage, suggesting no overt insulin resistance. A short series suggested that a severe defect of insulin secretion was the primary cause of HNF1B-MODY in Japanese patients (34). In our patients, residual insulin secretion was documented in a large proportion of those in whom it was assessed. Accordingly, responsiveness to SU/repaglinide was observed in half the patients in whom it was tested and lasted for several years. It could have been hypothesized that treatment with an SU was not started because of reduced renal function, but eGFR at diabetes diagnosis was higher in the patients treated with insulin than in those treated with an SU (Supplementary Table 2). Thus, more patients with HNF1B diabetes could be treated efficiently with SU/repaglinide, from the onset of diabetes or after switching insulin for these drugs, when etiological diagnosis of diabetes is made. However, as a result of the progressive reduction of eGFR, eventual insulin therapy will be necessary in many patients.

After a median 15-year diabetes duration, the prevalence of retinopathy and/or peripheral neuropathy was 40%, associated with the same risk factors as those identified in other diabetes subtypes (Supplementary Table 3). Coronary artery disease was not systematically assessed, but these patients cumulated many risk factors and should benefit from aggressive prevention.

The characteristics of the HNF1B renal disease were similar to what has been published regarding kidney

Table 3—Factors associated with the presence of a decreased renal function at follow-up in patients with HNF1B molecular defects: univariate analysis

Decreased renal function* at follow-up	No (n = 58)	Yes (n = 111)	P value
Sex			
Male	21	55	
Female	37	56	0.10
Proband/relative	47/11	88/23	0.84
Genotype			
Mutation	20	71	
Deletion	38	40	0.0003
Age at diagnosis of renal disease (years)	19 (8.5–32) [31]	28 (18–39) [83]	0.036
Age at diagnosis of diabetes (years)	23 (18–32) [45]	31 (20–39) [97]	0.017
BMI at diabetes diagnosis (kg/m^2)	21.9 (18.7–24.3) [34]	23.4 (20.9–24.4) [67]	0.11
HbA_{1c} at diabetes diagnosis (%)	11.5 (8.3–15.6) [24]	9.15 (6.3–13.1) [40]	0.0388
HbA_{1c} at diabetes diagnosis (mmol/mol)	102.5 (67–146) [24]	76.5 (45–120) [40]	0.0388
Blood glucose at diabetes diagnosis (mmol/L)	19 (11–33) [25]	11.25 (7.2–22.5) [52]	0.0234
Insulin therapy at diabetes diagnosis: yes/no	24/18	37/52	0.13
eGFR at diabetes diagnosis†‡ (mL/min/1.73 m^2)	109 (99–121) [21]	44 (33–63) [46]	$<10^{-4}$
Renal function at diabetes diagnosis			
Normal	26	14	
Decreased	0	38	$<10^{-4}$
Age at follow-up (years)	33 (26–40) [58]	50 (37–59) [104]	$<10^{-4}$
Diabetes duration at follow-up (years)	11 (4–14) [45]	16 (9–27) [89]	0.0008
BMI at follow-up (kg/m^2)	23.7 (20.8–26) [51]	24.1 (21–27) [88]	0.45
HbA_{1c} at follow-up (%)	6.5 (5.9–8) [51]	7.2 (6.4–8.1) [92]	0.13
HbA_{1c} at follow-up (mmol/mol)	48 (41–64) [51]	55 (46–65) [92]	0.13
Insulin therapy at follow-up: yes/no	32/13	72/13	0.10
Systolic blood pressure at follow-up (mmHg)	120 (119–127) [49]	129 (120–139) [79]	0.0024
Diastolic blood pressure at follow-up (mmHg)	75 (70–80) [49]	75 (70–81) [78]	0.73
Arterial hypertension at follow-up: yes/no	13/36	62/18	$< 10^{-4}$
Hyperlipidemia at follow-up: yes/no	16/27	61/20	$< 10^{-4}$
Proteinuria at follow-up: yes/no	11/34	61/19	$< 10^{-4}$
Retinopathy and/or neuropathy at follow-up: yes/no	11/32	33/36	0.0281

Results are numbers or median (IQR) with numbers of available data in brackets. *Decreased renal function: CKD3– 4, defined by an eGFR between 59 and 15 mL/min/1.73 m^2, or ESRD defined by an eGFR $<$15 mL/min/1.73 m^2, dialysis, or transplantation. †Calculated by the CKD-EPI formula (30). ‡Excluding patients on dialysis or with kidney transplantation.

morphological abnormalities, decreased renal function, and hypomagnesemia (2,9). The rarity of normal renal imaging could have been related to a selection bias because, as in most series, patients were selected on the presence of renal disease (2,9). However, kidney morphological abnormalities were as frequent in relatives as in probands, indicating their high prevalence in individuals with *HNF1B* molecular defects, even when not selected on a renal phenotype. Also, the same prevalence of decreased renal function was observed in relatives and in probands, underlying the benefit of family screening. In keeping with the progressive decline of renal function reported in adult patients with HNF1B nephropathy (9), eGFR was correlated with age at follow-up. However, we identified modifiable risk factors associated with a poorer renal function at follow-up, particularly arterial hypertension (Table 3 and Supplementary Table 5). CKD was also associated with proteinuria, suggesting that diabetic glomerulopathy, observed in 5 of 20 kidney biopsy specimens, may have played a role in its occurrence. This is in keeping with a previous report showing that half the patients with *HNF1B* molecular defects referred for ESRD had a phenotype suggesting diabetic nephropathy (27).

Our study showed marked differences in the phenotypes of the patients with *HNF1B* deletion compared with those with mutations. Haploinsufficiency is acknowledged to be responsible for the clinical consequences of *HNF1B* molecular defects (2). Because *HNF1B* deletion is related to a 17q12 deletion encompassing 15 genes (15–17,19), we wondered whether deletion of genes other than *HNF1B* may alter disease phenotypes.

Patients with the whole gene deletion were leaner than those with a *HNF1B* point mutation (Table 4 and Supplementary Table 7). We speculate that the loss of two genes encompassed by the 17q12 deletion might account for this observation, namely, *ACACA*, which encodes the acetyl-CoA carboxylase 1 involved in lipogenesis in adipose tissue (35), and *ZNHIT3*, which encodes the thyroid hormone receptor-interacting protein 3 (Trip3), a peroxisome proliferator-activated receptor-γ coactivator, involved in the differentiation of preadipocytes into adipocytes (36). Of note, Trip3 is also a coactivator of *HNF4A*, haploinsufficiency of which is responsible for MODY1 (37). Thus, in patients with the 17q12 deletion, the loss of *ZNHIT3* might contribute to a more severe phenotype of diabetes at onset, as suggested by their more frequent requirement for insulin therapy (Table 4).

Patients with *HNF1B* mutations had a poorer renal prognosis than those with a whole gene deletion, as evidenced by a lower eGFR at follow-up and a higher frequency of CKD3–4 or ESRD (Table 4 and Supplementary Table 7). Several nonexclusive hypotheses can be raised. First, because HNF1B is only active as homodimers or heterodimers with HNF1A, certain mutations may have a dominant negative effect worsening the phenotype; however, no such effect has been documented for *HNF1B* mutations thus far (2). Second, genes predisposing to renal disease may be affected by the 17q12 deletion. Fatty acids have been shown to induce podocyte

Table 4—Genotype/phenotype correlations: univariate analysis

	Mutation (n = 101)	Deletion (n = 100)	P value
Sex			
Male	48	39	
Female	53	61	0.26
European Caucasian origin: yes/no	61/20	65/16	0.57
Probands/relatives	67/34	87/13	0.0008
At diagnosis of diabetes			
Age (years)	30 (19.5–37) [75]	26.5 (20–37) [84]	0.69
BMI (kg/m^2)	23.9 (22.2–25.8) [49]	21 (18.7–23.6) [62]	$<10^{-4}$
Symptoms of diabetes: yes/no	24/38	43/38	0.094
Blood glucose concentration (mmol/L)	10.6 (7.2–22.3) [36]	19.5 (8.8–30.3) [46]	0.086
HbA_{1c} (%)	8.6 (6.5–13.1) [28]	10.8 (7.1–14.4) [46]	0.14
HbA_{1c} (mmol/mol)	70.5 (48–120) [28]	94.5 (54–134) [46]	0.14
Insulin therapy: yes/no	24/44	44/28	0.0025
eGFR (mL/min/1.73 m^2)*	42 (30–55) [28]	86 (55–106) [29]	$<10^{-4}$
Renal function: normal/decreased†	8/27	32/11	$<10^{-4}$
At follow-up			
Age (years)	44.5 (33–57) [90]	38.5 (29–51) [90]	0.13
Diabetes duration (years)	16 (8–28) [69]	11 (5–16) [74]	0.033
BMI (kg/m^2)	24.9 (22–26.5) [72]	22.2 (20–26.2) [77]	0.0076
HbA_{1c} (%)	7.0 (6.2–8.0) [79]	7.1 (6.1–8.2) [73]	0.93
HbA_{1c} (mmol/mol)	53 (44–64) [79]	54 (43–66) [73]	0.93
Insulin therapy: yes/no	53/15	57/15	1.00
Systolic blood pressure (mmHg)	126.5 (120–137) [66]	122 (120–135) [63]	0.56
Diastolic blood pressure (mmHg)	74 (70–81) [65]	75 (70–80) [63]	0.98
Arterial hypertension: yes/no	44/23	31/32	0.076
Hyperlipidemia: yes/no	45/22	33/26	0.20
Age at diagnosis of kidney disease (years)	22 (10–36.5) [64]	28.5 (16–39) [58]	0.16
eGFR (mL/min/1.73 m^2)*	42.5 (30–71) [62]	75 (36–104) [63]	0.008
Renal function: normal/decreased†	20/71	38/40	0.0003
Kidney transplantation: yes/no	19/73	5/79	0.007
Proteinuria			
None	27	26	
Microalbuminuria	23	17	
Macroproteinuria	19	13	0.70
Retinopathy and/or neuropathy: yes/no	20/35	26/33	0.45

Results are actual numbers or median (IQR) with numbers of available data in brackets. *Calculated by the CKD-EPI formula (30). †Decreased renal function: CKD3–4, defined as an eGFR between 59 and 15 mL/min/1.73 m^2, or ESRD, defined as an eGFR $<$15 mL/min/1.73 m^2, dialysis, or kidney transplantation.

apoptosis, a critical step in the pathogenesis of diabetic nephropathy (38). Invalidation of both isoforms of acetyl-CoA carboxylase is required to inhibit this toxic effect of fatty acids (38), suggesting that the two isoforms are involved in diabetic nephropathy. Thus, haploinsufficiency of *ACACA* might decrease the risk of diabetic glomerular disease in patients with the 17q12 deletion.

Our study has several limitations. First, some data were missing as a result of its retrospective design, but it is by far the largest in patients with HNF1B-related disease. Second, a selection bias was obvious because most of the patients were referred as a result of the association of diabetes and renal disease. Owing to the rarity of HNF1B diabetes in children, this led us to include only patients aged ≥18 years at the time of follow-up, which may have introduced a bias in the observed phenotypes. Thus, our study cannot give an accurate frequency of diabetes in patients with *HNF1B* molecular defects or describe the full clinical spectrum of this disease. Prospective studies in children and results from large-scale next generation sequencing studies will help answer these questions.

In conclusion, this large series of patients with HNF1B-related disease allowed us to describe in detail the phenotype of HNF1B diabetes. Our results suggest that some patients might be misdiagnosed as having type 1 diabetes at onset and that some could be treated with SU/repaglinide at least for several years. We showed that diabetes complications and cardiovascular risk factors are frequent in these patients, who should benefit from prevention. We also confirmed that renal failure is a major issue in adult patients with *HNF1B* molecular defects. Lastly, we evidenced genotype/phenotype correlations that may have implications for the prognosis of these patients.

Acknowledgments. The authors thank the patients who participated in the study, the members of the French Monogenic Diabetes Study Group (see Supplementary Data) for their collaboration, C. Vigouroux (Department of Endocrinology, Saint-Antoine Hospital, Assistance Publique-Hôpitaux de Paris) for helpful discussion, and F. Bellanger, S. Clauin, G. Leroy, and C. Vaury (Department of Genetics, Pitié-Salpétrière Hospital, Assistance Publique-Hôpitaux de Paris) for molecular genetic analyses.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. D.D.-L., E.K., and J.T. collected clinical data. D.D.-L., C.B.-C., and J.T. designed the study. C.S.-M. and C.B.-C. performed genetic analyses. J.C. performed statistical analyses. All authors were involved in the writing of the manuscript. D.D.-L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Chen YZ, Gao Q, Zhao XZ, et al. Systematic review of *TCF2* anomalies in renal cysts and diabetes syndrome/maturity onset diabetes of the young type 5. Chin Med J (Engl) 2010;123:3326–3333
2. Clissold RL, Hamilton AJ, Hattersley AT, Ellard S, Bingham C. HNF1B-associated renal and extra-renal disease-an expanding clinical spectrum. Nat Rev Nephrol 2015;11:102–112
3. Horikawa Y, Iwasaki N, Hara M, et al. Mutation in hepatocyte nuclear factor-1 β gene (*TCF2*) associated with MODY. Nat Genet 1997;17:384–385
4. Bellanné-Chantelot C, Chauveau D, Gautier JF, et al. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med 2004;140:510–517
5. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1β and their related phenotypes. J Med Genet 2006;43:84–90
6. Bingham C, Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1β. Nephrol Dial Transplant 2004;19:2703–2708
7. Ulinski T, Lescure S, Beaufils S, et al. Renal phenotypes related to hepatocyte nuclear factor-1beta (TCF2) mutations in a pediatric cohort. J Am Soc Nephrol 2006;17:497–503

8. Heidet L, Decramer S, Pawtowski A, et al. Spectrum of *HNF1B* mutations in a large cohort of patients who harbor renal diseases. Clin J Am Soc Nephrol 2010;5:1079–1090
9. Faguer S, Decramer S, Chassaing N, et al. Diagnosis, management, and prognosis of *HNF1B* nephropathy in adulthood. Kidney Int 2011;80: 768–776
10. Haldorsen IS, Vesterhus M, Raeder H, et al. Lack of pancreatic body and tail in *HNF1B* mutation carriers. Diabet Med 2008;25:782–787
11. Iwasaki N, Ogata M, Tomonaga O, et al. Liver and kidney function in Japanese patients with maturity-onset diabetes of the young. Diabetes Care 1998;21:2144–2148
12. 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;8:2001–2008
13. Bingham C, Ellard S, Cole TR, et al. Solitary functioning kidney and diverse genital tract malformations associated with hepatocyte nuclear factor-1beta mutations. Kidney Int 2002;61: 1243–1251
14. Raile K, Klopocki E, Holder M, et al. Expanded clinical spectrum in hepatocyte nuclear factor 1b-maturity-onset diabetes of the young. J Clin Endocrinol Metab 2009;94:2658–2664
15. Loirat C, Bellanné-Chantelot C, Husson I, Deschênes G, Guigonis V, Chabane N. Autism in three patients with cystic or hyperechogenic kidneys and chromosome 17q12 deletion. Nephrol Dial Transplant 2010;25:3430–3433
16. Laffargue F, Bourthoumieu S, Llanas B, et al. Towards a new point of view on the phenotype of patients with a 17q12 microdeletion syndrome. Arch Dis Child 2015;100:259–264
17. Clissold RL, Shaw-Smith C, Turnpenny P, et al. Chromosome 17q12 microdeletions but not intragenic *HNF1B* mutations link developmental kidney disease and psychiatric disorder. Kidney Int 2016;90:203–211
18. Dubois-Laforgue D, Bellanné-Chantelot C, Charles P, et al.; Monogenic Diabetes Study Group of the Société Francophone du Diabète (SFD). Intellectual disability in patients with MODY due to *hepatocyte nuclear factor 1B* (*HNF1B*) molecular defects. Diabetes Metab 2017;43:89–92
19. Bellanné-Chantelot C, Clauin S, Chauveau D, et al. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity onset diabetes of the young (MODY) 5. Diabetes 2005;54:3126–3132
20. Edghill EL, Oram RA, Owens M, et al. Hepatocyte nuclear factor-1beta gene deletions–a common cause of renal disease. Nephrol Dial Transplant 2008;23:627–635
21. Richards S, Aziz N, Bale S, et al.; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–424
22. Exome Aggregation Consortium (ExAC) Browser [Internet]. Cambridge, MA [updated 14 Mar 2016]. Available from http://exac.broadinstitute.org. Accessed 26 April 2016
23. The Human Gene Mutation Database (HGMD) [Internet]. Cardiff, U.K. [updated 2015]. Available from http://www.hgmd.org. Accessed 30 April 2016
24. Combined Annotation Dependent Depletion (CADD) [Internet]. Seattle, WA. [Updated 29 July 2015]. Available from http://cadd.gs.washington.edu. Accessed 5 September 2016
25. Carette C, Vaury C, Barthélémy A, et al. Exonic duplication of the hepatocyte nuclear factor-1beta gene (transcription factor 2, hepatic) as a cause of maturity onset diabetes of the young type 5. J Clin Endocrinol Metab 2007;92:2844–2847
26. Zuber J, Bellanné-Chantelot C, Carette C, et al. HNF1B-related diabetes triggered by renal transplantation. Nat Rev Nephrol 2009;5:480–484
27. Poitou C, François H, Bellanné-Chantelot C, et al. Maturity onset diabetes of the young: clinical characteristics and outcome after kidney and pancreas transplantation in MODY3 and RCAD patients: a single center experience. Transpl Int 2012;25:564–572
28. Dubois-Laforgue D, Bellanné-Chantelot C, Subra JF, Timsit J. Pectus excavatum is part of the clinical spectrum of HNF1B MODY5. Diabetes Care 2014;37:e72–e73
29. Cheurfa N, Dubois-Laforgue D, Ferrarezi DA, et al. The common −866G>A variant in the promoter of UCP2 is associated with decreased risk of coronary artery disease in type 2 diabetic men. Diabetes 2008;57:1063–1068
30. Murphy D, McCulloch CE, Lin F, et al.; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in prevalence of chronic kidney disease in the United States. Ann Intern Med 2016;165:473–481
31. American Diabetes Association. Standards of medical care in diabetes–2010. Diabetes Care 2010;33(Suppl. 1):S11–S61
32. Pihoker C, Gilliam LK, Ellard S, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013;98:4055–4062
33. Brackenridge A, Pearson ER, Shojaee-Moradie F, Hattersley AT, Russell-Jones D, Umpleby AM. Contrasting insulin sensitivity of endogenous glucose production rate in subjects with hepatocyte nuclear factor-1β and -1α mutations. Diabetes 2006;55:405–411
34. Horikawa Y, Enya M, Fushimi N, Fushimi Y, Takeda J. Screening of diabetes of youth for hepatocyte nuclear factor 1 mutations: clinical phenotype of HNF1β-related maturity-onset diabetes of the young and HNF1α-related maturity-onset diabetes of the young in Japanese. Diabet Med 2014;31:721–727
35. Mao J, Yang T, Gu Z, et al. aP2-Cre-mediated inactivation of acetyl-CoA carboxylase 1 causes growth retardation and reduced lipid accumulation in adipose tissues. Proc Natl Acad Sci U S A 2009;106:17576–17581
36. Koppen A, Houtman R, Pijnenburg D, Jeninga EH, Ruijtenbeek R, Kalkhoven E. Nuclear receptor-coregulator interaction profiling identifies TRIP3 as a novel peroxisome proliferator-activated receptor γ cofactor. Mol Cell Proteomics 2009;8: 2212–2226
37. Iwahashi H, Yamagata K, Yoshiuchi I, et al. Thyroid hormone receptor interacting protein 3 (trip3) is a novel coactivator of hepatocyte nuclear factor-4alpha. Diabetes 2002;51: 910–914
38. Kampe K, Sieber J, Orellana JM, Mundel P, Jehle AW. Susceptibility of podocytes to palmitic acid is regulated by fatty acid oxidation and inversely depends on acetyl-CoA carboxylases 1 and 2. Am J Physiol Renal Physiol 2014;306: F401–F409