

# Mutations in the Hepatocyte Nuclear Factor-1 $\alpha$ Gene Are a Common Cause of Maturity-Onset Diabetes of the Young in the U.K.

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**Mutations in the hepatocyte nuclear factor-1 $\alpha$  (HNF-1 $\alpha$ ) gene have recently been shown to cause maturity-onset diabetes of the young (MODY). We have examined 15 U.K. MODY families for mutations in the coding region of the HNF-1 $\alpha$  gene. Eight different mutations, three frameshift (P291fsinsC, P379fsdelCT, and A443fsdelCA) and five missense mutations (P129T, R131W, R159W, P519L, and T620I), were identified in eleven families (73%). The previously reported mutation P291fsinsC was found in four pedigrees. A screen of a further 32 probands with early onset (<40 years of age) NIDDM showed the mutation in two additional families. This common mutation was present on at least three different haplotypes, suggesting that its high frequency is due to recurrent mutation rather than a founder effect. We have demonstrated that mutations in the HNF-1 $\alpha$  gene are a common cause of MODY in U.K. families and result in early onset NIDDM with a progressive clinical course. Mutation-based genetic counseling can now be considered for the majority of patients with MODY. *Diabetes* 46:720-725, 1997**

**N**IDDM affects 2-6% of the world population and is a major cause of morbidity and mortality. Both genetic and nongenetic factors contribute to the development of this heterogeneous disorder. Maturity-onset diabetes of the young (MODY) is a monogenic subgroup of early onset NIDDM inherited as a highly penetrant autosomal dominant trait (1-3). MODY accounts for 1-2% of NIDDM, with an estimated prevalence in the U.K. between 1 in 2,500 and 1 in 5,000 (4). Linkage analysis has defined three loci in MODY on chromosomes 20q (MODY1)

(5), 7p (glucokinase) (6,7), and 12q (MODY3) (8). MODY1 and MODY3 have recently been shown to be the transcription factors hepatocyte nuclear factor (HNF)-4 $\alpha$  and HNF-1 $\alpha$ , respectively (9,10). These genes are expressed in a number of tissues, including the islets of Langerhans (11).

The prevalence of HNF-1 $\alpha$  mutations in MODY is uncertain. In a large French series, glucokinase mutations were present in 56% of MODY families (12). Linkage to MODY3 was found in 50% of the remaining nonglucokinase families (8), suggesting a prevalence of <25%. In contrast, glucokinase mutations are uncommon in U.K. MODY (11%) (13,14) and Japanese early onset NIDDM (0.5%) (15). It has been suggested that the difference between France and the U.K. reflects ascertainment differences resulting in a milder phenotype being more commonly collected in France (3,13).

Here we report the results of screening a series of U.K. families with MODY for mutations in the HNF-1 $\alpha$  gene. This study shows that mutations in this gene are the principal cause of MODY in this population.

## RESEARCH DESIGN AND METHODS

**MODY families studied.** Members of fifteen pedigrees with MODY were selected for the initial mutation screen. All these families had at least two members with NIDDM diagnosed before the age of 25 years, and diabetes was inherited as an autosomal dominant trait with at least three generations of diabetic subjects. An example of a MODY pedigree is shown in Fig. 1. Linkage studies had been performed in five of these families, and logarithm of odds scores of 1.0 or above were obtained in three families using closely linked markers (16). In addition, we studied an extension of the Edinburgh pedigree in which the mutation had already been described (10).

An additional 32 subjects who had an early onset of diabetes (<40 years of age), which in some cases was familial, but did not fulfill our strict diagnostic criteria for MODY, were screened for those mutations that were found in more than one of the initial 15 families.

DNA was isolated from peripheral blood lymphocytes using the Nucleon DNA Extraction kit according to the manufacturer's instructions (Scot Lab).

**Identification of mutations in the HNF-1 $\alpha$  gene.** The 10 exons and flanking introns of the HNF-1 $\alpha$  gene were amplified by polymerase chain reaction (PCR) using genomic DNA from a single proband and sequence-specific primers (10). PCR was performed in a 25- $\mu$ l volume containing 10 mmol/l Tris-HCl, pH 8.3, 50 mmol/l KCl, 1-1.5 mmol/l MgCl<sub>2</sub>, 200  $\mu$ mol/l dNTPs, 250  $\mu$ mol/l each primer, 0.25 U AmpliTaq Gold Taq polymerase (Perkin-Elmer), and 100 ng DNA. The cycling conditions were 15 min at 95°C followed by 30 cycles consisting of 30 s at 94°C, 30 s at 62°C, and 45 s at 72°C, with the exception of exon 9, for which the annealing temperature was reduced to 52°C.

The PCR products were purified using a Microcon-100 (Amicon) before both strands were sequenced using an AmpliTaq FS Dye Terminator Cycle Sequencing Kit (Perkin-Elmer Applied Biosystems) according to the manufacturer's recommendations. The reactions were analyzed on an ABI Prism 377 DNA Sequencer.

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HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of the young; PCR, polymerase chain reaction.

TABLE 1  
HNF-1 $\alpha$  gene mutations in U.K. MODY3 families

Family	Exon	Codon	Nucleotide change	Coding effect	Mutation designation	Number of diabetics with the mutation	Mean age at diagnosis (range)	Treatment		
								Diet	OHA	Insulin
65	2	129	CCA→ACA	Pro→Thr	P129T	1	21		1	
44	2	131	CGG→TGG	Arg→Trp	R131W	3	18.7 (9–31)		2	1
45	2	159	CGG→TGG	Arg→Trp	R159W	2	15.5 (11–20)		1	1
19*	4	291	Insertion C	Frameshift	P291fsinsC	10	20.4 (14–38)	3	3	4
2	4	291	Insertion C	Frameshift	P291fsinsC	4	27.5 (12–70)		1	3
6	4	291	Insertion C	Frameshift	P291fsinsC	3	17 (14–23)	1	1	1
25	4	291	Insertion C	Frameshift	P291fsinsC	1	21		1	
34	4	291	Insertion C	Frameshift	P291fsinsC	7	27.4 (13–37)	3	2	2
48	4	291	Insertion C	Frameshift	P291fsinsC	3	22 (8–45)	1	2	
59	4	291	Insertion C	Frameshift	P291fsinsC	2	23.5 (21–26)		2	
14†	6	379	Deletion CT	Frameshift	P379fsdelCT	5	16.8 (12–21)	3	2	
37	6	379	Deletion CT	Frameshift	P379fsdelCT	2	19 (13–25)	1		1
4	7	443	Deletion CA	Frameshift	A443fsdelCA	4	21.5 (10–30)		3	1
17‡	7	447	CCG→CTG	Pro→Leu	P447L	7	20.3 (6–36)	1	2	4
22	8	519	CCG→CTG	Pro→Leu	P519L	3	17 (16–18)	2		1
96	10	620	ACC→ATC	Thr→Ile	T620I	7	34 (15–77)	1	5	1
<b>Total</b>						<b>64</b>	<b>22.5 (6–77)</b>	<b>16</b>	<b>28</b>	<b>20</b>

\*Additional members of the Edinburgh family from Yamagata et al. (10). †Family R from Yamagata et al. (10). ‡Family A from Yamagata et al. (10). OHAs, oral hypoglycemic agents.

Heterozygous sequence changes were considered likely to be mutations if they 1) resulted in the replacement of a conserved amino acid or in a change in reading frame (frameshift), 2) cosegregated with diabetes within the pedigree, and 3) were not present in 50 normal chromosomes. Representative examples of heterozygous mutations are shown in Fig. 2.

**Haplotypes.** Haplotypes were constructed using the intragenic polymorphisms described in Tables 2 and 3 by inspection of segregation patterns and assuming a minimal number of crossovers. No crossover events were observed in the region spanned by the five polymorphisms in any of the families studied.

## RESULTS

Mutations in the HNF-1 $\alpha$  gene were identified in 11 of the initial 15 families and 2 of the further 32 probands screened for the two mutations, which were found in more than one family. A summary of all mutations in U.K. MODY families and their clinical characteristics is presented in Table 1. This includes the three U.K. families described by Yamagata et al. (10) (the R family, A family, and Edinburgh family, which correspond to pedigrees 14, 17, and 19, respectively). A total of nine different mutations have been observed in 16 U.K. families, of which six are newly described.

The novel mutations identified in the U.K. families include one frameshift (A443fsdelCA) and five missense mutations: P129T, R131W, R159W, P519L, and T620I. The mutations P129T, R131W, and R159W alter an amino acid that is conserved in the sequences of human, rat, mouse, hamster, chicken, salmon, and *Xenopus* HNF-1 $\alpha$  and the functionally and structurally related human and mouse HNF-1 $\beta$  proteins. The mutation P519L involves a residue that is conserved in all but the sequence of salmon HNF-1 $\alpha$ , where it is serine. Similarly, residue 620 is threonine in human, rat, mouse, hamster, and chicken HNF-1 $\alpha$ , and the conservative replacement of serine occurs in the *Xenopus* and salmon proteins (this region of the protein is not present in HNF-1 $\beta$ ). In five families, DNA was available from other members. The mutations cosegregated with diabetes within the families and

were not present in normal healthy nondiabetic family members, except for one individual in family 96 who was not diabetic at age 42.

The frameshift mutation in exon 4 P291fsinsC resulting from the insertion of a C in the C-tract encoding the sequence 289-ProProPro-291 was present in 4 of the 15 families (2, 6, 34, and 48). Subsequent specific mutation testing (sequencing of exon 4 only) in a further 32 probands identified two further families with this same mutation (25 and 59). The P291fsinsC mutation had previously been described in a branch of the Edinburgh family (10) and was shown to be present in 11 additional diabetic members of this family and also in two subjects, both aged 8 years, who had normal glycated hemoglobin levels. The only other subjects in whom this mutation was not associated with a clinical diagnosis of diabetes were two individuals (03 and 12) in pedigree 34 (Fig. 1) who had fasting blood glucose values of 4.5 and 4.3 mmol/l at ages 26 and 22, respectively (oral glucose tolerance tests not performed).

The seven U.K. MODY families with the P291fsinsC mutation were not known to be related; however, a founder effect had previously been demonstrated in four apparently unrelated U.K. families with the same glucokinase mutation (17). The results of intragenic polymorphism analysis (Table 2) show that this mutation occurs on at least three different haplotypes, making a common ancestor unlikely.

The P379fsdelCT mutation was found in pedigrees 14 and 37. These families were not known to be related, and a similar intragenic polymorphism analysis argued against a founder effect (Table 3). As previously stated, a further 32 probands were screened for this mutation, but no more subjects with this mutation were identified.

In addition to the diabetes-associated mutations described above, we found four new polymorphisms, including three novel silent mutations and one intronic polymorphism (Table 4).

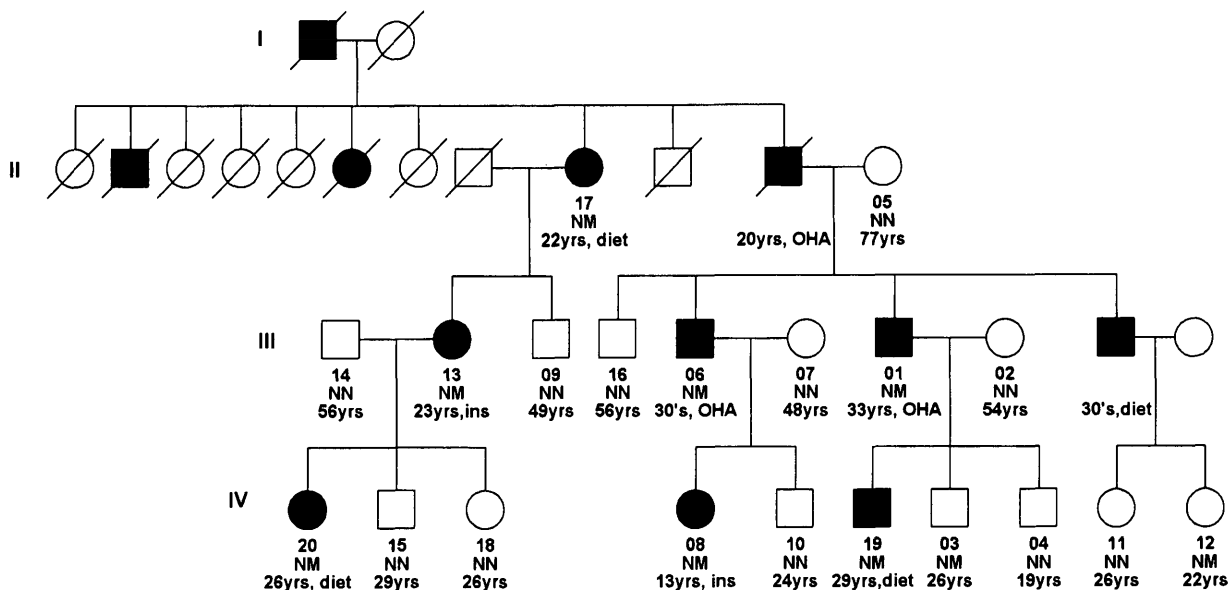


FIG. 1. Pedigree 34, showing inheritance of the HNF-1 $\alpha$  mutation P291fsinsC. Roman numerals on the left of the figure indicate generation number, and numbers below the symbol indicate individuals from whom DNA was available. The HNF-1 $\alpha$  genotype of each individual tested is indicated below the symbol: N, normal; M, P291fsinsC. The age of diagnosis and treatment (ins, insulin; OHA, oral hypoglycemic agents) or age of testing fasting blood glucose is shown below the genotype information.

DISCUSSION

This study demonstrates that mutations in the HNF-1 $\alpha$  gene are a common cause of MODY in the U.K. Mutations were found in 11 of the 15 previously untested families (73%) chosen by strict clinical criteria. In addition, we found the common P291fsinsC mutation in 2 of 32 less stringently defined families. This high prevalence is compatible with the low frequency of glucokinase mutations found in U.K. MODY families (13,14) and it contrasts with results from France, where the majority of MODY results from glucokinase mutations, with <25% of MODY families linked to the MODY 3 locus (8). This probably reflects an ascertainment bias; our U.K. patients are predominantly referred by hospital consultants and have clinical diabetes often requiring tablet or insulin treatment and are frequently associated with complications (the HNF-1 $\alpha$  phenotype). In the French series, subjects with the mild fasting hyperglycemia or glucose intolerance associated with glucokinase mutations were more likely to be detected by screening young relatives of families with NIDDM.

The mutations we describe are associated with a discrete clinical phenotype of diabetes, diagnosed at a mean age of

22.5 years, usually with symptoms of hyperglycemia, with only 3 of 64 diabetic subjects being diagnosed after 40 years. Treatment with diet may be adequate initially, but there is a progressive increase in hyperglycemia, with most patients eventually requiring tablets or insulin. Of our 64 patients with HNF-1 $\alpha$  mutations, 25% are treated by diet, 44% with tablets, and 31% with insulin. There is a high penetrance, with only 5 of 69 (7%) subjects with a mutation not having clinical diabetes. Four of these subjects, aged 8, 8, 22, and 26 years, may develop diabetes later in life. One nondiabetic subject with the T620I mutation did not have diabetes at age 42 years and may be nonpenetrant.

In our series, we observed a common mutation, P291fsinsC in exon 4, in seven families. Intragenic polymorphism analysis suggests that the common finding was not as a result of single founder mutation in an isolated population, since the mutation was inherited with at least three different haplotype patterns. The C-tract in which this insertion occurs consists of eight or nine cytosines (depending on the G/C polymorphism at codon 288). Because runs of identical bases are prone to deletion or insertion of one base by slipped mis-

TABLE 2  
Haplotype analysis in families with the P291fsinsC mutation

	Exon 4 codon 288	Exon 7 codon 459	Exon 7 codon 487	Intron 7 nucleotide 7	Exon 8 codon 515
Frequency	0.67 G	0.63 C	0.72 G	0.57 G	0.79 G
Family					
2	C	C	G	G	A
19	C	C	G	G	A
48	C	C	G	G	A
34	G	C	G	G	G
6	G	C	G	G	G
59	G	C	G	A	G
25	G/C	C	G	G	G/A

Allele frequencies from Yamagata et al. (10).

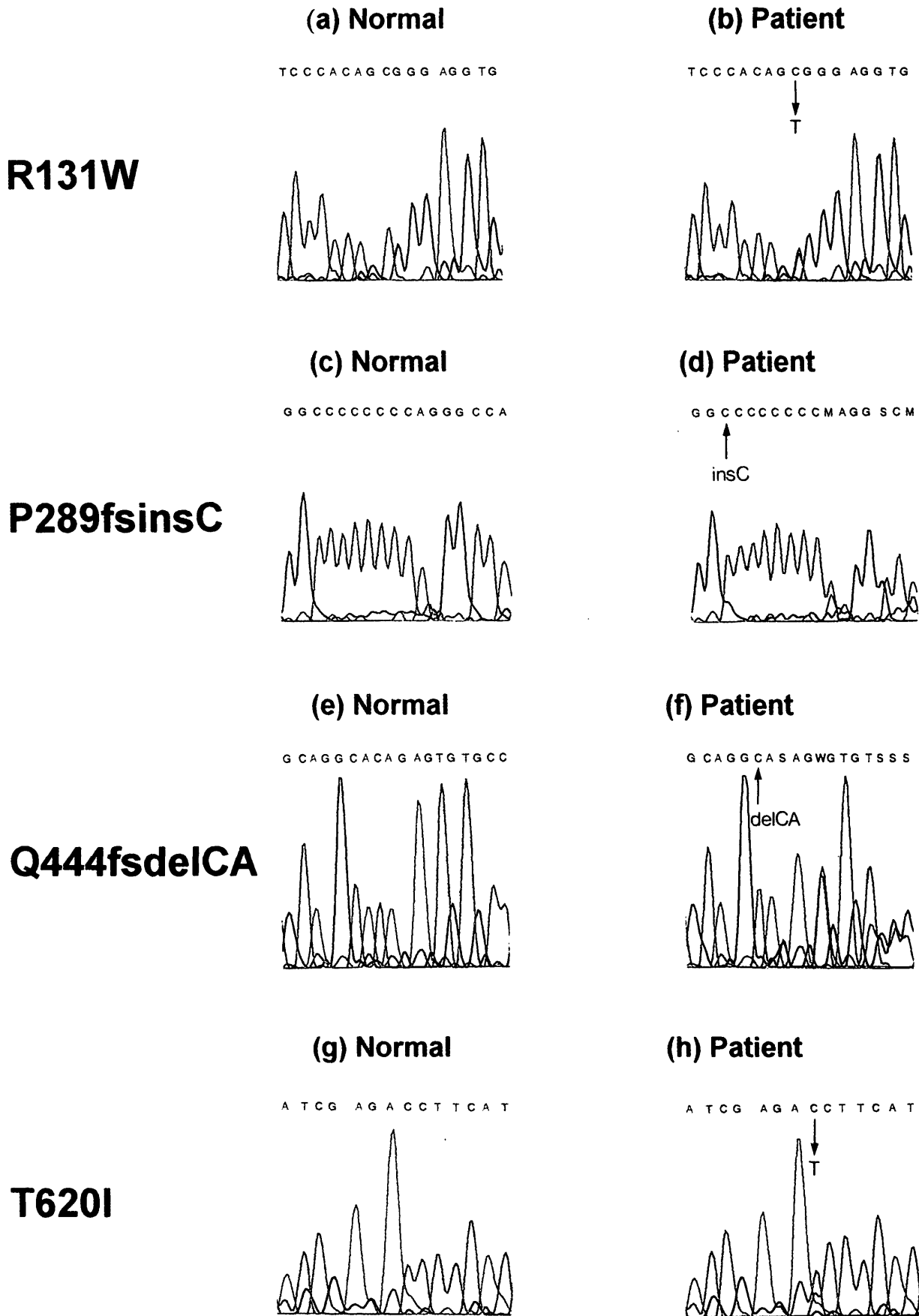


FIG. 2. Heterozygous HNF-1 $\alpha$  gene mutations and normal sequences for the mutations R131W, P291fsinsC, A443fsdelCA, and T620I. Partial sequences of exon 2, normal (a); exon 2, Pedigree 44 (b); exon 4, normal (c); exon 4, Pedigree 2 (d); exon 7, normal (e); exon 7, Pedigree 4 (f); exon 10, normal (g); and exon 10, Pedigree 96 (h).

TABLE 3  
Haplotype analysis in families with the P379fsdelCT

	Exon 4 codon 288	Exon 7 codon 459	Exon 7 codon 487	Intron 7 nucleotide 7	Exon 8 codon 515
Frequency	0.67 G	0.63 C	0.72 G	0.57 G	0.79
Family					
14	C	C	G	G	G
37	G	C	G	G	G

Allele frequencies from Yamagata et al. (10).

pairing at the replication fork, the existence of a long C-tract will make this a potential source of mutations of this type, and it may well be that each family represents an isolated spontaneous mutation. Further work is required to confirm this hypothesis. The A443fsdelCA mutation is a two base pair deletion that occurs within a CACA repeat and may also be due to slipped mispairing during DNA replication.

The three frameshift mutations (P291fsinsC, P379fsdelCT, and A443fsdelCA) are predicted to result in the production of truncated proteins of 316, 417, and 501 amino acids, respectively. COOH-terminal deletions of HNF-1 $\alpha$ , which reduce the protein length to between 348 and 416 residues, have been found to accumulate outside the nuclear membrane, where they are unable to activate the target gene (18). Further investigations are required to determine whether any of these truncated proteins are localized in the cytoplasm rather than the nucleus.

The role of the five novel missense mutations, P129T, R131W, R159W, P519L, and T620I, in causing disease is not well defined. In the absence of a functional assay, it is impossible to formally rule out a rare "private" linked polymorphism. However, it is likely that these mutations are significant, since they result in the substitution of conserved amino acids. Five of the six point mutations were C-to-T transitions, with four of these occurring at CpG dinucleotides. These are known to be mutation hot spots (19), presumably due to the deamination of methylated cytosine to thymidine.

Whether predisposing mutations in HNF-1 $\alpha$  are important in some subjects with NIDDM is not known. Studies in French, Mexican-American, and Japanese families suggest that it is unlikely to play a major role (20,21) (N. Iwasaki, G.I.B., unpublished observations). However, the recent description of linkage of the MODY3 region in a subgroup of Finnish NIDDM families with a mean age of 58 years but a low insulin response suggests that as much as 25% of NIDDM could be explained by mutations in this gene (22). Other HNF-1 $\alpha$  mutations may be associated with a less severe or more slowly progressing  $\beta$ -cell defect, which results in the development of NIDDM in older age. This warrants further investigation.

TABLE 4  
Novel DNA polymorphisms in the HNF-1 $\alpha$  gene

	Location	Nucleotide (amino acid) change	Frequency
Exon 2	Codon 126	CAC (His) $\rightarrow$ CAT (His)	C, 0.97; T, 0.03
Exon 4	Codon 290	CCC (Pro) $\rightarrow$ CCT (Pro)	C, 0.99; T, 0.01
Exon 9	Codon 550	GAG (Ser) $\rightarrow$ CAG (Ser)	G, 0.90; C, 0.10
Intron 1	Nucleotide -52	T $\rightarrow$ G	T, 0.96; G, 0.04

Our work suggests that mutations in HNF-1 $\alpha$  are a common cause of MODY, especially when patients present with symptomatic diabetes before the age of 25 years. MODY affects between 1 in 2,500 and 1 in 5,000 people in the U.K., and mutation-based predictive testing can now be offered to the majority of these families.

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