Mutations in the Hepatocyte Nuclear Factor-1α/MODY3 Gene in Japanese Subjects With Early- and Late-Onset NIDDM

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Recent studies have shown that mutations in the hepatocyte nuclear factor (HNF)-1α gene are the cause of maturity-onset diabetes of the young type 3 (MODY3). We have screened 193 unrelated Japanese subjects with NIDDM for mutations in this gene: 83 with early-onset NIDDM (diagnosis at <30 years of age) and 110 with late-onset NIDDM (diagnosis ≥30 years of age). All of the members of the latter group also had at least one sibling with NIDDM. The 10 exons, flanking introns, and promoter region were amplified using polymerase chain reaction and were sequenced directly. Mutations were found in 7 of the 83 (8%) unrelated subjects with early-onset NIDDM. The mutations were each different and included four missense mutations (L12H, R131Q, K205Q, and R263C) and three frameshift mutations (P379fsdelCT, T392fsdelA, and L584S585fsinsTC). One of the 110 subjects with late-onset NIDDM was heterozygous for the missense mutation G191D. This subject, who was diagnosed with NIDDM at 64 years of age, also had a brother with NIDDM (age at diagnosis, 54 years) who carried the same mutation, suggesting that this mutation contributed to the development of NIDDM in these two siblings. None of these mutations were present in 50 unrelated subjects with normal glucose tolerance (100 normal chromosomes). Mutations in the HNF-1α gene occur in Japanese subjects with NIDDM and appear to be an important cause of early-onset NIDDM in this population. In addition, they are present in about 1% of subjects with late-onset NIDDM. *Diabetes* **46:1504–1508, 1997**

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MODY, maturity-onset diabetes of the young; HNF, hepatocyte nuclear factor; OGTT, oral glucose tolerance test; OHA, oral hypoglycemic agent; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

NIDDM affects about 10% of Japanese over 40 years of age (1) and represents a major public health problem in this population as in others (2). We and others have begun a search for the genes that contribute to the development of NIDDM in Japanese in order to improve its diagnosis, treatment, and prevention in this population; the search has included direct analysis of candidate genes for diabetes-associated mutations. These studies have found mutations in the glucokinase (3), insulin (4), insulin receptor (5), insulin receptor substrate-1 (6), GLUT2 (7,8), and islet amyloid polypeptide genes (9) as well as in the maternally inherited mitochondrial genome (10). However, none of these genes is a major determinant of diabetes susceptibility in Japanese.

Recent studies have shown that mutations in the functionally related transcription factors hepatocyte nuclear factor (HNF)-1α (11) and HNF-4α (12) can cause maturity-onset diabetes of the young (MODY) (13), an early-onset form of NIDDM. Here we report the identification of eight different mutations in the HNF-1α gene in Japanese subjects with NIDDM. Mutations in the HNF-1α gene were found in 8% of subjects with early-onset NIDDM, and as such they represent the most common cause of early-onset NIDDM/MODY in Japanese identified to date. In addition, mutations in the HNF-1α gene can be found at a low frequency (~1%) in subjects with late-onset NIDDM.

RESEARCH DESIGN AND METHODS

Subjects. All subjects were ascertained from among patients attending the outpatient clinic of the Diabetes Center, Tokyo Women's Medical College. NIDDM was diagnosed using World Health Organization criteria (14). At the time of recruitment, informed consent was obtained from each subject and a blood sample was taken for DNA isolation. Subjects were divided into two groups based on age at diagnosis. The early-onset group included 83 unrelated subjects who were diagnosed with NIDDM before 30 years of age, including 41 with a clinical diagnosis of MODY. The late-onset group (age at diagnosis ≥30 years of age) included 110 unrelated subjects from a sample of affected sib pairs in which we are carrying out a genomewide screen for NIDDM susceptibility genes (15). The clinical characteristics of the two groups are summarized in Table 1. Retinopathy was evaluated by an ophthalmologist at the diabetes center. Nephropathy was diagnosed by testing for microalbuminuria or proteinuria. The control group consisted of 50 normal healthy Japanese subjects without a family history of diabetes and with normal glucose tolerance as determined by the results of a 75-g oral glucose tolerance test (OGTT).

Mutation analysis. The 10 exons, flanking introns, and minimal promoter of the HNF-1α gene were screened for mutations after polymerase chain reaction (PCR) amplification and direct sequencing of both strands of the PCR product as described previously (11,16). The sequence of each mutation was confirmed by

cloning the PCR product into pGEM-T (Promega, Madison, WI) and sequencing clones representing both alleles. The occurrence of putative mutations in other family members and normal healthy subjects was determined by PCR–restriction fragment length polymorphism (RFLP) if the nucleotide substitution resulted in the gain or loss of a site for a restriction endonuclease or by direct sequencing of the PCR product if there was no change in a site.

RESULTS

Mutations in the HNF-1α gene. Eight mutations (Table 2) were found on screening the 10 exons, flanking introns, and minimal promoter in the 193 Japanese subjects with NIDDM. All of the mutations were located in the coding region of the gene and included five missense (L12H, R131Q, G191D, K205Q, and R263C) and three frameshift mutations (P379fsdelCT, T392fsdelA, and L584S585fsinsTC). No mutations or polymorphisms were found in the minimal promoter of the HNF-1α gene, a region containing the binding sites for HNF-4α and HNF-3, both of which have been implicated in the regulation of HNF-1α expression (16). None of the mutations were found in 50 normal healthy subjects (100 normal chromosomes).

DNA polymorphisms in the HNF-1α gene. Twelve polymorphisms were observed in our Japanese subjects (Table 3), three of which (Leu^{459}, CTG → CTA; intron 5, nt +9; and intron 5, nt –42) were not observed in whites (11). Six sites that are polymorphic in whites (codons 98, 288, and 515; intron 1, nt –91; intron 5, nt –47; and intron 9, nt +44) are monophoric in Japanese. Of these, the very low frequency of the GGC allele at Gly^{288} in Japanese subjects is noteworthy. In whites, this allele is associated with recurrent insertions and deletions of a cytosine in the oligo-C tract following codon 288 (16,17). The low frequency of the GGC allele at Gly^{288} in Japanese suggests that the oligo-C tract following this codon will not be a mutational hotspot in this population as it is in whites.

Clinical features of subjects with HNF-1α mutations. Seven mutations were found in subjects from the early-onset group and one in a subject from the late-onset group. The clinical features and pedigrees of six of the subjects with early-onset NIDDM (J2-10, -15, -22, -86, -91 and -105; Table 4 and Fig. 1) are consistent with a diagnosis of MODY. Genotyping of other affected members of the J2-10 and -86 families showed that they had inherited the same mutation as the proband. Subject J2-41 had no family history of diabetes by interview, and other family members were not available for testing. Three of the seven early-onset subjects with mutations were being treated with diet, one was being treated with an oral hypoglycemic agent, and the remaining three were being treated with insulin. The three subjects being treated with insulin had NIDDM of long duration, and all showed evidence of microvascular complications (proliferative retinopathy or nephropathy).

TABLE 1
Clinical features of Japanese subjects with early- and late-onset NIDDM

	Early-onset	Late-onset
n (M/F)	83 (43/40)	110 (60/50)
Age at diagnosis (years)	17.9 ± 4.7 (9–29)	45.8 ± 9.5 (30–74)
Fasting glucose (mmol/l)	8.8 ± 3.3	8.8 ± 2.6
Fasting insulin (pmol/l)	51.8.0 ± 32.3	44.4 ± 18.7
Treatment (diet/OHA/insulin)	16/14/53	29/48/33

Data are *n* or means ± SD (range). The values for fasting glucose and insulin are current values measured with the subjects on diabetes treatment. OHA, oral hypoglycemic agent.

The one subject with late-onset NIDDM, J1-58, is quite interesting, since all mutations in HNF-1α identified to date have been found in subjects with early-onset NIDDM/MODY (11,16–18). This subject was 64 years of age when diagnosed with NIDDM. An OGTT at 62 years of age was normal, suggesting that he had late-onset NIDDM rather than undiagnosed MODY. His brother, who was diagnosed with diabetes at age 54 years, also had inherited the mutant allele, a result consistent with the G191D mutation, which contributes, at least in part, to the development of NIDDM. Clinical and genetic studies of other members of this family, as well as molecular biological studies of the effect of the G191D mutation on HNF-1α function, may clarify the relationship between HNF-1α mutations and late-onset NIDDM.

DISCUSSION

Mutations in the HNF-1α gene are associated with MODY (11), an autosomal dominant form of NIDDM characterized by a primary defect in insulin secretion (18,19). HNF-1α is one of several transcription factors that function in tissue-specific regulation of genes in the liver (20). It is also expressed in pancreatic β-cells, although the HNF-1α–dependent target genes in β-cells are unknown (20). The molecular mechanism (e.g., loss of function, dominant negative) by which mutations in HNF-1α cause diabetes is unknown, but the effect of these mutations on cellular function appears to be relatively specific to the β-cell because subjects with such mutations have no evidence of hepatic, intestinal, or renal dysfunction.

TABLE 2
Mutations in the HNF-1α gene in Japanese subjects with NIDDM

Subject	Location of mutation: Exon	Location of mutation: Codon	Nucleotide change	Amino acid change	Designation	RFLP
J1-58	3	191	GGT→GAT	Gly→Asp	G191D	Loss of *Hph* I site
J2-10	3	205	AAG→CAG	Lys→Gln	K205Q	Gain of *Bsr* I site
J2-15	6	379	Deletion of CT	Frameshift	P379fsdelCT	—
J2-22	9	584/585	Insertion of TC	Frameshift	L584S585fsinsTC	Loss of *Blp* I site
J2-41	4	263	CGT→TGT	Arg→Cys	R263C	—
J2-86	6	392	ACA→_CA	Frameshift	T392fsdelA	Gain of *Sfa*NI site
J2-91	2	131	CGG→CAG	Arg→Gln	R131Q	Loss of *Msp*AII site
J2-105	1	12	CTC→CAC	Leu→His	L12H	Loss of *Ban* II site

TABLE 3
DNA polymorphisms in human HNF-1α gene in Japanese subjects

Location Exon/intron	Codon/nt	Nucleotide change	Frequency
Exon 1	Codon 17	CTC (Leu)→CTG (Leu)	C = 0.54, G = 0.46
	Codon 27	ATC (Ile)→CTC (Leu)	A = 0.51, C = 0.49
	Codon 98	GCC (Ala)→GTC (Val)	C = 1.00, T = 0.00
Exon 4	Codon 288	GGG (Gly)→GGC (Gly)	G = 1.00, C = 0.00
Exon 7	Codon 459	CTG (Leu)→TTG (Leu)	C = 0.45, T = 0.55
		CTG (Leu)→CTA (Leu)	G = 0.99, A = 0.01
	Codon 487	AGC (Ser)→AAC (Asn)	G = 0.49, A = 0.51
Exon 8	Codon 515	ACG (Thr)→ACA (Thr)	G = 1.00, A = 0.00
Intron 1	nt −91	A→G	A = 1.00, G = 0.00
	nt −42	G→A	G = 0.58, A = 0.42
Intron 2	nt −51	T→A	T = 0.86, A = 0.14
	nt −23	C→T	C = 0.50, T = 0.50
Intron 5	nt +9	C→G	C = 0.98, G = 0.02
	nt −47	C→T	C = 1.00, T = 0.00
	nt −42	G→T	G = 0.76, T = 0.24
Intron 7	nt +7	G→A	G = 0.50, A = 0.50
Intron 9	nt +44	C→T	C = 1.00, T = 0.00
	nt −24	T→C	T = 0.50, C = 0.50

The frequency of each polymorphism was based on the results of genotyping the 193 unrelated Japanese subjects described in METHODS. DNA polymorphisms found in introns are noted with respect to the splice donor or acceptor site. Sites that are shown as being monomorphic in Japanese are polymorphic in white subjects (11).

We have identified eight different mutations in the HNF-1α gene in Japanese subjects with diabetes (Table 2), six of which have not been previously described. The R131Q mutation was found in unrelated U.S. and German MODY subjects (11,16), and the P379fsdelCT mutation was found in two British (11,17) and one French subject (21).

The four new missense mutations described in this report—L12H, R131Q, K205Q, and R263C—affect residues that are conserved in human, rat, mouse, hamster, chicken, frog (*Xenopus*), and fish (salmon) HNF-1α and in the structurally related protein human HNF-1β. The L12H mutation is located in the dimerization domain of HNF-1α (20) and could affect the formation of homo- or heterodimers (with HNF-1β). The R131Q mutation is located in the linker region between the dimerization and DNA-binding regions, the function of which is unknown. K205Q and R263C are located in the DNA-binding domain and could affect DNA recognition and/or binding. The mutation G191D affects a residue in the DNA-binding domain that is conserved in human, rat, mouse, hamster, chicken, and fish HNF-1α but not in frog HNF-1α or human HNF-1β. It is predicted to be located in the turn between α-helices 2 and 3 of the POU subdomain (22,23) and thus could affect DNA recognition and/or binding.

The frameshift mutations, P379fsdelCT and T392fsdelA, would generate mutant truncated proteins of 416 and 411 amino acids, respectively, whereas the L584S585fsinsTC mutation would result in the synthesis of a mutant protein of 659 amino acids, which is larger than the normal protein (631 residues). These frameshift mutations affect the COOH-terminal transactivation domain of HNF-1α, and as such, the mutant proteins would be predicted to be impaired in transactivation (20).

TABLE 4
Clinical characteristics of Japanese subjects with mutations in the HNF-1α gene

Subject	Mutation	Age at diagnosis (years)	Duration of NIDDM (years)	Fasting BMI/Max BMI (kg/m^2)	glucose (mmol/l)	Insulin (pmol/l) Fasting	Insulin (pmol/l) 30-min	Current therapy	Complications
J1-58	G191D	64	4	20.9/23.1	6.2	45.6	146.4	Diet	Absent
J2-10	K205Q	17	21	17.5/19.1	5.1	31.2	221.4	Diet	Absent
J2-15	P379fsdelCT	15	15	19.5/20.2	10.2	50.4	128.4	OHA	Absent
J2-22	L584S585fsinsTC	13	23	20.3/22.7	—	—	—	Insulin	PDR, CRF
J2-41	R263C	28	7	22.2/23.6	7.4	18.0	32.4	Diet	Absent
J2-86	T392fsdelA	16	20	22.4/23.5	—	—	—	Insulin	PDR
J2-91	R131Q	9	21	20.9/21.3	—	—	—	Insulin	PDR; macroproteinuria
J2-105	L12H	9	1	20.7/20.7	6.1	174.0	240.6	Diet	Absent

The fasting and 30-min insulin values in normal healthy Japanese subjects are 43.9 ± 18.1 and 228.3 ± 180.0 pmol/l, respectively (mean ± SD). OHA, oral hypoglycemic agent; PDR, proliferative diabetic retinopathy; CRF, chronic renal failure.

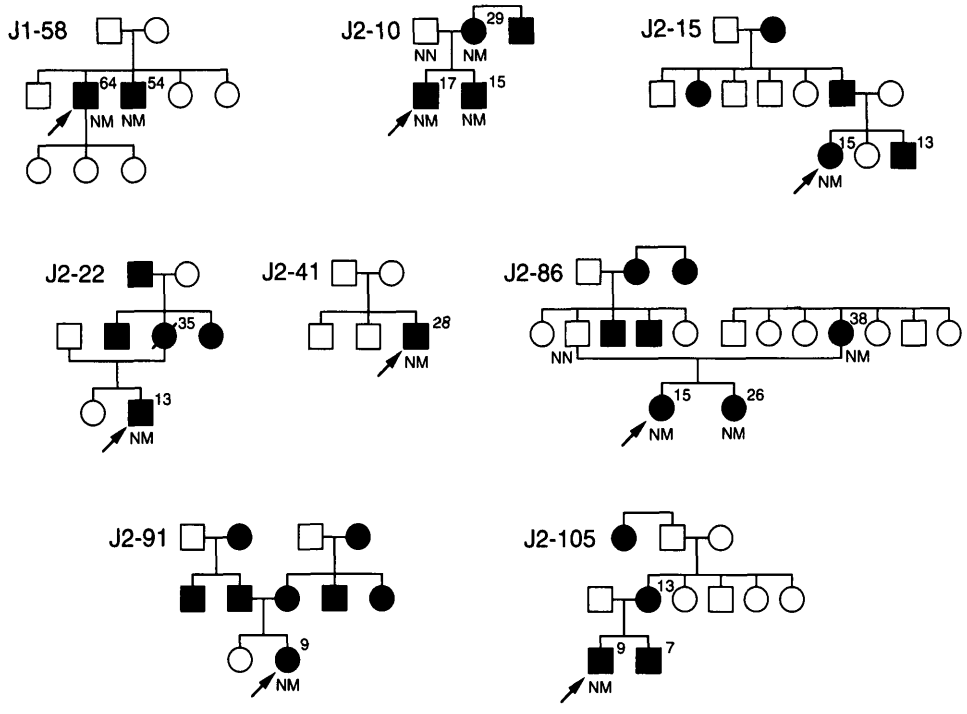

FIG. 1. Pedigrees of Japanese families with mutations in the HNF-1α gene. Individuals with NIDDM/MODY are noted by black symbols and non-diabetic subjects by open symbols. The age at diagnosis of diabetes, if known, is indicated at the top right corner of the symbol. The arrow shows the subject who was screened for mutations. The HNF-1α genotype, if known, is indicated below the symbol: N, normal; M, mutant.

Mutations in the HNF-1α gene have been found in white subjects with MODY of British (11,16,17), Danish (16,24), French (21), German (16), and Finnish ancestry (19) and are a common cause of MODY in these populations. The present study shows that mutations in the HNF-1α gene are also associated with early-onset NIDDM/MODY in Japanese and may be an uncommon cause of late-onset NIDDM as well. Mutations in the HNF-1α gene were found in 8% of Japanese with early-onset NIDDM and 15% (6 of 41) with MODY and are the most common cause of this form of diabetes in Japanese identified to date. Thus subjects with early-onset NIDDM/MODY should be screened for mutations in the HNF-1α gene. When mutations are found, other family members should be tested in order to identify those who are genetically at risk of developing diabetes, since early diagnosis and prompt treatment may reduce the risk of complications (25).

Mahtani et al. (26) have proposed that NIDDM2, a locus causing NIDDM associated with low insulin secretion, is allelic with *MODY3*, the HNF-1α gene, with severe mutations causing MODY and milder mutations giving rise to later-onset NIDDM. Our identification of a mutation in a subject with late-onset NIDDM is consistent with this hypothesis. Moreover, this result suggests that 0.9% of Japanese with late-onset NIDDM, or as many as 45,000 people, may have NIDDM because of mutations in the HNF-1α gene.

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