Table 1. Patient characteristics of novel missense or promoter polymorphisms

Site	Codon	bp change (aa change)	Family history of diabetes	Diagnosis			Subsequent therapy at 6 years
				Age (yrs)	Fasting glucose (mmol/l)	BMI (kg/m^2)	
Promoter	–237	G > A	Yes (not insulin)	42	6.2	25	Diet, fasting glucoses 6.4–8.5 mmol/l
Promoter	–8–9	2 bp deletion	No	33	7.2	22	Diet, fasting glucoses 4.9–5.3 mmol/l
Exon 4	301	G > A (Ala/Thr)	No	45	7.2	25	Insulin 24 U (1), fasting glucoses 4.9–8.5 mmol/l
Exon 7	492	C > T (Thr/Ile)	No	37	8	23	Chlorpropamide 100 mg (2), fasting glucoses 5.3–7.2 mmol/l
Exon 7	498	C > A (Ser/Arg)	Yes	46	13	38	Glibenclamide (3) 20 mg & metformin 2550 mg, fasting glucose 12 mmol/l

(1) Insulin requiring when symptomatic on maximum sulphonylurea and metformin therapies
(2) Allocated to chlorpropamide as fasting glucose > 6.0 mmol/l
(3) Allocated to diet and transferred to sulphonylurea therapy when fasting glucose > 15 mmol/l

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Molecular genetics of MODY in Germany

Dear Sir,
Ledermann has suggested that approximately 2 % of all diabetic patients in Germany are likely to have maturity-onset diabetes of the young (MODY) [1]. The contribution of mutations in the known MODY genes to the overall prevalence of this form of diabetes in Germany is not known. As a first step in addressing this problem, we have studied 11 families of German ancestry with a probable diagnosis of MODY, i.e. diagnosis of diabetes before 25 years of age in at least one family member and other first-degree relatives with MODY or Type II (non-insulin-dependent) diabetes (Fig. 1). Family Dresden-1 was from the state of North Rhine-Westfalia, families Dresden-2, –4, –6, –7, –13, –15, and –17 from Saxony, and families Dresden-3, –5, and –11 were from Thuringia. The average age at diagnosis of diabetes in the probands was 18.2 ± 6.6 (range 12–25 years) (means ± SEM) and included four men and seven women. Of the eleven probands, six, two and three were currently being treated with insulin, oral hypoglycaemic agents and diet, respectively. The average body mass index (BMI) was 25.7 ± 5.9 kg/m^2 (range

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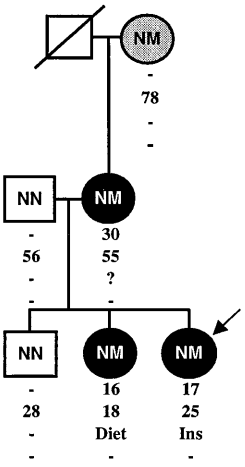
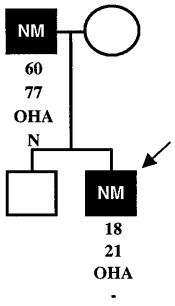
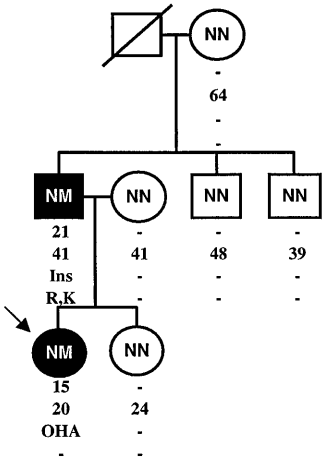
Dresden-1
(*HNF-1α*, P291fsinsC)



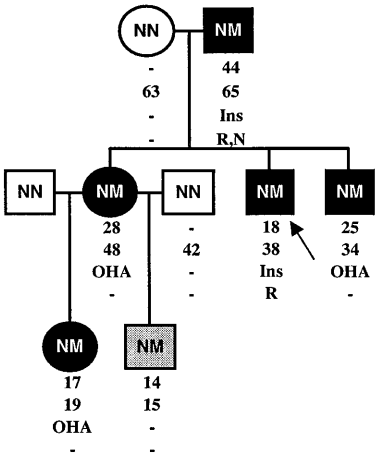
Dresden-2
(*HNF-1α*, R131Q)



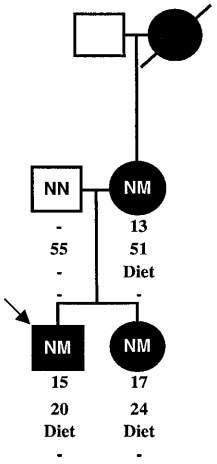
Dresden-3
(*HNF-1α*, R229Q)



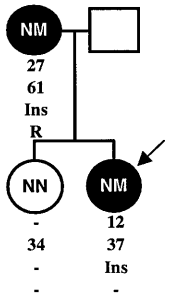
Dresden-11
(*HNF-4α*, R154X)



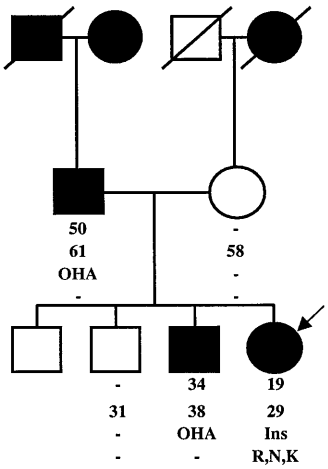
Dresden-7
(GCK, V154fsdelTG)



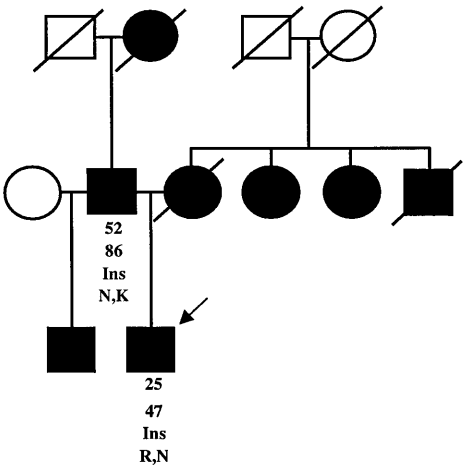
Dresden-17
(*HNF-1α*, R272fsdelGC)



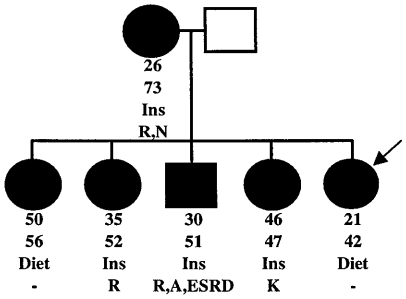
Dresden-4



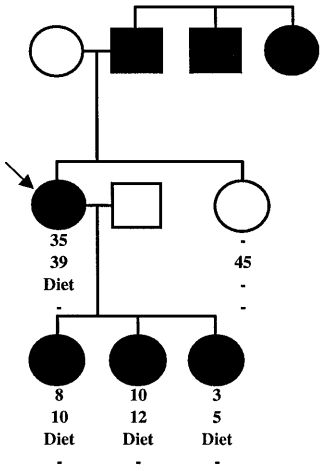
Dresden-5



Dresden-6



Dresden-13



Dresden-15

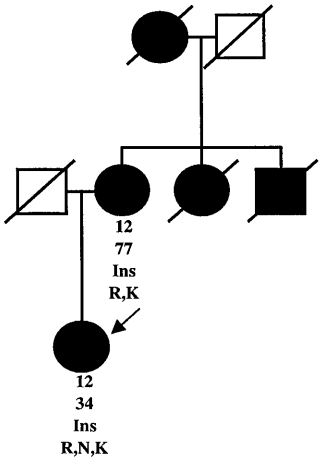


Fig. 1. Pedigrees of German families with MODY. Diabetic subjects are indicated with solid black symbols. Nondiabetic subjects and subjects with unknown affection status are indicated with open symbols. The at risk subjects in Dresden-1, and –11 are shown as a shaded symbol. The genotype of family members, if known, is indicated: N, normal allele; and M, mutant allele. The probands are indicated by arrows. Available clinical information is indicated below the symbol and includes in descending order: age at diagnosis (years); current age (years); current treatment – diet, oral hypoglycaemic agent (OHA) and insulin (Ins); and complications – retinopathy (R), nephropathy (K), end-stage renal disease (ESRD), obstructive artery disease (A) and neuropathy (N). The Dresden-1, –2, –3 and –11 families have been described previously [6, 7]

19.3–39.5). At the time of recruitment informed consent was obtained from each subject and blood and urine samples were obtained for DNA isolation and clinical testing.

The promoter, coding and flanking intron regions of the hepatocyte nuclear factor *HNF-1α*, *HNF-1β* and *HNF-4α* genes were screened for mutations as were the coding and flanking intron regions of the glucokinase and insulin promoter factor *(IPF)-1* genes by direct sequencing of polymerase chain reaction (PCR) products [2]. Since glucokinase mutations are associated with a mild increase in fasting and postprandial blood glucose concentrations or impaired glucose tolerance usually treated with diet, we only screened families with mild diabetes for mutations in this gene (i.e. Dresden-6, –7, and –13).

Mutations associated with diabetes were identified in six families. We found four families with mutations in the *HNF-1α* gene (Dresden-1, P291fsinsC; Dresden-2, R131Q; Dresden-3, R229Q; and Dresden-17, R272fsdelGC), one had a mutation in the *HNF-4α* gene (Dresden-11, R154X) and one had a novel frameshift mutation in the glucokinase gene (Dresden-7) (V154fsdelTG). All of these mutations co-segregated with diabetes suggesting that they play a causal role in its development (Fig. 1). No mutations were found in the *HNF-1β* or *IPF-1* genes in families Dresden-4, –5, –6, –7, –13, –15, –17 (the probands of Dresden-1, –2, –3 and –11 were not screened for mutations in these genes because they had mutations in other MODY genes). A variety of previously described silent mutations and polymorphisms were observed in the *HNF-1α*, *-1β* and *-4α* genes in a number of subjects as were several novel nucleotide substitutions including a silent mutation in the codon for Ala392 (exon 2) (N392, AAC→AAT) of the *HNF-4α* gene and a T→C transition in intron 6 of the *HNF-1β* gene (IVS6nt + 27T→C). No mutations in the *HNF-1α* and *-4α* genes were found in families Dresden-4, –5, –6, –7 –13, –15. The genetic basis of MODY in these families is not known. We cannot exclude glucokinase mutations in families Dresden-4, –5, and –15 since we did not screen families with severe diabetes for mutations in this gene. These MODYx families could be useful in mapping and identifying other MODY genes. There was no evident difference in phenotype between these MODYx probands compared with those with mutations in the *HNF-1α* and *-4α* genes.

This study indicates that mutations in the *HNF-1α*, *HNF-4α* and glucokinase genes are the cause of diabetes in 55% of our MODY families: *HNF-1α*, 36% (4/11); *HNF-4α*, 9% (1/11); glucokinase, 8% (1/11). We found no mutations in the *HNF-1β* and *IPF-1* genes. The trend of these results is similar to those of a study of molecular genetics of MODY in the United Kingdom that reported mutations in *HNF-1α* in 65% (36/55) of MODY families, glucokinase in 11% (8/55), *HNF-4α* in 4% (2/55) and no mutations in *HNF-1β* or *IPF-1* [3]. Another study of MODY in France found glucokinase mutations to be the most common cause of MODY, accounting for 63% (42/67) of cases and *HNF-1α* mutations being responsible for 21% (14/67) with no mutations in *HNF-1β*, *HNF-4α* and *IPF-1* [4]. These contrasting results could be caused by the different types of patients studied; adult diabetic patients in the German and United Kingdom study, whereas in France most patients were referred by paediatric clinics [3]. The failure to find mutations in known MODY genes in all three studies implies that there are unknown MODY genes. The variable clinical phenotype of our so-called MODYx families suggests that there could be at least two unknown loci with one responsible for the mild form of diabetes seen in Dresden-13 and the other for the more severe and often insulin requiring form of MODY seen in Dresden-5, –6 and –15.

Ledermann has suggested that 2% (60000 patients) of all diabetic patients in Germany have MODY [1, 5]. Our results suggest that 22800 patients have mutations in the *HNF-1α* gene and 4800 each could have mutations in the *HNF-4α* and glucokinase genes. These patients and their families would benefit from genetic counselling since prompt diagnosis and treatment can reduce the complications of *HNF-1α* and *HNF-4β* diabetes.

Yours sincerely,
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