

REVIEW

Genetic, metabolic and clinical characteristics of maturity onset diabetes of the young

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Abstract

Maturity onset diabetes of the young (MODY) is a genetically and clinically heterogeneous subtype of non-insulin-dependent diabetes mellitus (NIDDM) characterised by early onset, autosomal dominant inheritance and a primary defect in insulin secretion. To date, three MODY genes have been identified on chromosomes 20q (*MODY1/hepatic nuclear factor (HNF)-4 α*), 7p (*MODY2/glucokinase*) and 12q (*MODY3/HNF-1 α*). Mutations in *MODY2/glucokinase* result in mild chronic hyperglycaemia as a result of reduced pancreatic beta-cell responsiveness to glucose, and decreased net accumulation of hepatic glycogen and increased hepatic gluconeogenesis after meals. In contrast, *MODY1* and *MODY3* are characterised by severe insulin secretory defects, and by major hyperglycaemia associated with microvascular complications. The role of the three known MODY genes in susceptibility to the more common late-onset NIDDM remain uncertain. Genetic studies seem to exclude a role as major susceptibility genes, but leave unresolved whether they may have a minor role in a polygenic context or an important role in particular populations.

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MODY is a monogenic form of NIDDM

It is now recognised that non-insulin-dependent diabetes mellitus (NIDDM) is a genetically, metabolically and clinically heterogeneous syndrome of multifactorial aetiology (1). Although, in most cases, NIDDM seems to be a polygenic disorder, several monogenic forms have also been identified (2–5). Among those monogenic forms, maturity onset diabetes of the young (MODY) has been the most intensively investigated in the past few years, and a large body of data is now available on its genetic and pathophysiological mechanisms (6). MODY is characterised by familial NIDDM with an early age of onset (childhood, adolescence or young adulthood) and autosomal dominant inheritance, associated with defects of insulin secretion. The well-defined mode of inheritance, with high penetrance, and the early age of onset of the diabetes, which allows the collection of multigenerational pedigrees, made MODY an attractive model for genetic studies of NIDDM. The variable phenotype of subjects with MODY suggested that the disorder was genetically heterogeneous, an observation that was confirmed by genetic studies (Table 1). Mutations in genes on chromosomes 20q, 7p and 12q, designated *MODY1/hepatic nuclear factor 4 α* (*HNF-4 α*) (7, 8), *MODY2/glucokinase* (*GCK*) (5, 9, 10) and

MODY3/HNF-1 α (11, 12) respectively, can cause this form of diabetes. Moreover, there are likely to be additional MODY genes, as there are families in whom MODY does not co-segregate with markers tightly linked to the three known MODY loci (11), and no mutations are found in the known genes (13).

The prevalence of MODY remains unknown, but it seems to have a world-wide distribution (10, 14). Although it is commonly believed to be a relatively rare form of NIDDM, its frequency might have been underestimated, as the associated hyperglycaemia can remain undiagnosed until adulthood. Recent studies suggest that 2–5% of patients with NIDDM may in fact have MODY (15), and MODY was found in approximately 10% of the white families with NIDDM we have studied in France (5). The relative prevalences of the different MODY subtypes remain uncertain. Analyses of a set of 67 MODY families that we have now identified in France show that 63% (42 families) have the MODY2 and 21% (14 families) have the MODY3 subtypes (10, 13, 16). Thus the additional unknown MODY locus or loci represent 16% of the families in our group. In contrast, Frayling *et al.* (17) have observed that *MODY2/GCK* mutations represent only 11% of cases of MODY in a group of British kindreds, whereas *HNF-1 α* mutations are highly prevalent (73%) in that population. These

Table 1 Subtypes of maturity onset diabetes of the young (MODY).

	MODY1	MODY2	MODY3	IPF-1 related	Other MODY
Genetic locus	20q	7p	12q	13q	Unknown
Gene	HNF-4 α	Glucokinase	HNF-1 α	IPF-1	Unknown/heterogeneous?
Distribution (% of MODY families)	Rare	(10–65%) ^a	(20–75%) ^a	Rare	(10–20%)
Age at diagnosis	Post-pubertal	Childhood	Post-pubertal	Early adulthood	Heterogeneous?
Primary defect	Pancreas/other?	Pancreas/liver	Pancreas/kidney/other?	Pancreas/other?	Pancreas/heterogeneous?
Severity of diabetes	Severe	Mild	Severe	Mild?	Mild/heterogeneous?
Complications of diabetes	Frequent	Rare	Frequent	Unknown	Unknown

^a Different distributions in different populations. HNF, hepatic nuclear factor; IPF, insulin promoter factor.

contrasting results may be due to differences in the genetic background of the two populations, or they may reflect, at least partly, ascertainment bias in the recruitment of families.

Glucokinase and MODY

Glucokinase phosphorylates glucose to glucose-6-phosphate in pancreatic beta-cells and hepatocytes, and has a major role in the regulation and integration of glucose metabolism (18). More than 80 different GCK mutations have been observed to date (10, 19). Expression studies have shown that the enzymatic activity of the mutant proteins was impaired, with a decrease in V_{max} or a decrease of the affinity of the enzyme for glucose (20). Impairment in the enzymatic activity of mutant GCK results in decreased glycolytic flux in pancreatic beta-cells (21). This defect translates *in vivo* as a glucose-sensing defect, leading to an increase in the blood glucose threshold that triggers insulin secretion (22), and a rightward shift in the dose–response curve of glucose-induced insulin secretion (23). Comparison of insulin secretion rates in the presence of different concentrations of glucose demonstrated that those who are glucokinase deficient present an average 60% reduction in insulin secretion for a given glucose concentration. Interestingly, subjects carrying mutations that affect only mildly the enzymatic activity of glucokinase *in vitro* present a much lower reduction in insulin secretion rates compared with controls than do subjects carrying severe mutations. The release of insulin in response to arginine is usually well preserved (24), which suggests that this secretory defect is indeed related to glucose sensing.

Decreased net accumulation of hepatic glycogen (Fig. 1) and augmented hepatic gluconeogenesis after meals were observed in glucokinase-deficient patients (25). Because most of the glucose that is taken up by the liver after a meal is converted to hepatic glycogen (26), any decrease in net hepatic glycogen synthesis is expected to exacerbate postprandial hyperglycaemia. Normal glucose tolerance after a meal also depends on normal suppression of hepatic glucose production (27). In this regard, the increased rate of gluconeogenesis observed after a meal is also likely to be an important contributing factor to postprandial hyperglycaemia in glucokinase-deficient persons. In support of this, we have observed abnormal suppression of hepatic glucose production by physiological concentrations of insulin during an euglycaemic clamp (28). In addition, Tappy *et al.* (29) have shown that glucokinase-deficient patients have decreased hepatic glucose cycling, and an endogenous glucose production that is abnormally high in relation to their plasma glucose concentrations, and that they present a blunted suppression after oral administration of glucose. These results suggest that, in addition to the altered beta-cell function, abnormalities in liver glucose metabolism play an important part in

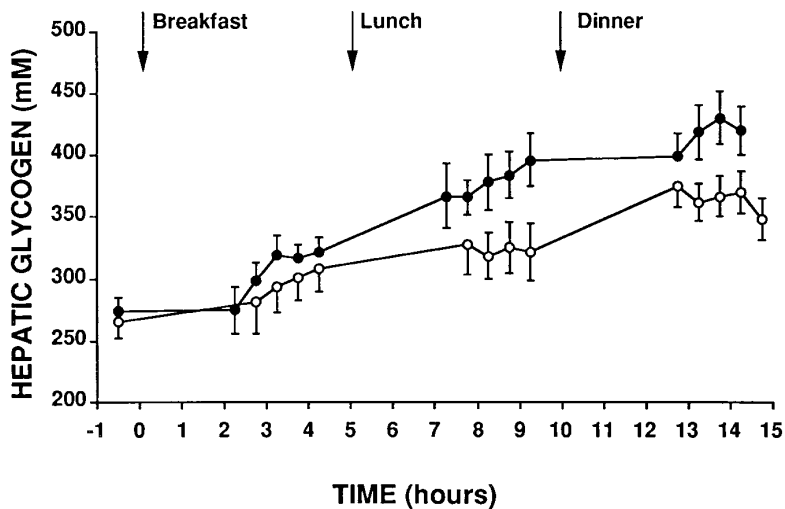


Figure 1 Time-course of change in mean hepatic glycogen concentration after breakfast, lunch and dinner, assessed by nuclear magnetic resonance spectroscopy in glucokinase-deficient MODY2 subjects (○) and control subjects (●). The increment in hepatic glycogen concentration after each meal was significantly less ($P < 0.04$) in patients than in controls. Data expressed as mean \pm S.E.M. (Adapted from reference 25, with permission.)

the pathogenesis of hyperglycaemia in patients with MODY2. In this regard, attenuation of pancreatic and hepatic glucokinase expression in transgenic mice results in pancreatic and hepatic defects comparable to those observed in GCK-deficient subjects (30–32).

Despite these multiple defects in the pancreas and the liver, the hyperglycaemia associated with GCK mutations is often mild, with fewer than 50% of subjects presenting overt diabetes (10). However, it develops during the early years of life (youngest age at diagnosis, 12 months) and its penetrance in the affected families is very rapidly complete, in that the individuals who carry the mutation are nearly always affected before puberty (10). In glucokinase-deficient subjects, we found no evidence for the well-established association of NIDDM or impaired glucose tolerance with a cluster of risk factors for macrovascular disease including hypertension, obesity and dyslipidaemia, which is consistent with the low frequency of coronary heart disease in these patients. Despite the long duration of hyperglycaemia, glucokinase deficiency is not associated with an increased frequency of late complications of diabetes. We have observed a lower prevalence of proliferative retinopathy, proteinuria and peripheral neuropathy in MODY2 than in other subtypes of MODY and late-onset NIDDM (10, 33). This may be a consequence of the relatively small increase in blood glucose concentrations and of the low prevalence of hypertension in these patients.

MODY3 (HNF-1 α) and MODY1 (HNF-4 α)

MODY3 was recently identified as the gene encoding HNF-1 α (12), a transcription factor involved in tissue-specific regulation of liver genes, but also expressed in pancreatic islets and other tissues (34). More than 50 different mutations in HNF-1 α were found to co-segregate with NIDDM in MODY families of various populations (12, 13, 16, 17, 35–38). An

insulin-secretory defect in the absence of insulin resistance was observed in diabetic and non-diabetic carriers of MODY3 mutations (39, 40), suggesting that HNF-1 α is indeed implicated in pancreatic beta-cell function. However, the mechanisms and the target genes associated with this beta-cell defect remain unknown.

Regarding the clinical presentation of diabetes, we have recently compared data from subjects with MODY2, MODY3 and late age of onset NIDDM (33). The clinical phenotype of MODY3 resembles late age of onset NIDDM in its natural history, with patients progressing rapidly from impaired glucose tolerance to overt diabetes, and with deterioration of insulin secretion. In contrast to the usually mild hyperglycaemia resulting from glucokinase deficiency, MODY3 is a severe form of diabetes, often evolving to insulin requirement. Proliferative retinopathy has been observed as frequently in patients with MODY3 as in those with late age of onset NIDDM (Table 2). When adjusted for the duration of the diabetes, the odds ratio to develop retinopathy was intermediate in patients with MODY3 compared with that in GCK-deficient patients (in whom it was threefold lower) and those with late age of onset NIDDM (in whom it was 2.6-fold higher). A trend towards a higher prevalence of proteinuria in patients with MODY3 was also observed. However, unlike NIDDM with late age of onset, the MODY3 subtype is associated with a low prevalence of obesity, dyslipidaemia and arterial hypertension. Moreover, unlike MODY2, MODY3 is not a disease of childhood, with hyperglycaemia usually developing after puberty.

MODY1 seems to be much less prevalent than the other subtypes of MODY. The American RW pedigree, comprising 360 identified members, including 72 known affected subjects, was, until recently, the only family found to show linkage with the MODY1 locus (7). Following the identification of MODY3 as the transcription factor HNF-1 α (12), MODY1 was identified as

Table 2 Retinopathy and proteinuria in patients with maturity onset diabetes of the young (MODY) and non-insulin-dependent diabetes mellitus (NIDDM). Values are expressed as mean \pm s.d.

	MODY3	GCK	Other MODY	NIDDM	P
Retinopathy					
Number of subjects	24	65	12	150	
Sex: M/F	8/16	27/38	6/6	71/79	0.56
Age (years)	44 \pm 18*	46 \pm 17*	49 \pm 21*	62 \pm 12	0.0001
Duration of known hyperglycaemia (years)	23 \pm 13	19 \pm 11	18 \pm 6	17 \pm 9	0.06
Fasting glucose concentration (mmol/l)	8.9 \pm 2.6	7.2 \pm 1.5*	6.4 \pm 1.2*	9.7 \pm 3.5	0.0001
Prevalence of proliferative retinopathy (n (%))	5 (21%)	2 (3%)	1 (8%)	34 (23%)	0.004
Odds ratio (95% confidence interval) ^a	–	0.27 (0.08–0.92) ^b	–	2.69 (1.27–5.74) ^c	
Proteinuria					
Number of subjects	26	78	12	166	
Sex: M/F	11/15	38/40	5/7	86/80	0.45
Age (years)	42 \pm 17*	45 \pm 19*	53 \pm 13	63 \pm 12	0.0001
Duration of known hyperglycaemia (years)	22 \pm 13	18 \pm 10	19 \pm 5	18 \pm 9	0.20
Fasting glucose concentration (mmol/l)	8.7 \pm 2.8	7.1 \pm 0.9*	6.6 \pm 1.4*	9.9 \pm 3.7	0.0001
Systolic blood pressure (mmHg)	129 \pm 11*	127 \pm 17*	133 \pm 18	140 \pm 15	0.0001
Diastolic blood pressure (mmHg)	78 \pm 7	74 \pm 9*	70 \pm 12*	80 \pm 10	0.0001
Creatinine (μ mol/l)	84 \pm 28	84 \pm 21	75 \pm 17	86 \pm 25	0.55
Prevalence of proteinuria (n (%))	5 (19%)	4 (5%)	0 (0%)	11 (7%)	0.07

Statistics are contingency-table χ^2 test (qualitative traits) and ANOVA (quantitative traits).

* Statistically significant differences ($P < 0.05$) compared with NIDDM (Tukey–Kramer HSD test following ANOVA).

^a Odds ratio compared with MODY3 subjects; ^b $P = 0.03$; ^c $P = 0.009$.

(Data adapted from reference 33, with permission).

the gene encoding HNF-4 α (8), a member of the steroid/thyroid hormone receptor superfamily and upstream regulator of HNF-1 α expression. A nonsense mutation (Q268X) resulting in a truncated protein was found to co-segregate with MODY in the RW pedigree (8). The affected individuals from that pedigree also present a severe form of diabetes that requires insulin therapy in about 30% of cases and is associated with microvascular complications (41). A primary pancreatic beta-cell defect was observed in these patients (42, 43). Recently, a second mutation in the HNF-4 α gene has been identified in a British pedigree with MODY (44).

MODY genes and late onset NIDDM

Insulin resistance is a risk factor for the development of late onset subtypes of NIDDM (45). However, the full expression of diabetes also requires defective or deficient beta-cell function. For obvious reasons, the MODY genes were considered as strong candidate genes for the insulin secretory defect of late onset NIDDM. The GCK gene was intensively investigated in several populations. Positive associations between NIDDM with late age of onset and particular GCK alleles have been observed in black Americans and Mauritian Creoles (46), suggesting that the GCK locus might be implicated in diabetes in these populations. Mutations in the coding regions of GCK were not found in these subjects, or in other cohorts and populations, suggesting that GCK is unlikely to be a major susceptibility gene for late age of onset NIDDM (47). However, studies with transgenic mice have shown that mutations in the regulatory

regions upstream of the promoter have a drastic effect on transcription (48). The hypothesis that some forms of diabetes might be associated with mutation in these regulatory regions is supported by the co-segregation of a variant of the pancreatic promoter region with late age of onset NIDDM, observed in one French family (47). Furthermore, it was demonstrated recently that this variant was associated with reduced beta-cell function in Japanese-American subjects with normal or impaired glucose tolerance, and that this defect progressed during a 5-year follow-up (49). This mutant allele could contribute to a high risk of abnormal glucose tolerance in this population.

Linkage of the MODY3 locus with late onset NIDDM was excluded in a panel of 600 white French sib-pairs (50), but was observed in 53 white American sib-pairs (51). Moreover, genetic linkage has been reported between diabetes and markers on chromosome 12q in the region of MODY3 in a small cohort of Finnish families characterised by late onset NIDDM with defective insulin secretion (52). In that study, no linkage was observed when all families from the cohort were tested together, without stratification by the insulin secretory status. It is possible that MODY3 and this NIDDM locus represent different genes on chromosome 12q. Alternatively, they may represent different alleles of a single gene. Several common amino acid polymorphisms have been observed in the HNF-1 α gene and, although their allele frequencies do not seem to be different in NIDDM subjects compared with those in the general population (12, 53), it is possible that these polymorphisms may have a physiological or pathophysiological role in beta-cell function. Thus an amino acid polymorphism on

codon 98 of the *HNF-1 α* gene, observed in about 4% of Danish subjects regardless of the glucose tolerance status, was found to be associated with reduced insulin response to an oral glucose challenge in healthy young subjects (54).

Linkage of diabetes with the *MODY1* region on chromosome 20q was also negative in a panel of 20 multigenerational white French families with NIDDM (55). Negative results were also observed with sib-pair analysis of a small panel of British and Italian sibs (56), but, here again, positive results were observed in the same set of 53 white American sib-pairs who showed positive linkage with the *MODY3* locus (51). Recently, we have identified one family with late age of onset NIDDM, in whom a mutation in *HNF-4 α /MODY1* co-segregated with deficient insulin secretion and diabetes (57). Thus it is clear from all these results that the role of *MODY1* and *MODY3* loci on late onset NIDDM is only beginning to be established.

Insulin promoter factor-1 and diabetes

The insulin promoter factor (IPF)-1, which is also known as IDX-1, STF-1 and PDX-1, is a homeodomain transcription factor that regulates pancreatic development and the expression of various beta-cell genes, including the insulin gene (58). It has been shown that the disruption of the *IPF-1* gene in mice results in agenesis of the pancreas (59). Recently, a mutation in exon 1 of the *IPF-1* gene (Pro63fsdelC), resulting in a truncated protein, was found to co-segregate with diabetes in a large kindred presenting a consanguineous link (60). The phenotype of those who are heterozygous for the mutation ranges from normal to impaired glucose tolerance, to overt non-insulin-dependent diabetes. The average age of onset of chronic hyperglycaemia in this kindred (35 years) is greater than in typical *MODY* kindreds, but it ranges from 17 to 67 years. One child who is homozygous for the mutation was born with pancreatic agenesis, and suffers from diabetes in addition to exocrine insufficiency (61). The role of IPF-1 in *MODY* and late-onset NIDDM remains to be investigated.

Conclusions

MODY is a genetically heterogeneous subtype of NIDDM characterised by early onset, autosomal dominant inheritance and a primary defect in insulin secretion. It seems to be a relatively frequent disorder, as recent studies suggest that 2–5% of patients with NIDDM may in fact have *MODY*. The role of the known *MODY* genes in the susceptibility to the more common late-onset NIDDM remain uncertain. Genetic studies seem to exclude a role as major susceptibility genes, but leave unresolved whether they may have a minor role in a polygenic context or an important role in particular

populations. The nature or position of different mutations in these genes could explain diverse phenotypic presentations of diabetes. Mutations in sites affecting the function of the gene product in a major way might be sufficient to induce glucose intolerance early in life, regardless of the absence of other predisposing factors. Alternatively, mutations affecting this function only mildly could segregate in kindreds, without leading to hyperglycaemia at an early age. Later in life, other genetic or environmental factors could contribute to the development of diabetes. It is clear that further investigations in larger and well-phenotyped cohorts from different populations, stratified for particular phenotypes, are required to evaluate the role of the *MODY* genes in the common forms of NIDDM.

The identification of *GCK* as a diabetes susceptibility gene has provided a major impulse for the reassessment of the physiological role and the understanding of the pathophysiological importance of this key enzyme of glucose homeostasis. The recent identification of *MODY1* and *MODY3* as the genes encoding two physiologically related transcription factors opens entirely new perspectives in the understanding of the molecular basis, not only of *MODY*, but possibly also of other forms of NIDDM. It will contribute to our knowledge of glucose homeostasis and, possibly, to the definition of targets for new drugs for the treatment of diabetes. In this regard, *MODY* can be considered as a paradigm of NIDDM.

References

- 1 Velho G & Froguel P. The genetic determinants of NIDDM: strategies and recent results. *Diabetes and Metabolism* 1997 23 7–17.
- 2 Steiner DE, Tager HS, Chan SJ, Nanjo K, Sanke T & Rubenstein AH. Lessons learned from molecular biology of insulin-gene mutations. *Diabetes Care* 1990 13 600–609.
- 3 Van den Ouweland JMW, Lemkes HHPJ, Ruitenbeek W, Sandkuijl LA, De Vijlder ME, Struyvenberg PAA *et al.* Mutation in mitochondrial tRNA Leu(UUR) gene in a large pedigree with maternally transmitted type II diabetes and deafness. *Nature Genetics* 1992 1 368–371.
- 4 Taylor SI. Molecular mechanisms of insulin resistance: lessons from patients with mutations in the insulin-receptor gene. *Diabetes* 1992 41 1473–1490.
- 5 Froguel P, Zouali H, Vionnet N, Velho G, Vaxillaire M, Sun F *et al.* Familial hyperglycemia due to mutations in glucokinase: definition of a subtype of diabetes mellitus. *New England Journal of Medicine* 1993 328 697–702.
- 6 Froguel P, Vaxillaire M & Velho G. Genetic and metabolic heterogeneity of maturity onset diabetes of the young. *Diabetes Reviews* 1997 5 123–130.
- 7 Bell GI, Xiang KS, Newman MV, Wu SH, Wright LG, Fajans SS *et al.* Gene for non insulin dependent diabetes mellitus (maturity onset diabetes of the young subtype) is linked to DNA polymorphism on chromosome 20q. *Proceedings of the National Academy of Sciences of the USA* 1991 88 1484–1488.
- 8 Yamagata K, Furuta H, Oda O, Kaisaki PJ, Menzel S, Cox NJ *et al.* Mutations in the hepatocyte nuclear factor 4 alpha gene in maturity-onset diabetes of the young (*MODY1*). *Nature* 1996 384 458–460.
- 9 Froguel P, Vaxillaire M, Sun F, Velho G, Zouali H, Butel MO *et al.* The glucokinase locus on chromosome 7p is closely linked to early

- onset non insulin dependent diabetes mellitus. *Nature* 1992 **356** 162–164.
- 10 Velho G, Blanché H, Vaxillaire M, Bellanné-Chantelot C, Pardini VC, Timsit J *et al.* Identification of 14 new glucokinase mutations and description of the clinical profile of 42 MODY-2 families. *Diabetologia* 1997 **40** 217–224.
 - 11 Vaxillaire M, Boccio V, Philippi A, Vigouroux C, Terwilliger J, Passa P *et al.* A gene for maturity onset diabetes of the young (MODY) maps to chromosome 12q. *Nature Genetics* 1995 **9** 418–423.
 - 12 Yamagata K, Oda N, Kaisaki PJ, Menzel S, Furuta H, Vaxillaire M *et al.* Mutations in the hepatocyte nuclear factor 1 alpha gene in maturity-onset diabetes of the young (MODY3). *Nature* 1996 **384** 455–458.
 - 13 Chèvre JC, Hani EH, Boutin P, Vionnet N, Vaxillaire M, Yamagata K *et al.* Mutation screening of the hepatocyte nuclear factor-1 α and 4 α genes in MODY families: suggestion of the existence of at least a fourth MODY gene. *Diabetologia* 1997 **40** (Suppl 1) A157 (Abstract).
 - 14 Fajans SS. Scope and heterogeneous nature of MODY. *Diabetes Care* 1990 **13** 49–64.
 - 15 Ledermann HM. Is maturity onset diabetes at young age (MODY) more common in Europe than previously assumed? *Lancet* 1995 **345** 648 (Letter).
 - 16 Vaxillaire M, Rouard M, Yamagata K, Oda N, Kaisaki PJ, Boriraj VV *et al.* Identification of nine novel mutations in the hepatocyte nuclear factor 1 alpha gene associated with maturity-onset diabetes of the young (MODY3). *Human Molecular Genetics* 1997 **6** 583–586.
 - 17 Frayling TM, Bulman MP, Ellard S, Appleton M, Dronsfield MJ, Mackle ADR *et al.* Mutations in the hepatocyte nuclear factor-1 alpha gene are a common cause of maturity-onset diabetes of the young in the UK *Diabetes* 1997 **46** 720–725.
 - 18 Matschinsky FM. A lesson in metabolic regulation inspired by the glucokinase glucose sensor paradigm. *Diabetes* 1996 **45** 223–241.
 - 19 Blanché H, Carel J, Czernichow P, Froguel P, Guazzarotti L, Passa P *et al.* Criblage moléculaire de la glucokinase: 37 nouvelles mutations. *Diabète et Métabolisme* 1997 **23** (Suppl 1) 29 (Abstract).
 - 20 Gidh-Jain M, Takeda J, Xu LZ, Lange AJ, Vionnet N, Stoffel M *et al.* Glucokinase mutations associated with non insulin dependent (type 2) diabetes mellitus have decreased enzymatic activity: implications for structure/function relationships. *Proceedings of the National Academy of Sciences of the USA* 1993 **90** 1932–1936.
 - 21 Sturis J, Kurland IJ, Byrne MM, Mosekilde E, Froguel P, Pilakis SJ *et al.* Compensation in pancreatic beta-cell function in subjects with glucokinase mutations. *Diabetes* 1994 **43** 718–723.
 - 22 Velho G, Froguel P, Clément K, Pueyo ME, Rakotoambinina B, Zouali H *et al.* Primary pancreatic beta-cell secretory defect caused by mutations in the glucokinase gene in kindreds of maturity onset diabetes of the young. *Lancet* 1992 **340** 444–448.
 - 23 Byrne MM, Sturis J, Clément K, Vionnet N, Pueyo ME, Stoffel M *et al.* Insulin secretory abnormalities in subjects with hyperglycemia due to glucokinase mutations. *Journal of Clinical Investigation* 1994 **93** 1120–1130.
 - 24 Pueyo ME, Clément K, Vaxillaire M, Passa P, Froguel P, Robert JJ *et al.* Arginine-induced insulin release in glucokinase-deficient subjects. *Diabetes Care* 1994 **17** 1015–1021.
 - 25 Velho G, Petersen KF, Perseghin G, Hwang J-H, Rothman DL, Pueyo ME *et al.* Impaired hepatic glycogen synthesis in glucokinase-deficient (MODY-2) subjects. *Journal of Clinical Investigation* 1996 **98** 1755–1761.
 - 26 Moore MC, Cherrington AD, Cline G, Pagliassotti MJ, Jones EM, Neal DW *et al.* Sources of carbon for hepatic glycogen synthesis in the conscious dog. *Journal of Clinical Investigation* 1991 **88** 578–587.
 - 27 DeFronzo RA, Bonadonna RC & Ferrannini E. Pathogenesis of NIDDM: a balanced overview. *Diabetes Care* 1992 **15** 318–368.
 - 28 Clément K, Pueyo ME, Vaxillaire M, Rakotoambinina B, Thuillier F, Passa P *et al.* Assessment of insulin sensitivity in glucokinase-deficient subjects. *Diabetologia* 1996 **39** 82–90.
 - 29 Tappy L, Dussoix P, Iyenedjian P, Henry S, Schneiter P, Zahnd G *et al.* Abnormal regulation of hepatic glucose output in maturity onset diabetes of the young caused by a specific mutation of the glucokinase gene. *Diabetes* 1997 **46** 204–208.
 - 30 Efrat S, Leiser M, Wu YJ, Fusco-DeMane D, Emran OA, Surana M *et al.* Rybozyme-mediated attenuation of pancreatic beta-cell glucokinase expression in transgenic mice results in impaired glucose-induced insulin secretion. *Proceedings of the National Academy of Sciences of the USA* 1994 **91** 2051–2055.
 - 31 Bali D, Svetlanov A, Lee HW, Fusco-DeMane D, Leiser M, Li B *et al.* Animal model for maturity-onset diabetes of the young generated by disruption of the mouse glucokinase gene. *Journal of Biological Chemistry* 1995 **270** 21464–21467.
 - 32 Grupe A, Hultgren B, Ryan A, Ma YH, Bauer M & Stewart TA. Transgenic knockouts reveal a critical requirement for pancreatic beta cell glucokinase in maintaining glucose homeostasis. *Cell* 1995 **83** 69–78.
 - 33 Velho G, Vaxillaire M, Boccio V, Charpentier G & Froguel P. Diabetes complications in NIDDM kindreds linked to the MODY-3 locus on chromosome 12q. *Diabetes Care* 1996 **19** 915–919.
 - 34 Tronche F & Yaniv M. HNF1, a homeoprotein member of the hepatic transcription regulatory network. *Bioessays* 1992 **14** 579–587.
 - 35 Boutin P, Chèvre JC, Gomis R, Pardini VC, Guillausseau PJ, Velho G *et al.* An automated fluorescent SSCP technique for screening for mutations the hepatocyte nuclear factor 1 alpha gene (MODY3). *Diabetes* 1997 **46** 2108–2109.
 - 36 Kaisaki PJ, Menzel S, Lindner T, Oda N, Rjasanowski I, Sahn J *et al.* Mutations in the hepatocyte nuclear factor-1 alpha gene in MODY and early-onset NIDDM: evidence for a mutational hotspot in exon 4. *Diabetes* 1997 **46** 528–535.
 - 37 Hansen T, Eiberg H, Rouard M, Vaxillaire M, Moller AM, Rasmussen SK *et al.* Novel MODY3 mutations in the hepatocyte nuclear factor-1 alpha gene: evidence for a hyperexcitability of pancreatic beta-cells to intravenous secretagogues in a glucose-tolerant carrier of a P447L mutation. *Diabetes* 1997 **46** 726–730.
 - 38 Glucksmann MA, Lehto M, Tayber O, Scotti S, Berkemeier L, Pulido JC *et al.* Novel mutations and a mutational hotspot in the MODY3 gene. *Diabetes* 1997 **46** 1081–1086.
 - 39 Velho G, Pueyo ME, Clément K, Froguel P & Robert J-J. Assessment of insulin secretion and sensitivity in carriers of the diabetes susceptibility haplotype at the MODY-3 locus. *Diabetes* 1996 **45** (Suppl 2) 297A (Abstract).
 - 40 Byrne MM, Sturis J, Menzel S, Yamagata K, Fajans SS, Dronsfield MJ *et al.* Altered insulin secretory responses to glucose in diabetic and nondiabetic subjects with mutations in the diabetes mellitus susceptibility gene MODY on chromosome 12. *Diabetes* 1996 **45** 1503–1510.
 - 41 Fajans SS, Bell GI, Bowden DW, Halter JB & Polonsky KS. Maturity-onset diabetes of the young. *Life Sciences* 1994 **55** 413–422.
 - 42 Herman WH, Fajans SS, Ortiz FJ, Smith MJ, Sturis J, Bell GI *et al.* Abnormal insulin secretion, not insulin resistance, is the genetic or primary defect of MODY in the RW pedigree. *Diabetes* 1994 **43** 40–46.
 - 43 Byrne MM, Sturis J, Fajans SS, Ortiz FJ, Stoltz A, Stoffel M *et al.* Altered insulin secretory responses to glucose in subjects with a mutation in the MODY1 gene on chromosome 20. *Diabetes* 1995 **44** 699–704.
 - 44 Bulman MP, Dronsfield MJ, Frayling T, Appleton M, Bain SC, Ellard S *et al.* A missense mutation in the hepatocyte nuclear factor 4 alpha gene in a UK pedigree with maturity-onset diabetes of the young. *Diabetologia* 1997 **40** 859–862.
 - 45 Yki-Jarvinen H. Role of insulin resistance in the pathogenesis of NIDDM. *Diabetologia* 1995 **38** 1378–1388.
 - 46 Permutt MA, Chiu KC & Tanizawa Y. Glucokinase and NIDDM: a candidate gene that paid off. *Diabetes* 1992 **41** 1367–1372.
 - 47 Zouali H, Vaxillaire M, Lesage S, Sun F, Velho G, Vionnet N *et al.* Linkage analysis and molecular scanning of the glucokinase gene in NIDDM families. *Diabetes* 1993 **42** 1238–1245.

- 48 Shelton KD, Franklin AJ, Khoor A, Beechem J & Magnuson MA. Multiple elements in the upstream glucokinase promoter contribute to transcription in insulinoma cells. *Molecular and Cellular Biology* 1992 **12** 4578–4589.
- 49 Stone LM, Kahn SE, Fujimoto WY, Deeb SS & Porte D Jr. A variant at position -30 of the β -cell glucokinase gene promoter is associated with reduced β -cell function in middle-aged Japanese-American men. *Diabetes* 1996 **45** 422–428.
- 50 Lesage S, Hani EH, Philippi A, Vaxillaire M, Hager J, Passa P *et al.* Linkage analyses of the MODY3 locus on chromosome 12q with late-onset NIDDM. *Diabetes* 1995 **44** 1243–1247.
- 51 Bowden DW, Sale M, Howard TD, Qadri A, Spray BJ, Rothschild CB *et al.* Linkage of genetic markers on human chromosomes 20 and 12 to NIDDM in Caucasian sib pairs with a history of diabetic nephropathy. *Diabetes* 1997 **46** 882–886.
- 52 Mahtani MM, Widén E, Lehto M, Thomas J, McCarthy M, Brayer J *et al.* Mapping of a gene for type 2 diabetes associated with an insulin secretion defect by a genome scan in Finnish families. *Nature Genetics* 1996 **14** 90–94.
- 53 Urhammer SA, Rasmussen SK, Kaisaki PJ, Oda N, Yamagata K, Moller AM *et al.* Genetic variation in the hepatocyte nuclear factor-1 alpha gene in Danish Caucasians with late-onset NIDDM. *Diabetologia* 1997 **40** 473–475.
- 54 Urhammer SA, Fridberg M, Hansen T, Rasmussen SK, Moller AM, Clausen JO *et al.* A prevalent amino acid polymorphism at codon 98 in the hepatocyte nuclear factor-1 alpha gene is associated with reduced serum C-peptide and insulin responses to an oral glucose challenge. *Diabetes* 1997 **46** 912–916.
- 55 Vaxillaire M, Butel MO, Zouali H, Sun F, Lesage S, Clément K *et al.* Linkage studies give evidence for genetic heterogeneity in type 2 diabetes mellitus. *Diabetologia* 1992 **35** A62 (Abstract).
- 56 Baroni MG, Alcolado JC, Needham EWA, Pozzilli P, Stocks J & Galton DJ. Sib-pair analysis of adenosine deaminase locus in NIDDM. *Diabetes* 1992 **41** 1640–1643.
- 57 Hani EH, Suaud L, Boutin P, Chevre JC, Durand E, Philippi A *et al.* A missense mutation in the Hepatocyte Nuclear Factor 4-Alpha, resulting in a reduced transactivational activity, in human late-onset non insulin-dependent diabetes mellitus. *Journal of Clinical Investigation* 1998 (In Press).
- 58 Ohlsson H, Karlsson K & Edlund T. IPF1, a homeodomain-containing transactivator of the insulin gene. *EMBO Journal* 1993 **12** 4251–4259.
- 59 Jonsson J, Carisson L, Edlund T & Edlund H. Insulin-promoter-factor 1 is required for pancreas development in mice. *Nature* 1994 **371** 606–609.
- 60 Stoffers DA, Ferrer J, Clarke WL & Habener JF. Early-onset type 2 diabetes mellitus (MODY4) linked to IPF1. *Nature Genetics* 1997 **17** 138–139.
- 61 Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL & Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. *Nature Genetics* 1997 **15** 106–110.

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