

Monogenic Diabetes in the Young, Pharmacogenetics and Relevance to Multifactorial Forms of Type 2 Diabetes

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Most valuable breakthroughs in the genetics of type 2 diabetes for the past two decades have arisen from candidate gene studies and familial linkage analysis of maturity-onset diabetes of the young (MODY), an autosomal dominant form of diabetes typically occurring before 25 years of age caused by primary insulin secretion defects. Despite its low prevalence, MODY is not a single entity but presents genetic, metabolic and clinical heterogeneity. MODY can result from mutations in at least six different genes encoding the glucose sensor enzyme glucoki-

nase and transcription factors that participate in a regulatory network essential for adult β -cell function. Additional genes have been described in other discrete phenotypes or syndromic forms of diabetes. Whereas common variants in the MODY genes contribute very modestly to type 2 diabetes susceptibility in adults, major findings emerging from the advent of genome-wide association studies will deliver an increasing number of genes and new pathways for the pathological events of the disease. (Endocrine Reviews 29: 254–264, 2008)

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I. Introduction

TYPE 2 DIABETES (T2D) is a heterogeneous metabolic disease that recently reached epidemic proportions in Western industrialized countries because of deleterious en-

vironmental factors, mainly an increased availability of high-caloric diets, together with a sedentary lifestyle and reduced physical activity (1–3). Moreover, the heritability of T2D is one of the best established among the common diseases (3); consequently variations within several genetic loci interact with these predisposing/environmental factors and influence a number of intermediate traits of relevance to the diabetic phenotype (β -cell mass, insulin secretion, insulin action, fat distribution, obesity) (2). In the pathogenesis of T2D, concomitant or interdependent defects of both insulin secretion by the pancreatic β -cells and insulin sensibility of peripheral tissues (liver, skeletal muscle, and adipose tissue) result in the decompensation of β -cell functions and chronic hyperglycemia (1, 2). As a clinically heterogeneous metabolic disorder, T2D is recognized as composed of many different subtypes: in adulthood where genetic susceptibility is strongly associated with environmental factors, representing the common polygenic forms of T2D, and more penetrant genetic forms in the young, which are defined as monogenic diabetes (3). This gives rise to a spectrum of variable diabetes phenotypes ranging from early-onset diabetes, resulting in most cases from a pancreatic β -cell dysfunction, to diabetes that develops in later life with insulin resistance and that is frequently associated with overweight or obesity (this is illustrated in Fig. 1). Although the current worldwide epidemic of T2D is greatly driven by lifestyle and dietary changes, a combination of these environmental factors and susceptible genetic determinants contributes to the development of T2D (4). In common forms of T2D that are diagnosed in adulthood, the simultaneous action of several susceptibility alleles and multiple combinations of frequent variants at several loci may have deleterious effects when interacting with predisposing environmental factors. At the opposite side of disease phenotypes, several monogenic forms of diabetes have been identified, such as maturity-onset diabetes of the young (MODY) (5) and maternally inherited diabetes and deafness (MIDD) (6). Moreover,

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Abbreviations: CEL, Carboxyl ester lipase; ER, endoplasmic reticulum; GCK, glucokinase; GKA, GK activator; GWA, genome-wide association; HNF, hepatocyte nuclear factor; IB1, islet brain-1; IPF1, insulin promoter factor 1; KLF11, Krüppel-like factor 11; MAF, minor allele frequency; MIDD, maternally inherited diabetes and deafness; MODY, maturity-onset diabetes of the young; NDM, neonatal diabetes mellitus; NeuroD1, neurogenic differentiation factor 1; OR, odds ratio; PDX1, pancreatic duodenal homeobox-1; T2D, type 2 diabetes; TG2, transglutaminase 2; WS, Wolfram syndrome.

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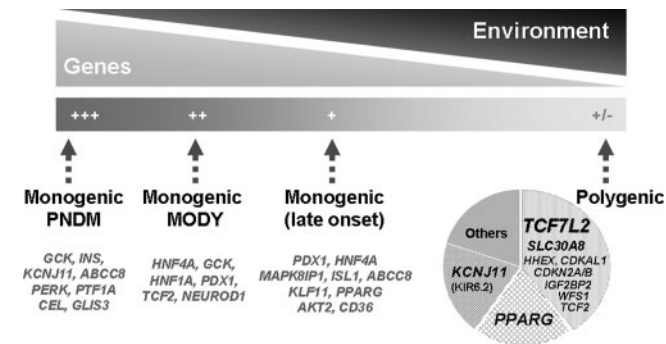


FIG. 1. Schematic representation illustrating the concept of diabetes spectrum with the genes responsible for the variable phenotypes. The gene symbols indicate that specific mutations are associated with a clinical presentation of the disease (monogenic phenotype), or common polymorphisms were shown to modulate disease risk (polygenic type 2 diabetes in adults). The genes are listed from *left to right* according to the variable penetrance depicted in the *gray bar*.

the hypothesis for a fetal origin of the disease is likely corroborated by retrospective studies having shown that low birth weight is associated with insulin resistance and T2D in adulthood, which may result from a metabolic adaptation to poor fetal nutrition (7). However, given that gene variants may contribute both to variation in fetal growth and to T2D susceptibility, such a metabolic “programming” could also be partly genetically determined (8).

The current picture of T2D susceptibility in adulthood is that, as a complex metabolic trait, it likely results from the effects of environmental factors on predisposed individuals carrying a combination of at-risk genetic variants or “susceptibility” alleles. It is thought that each susceptibility allele, taken individually, has a modest effect on the disease risk (in the range of odds ratios of 1.10–1.50). Such modest effects can be retrieved by studying large population-based samples and patients selected for familiarity and early-onset diabetes. A great part of monogenic diabetes forms, like neonatal diabetes mellitus (NDM) (9) or early-onset diabetes (MODY), have been elucidated so far from both familial genome-wide linkage and candidate gene studies.

In this chapter, we review the clinical and genetic features of several monogenic conditions of diabetes in the young, including the MODY subtypes and other forms of familial diabetes with later age of onset, and how the molecular understanding of these types of diabetes has led to pharmacogenomic approaches of the disease. The last part of our review underlines the contribution of several genes being involved in monogenic diabetes to more common multifactorial forms of type 2 diabetes in adulthood.

II. Maturity-Onset Diabetes of the Young, a Paradigm of Monogenic Diabetes

The term “maturity-onset diabetes of the young” or MODY relies on the old classification of diabetes into juvenile-onset and maturity-onset diabetes. A revised, etiology-based classification for diabetes has been introduced by both the American Diabetes Association (ADA) and the World Health Organization (WHO), and MODY is now included in

the group of “genetic defect in β -cell function” with a sub-classification according to the gene involved.

MODY was defined as a familial form of early-onset type 2 diabetes, which usually develops in childhood, adolescence, or young adulthood, and was characterized to be mainly associated with primary defects of insulin secretion (5).

At least five major diagnostic criteria for MODY are usually accepted:

1. Hyperglycemia usually diagnosed before age 25 yr in at least one and ideally two family members. It is noteworthy that “anticipation” or progressive reduction in the age of diagnosis in succeeding generations was reported, probably because of enhanced awareness of diabetes leading to earlier testing.

2. Autosomal-dominant pattern of inheritance, with a vertical transmission of diabetes through at least three generations, and a similar phenotype shared by diabetic family members.

3. Absence of insulin therapy at least 5 yr after diagnosis or significant C-peptide levels even in a patient on insulin treatment.

4. Insulin levels are often in the normal range, though inappropriately low for the degree of hyperglycemia, suggesting a primary defect in β -cell function.

5. Overweight or obesity is rarely associated with diabetes in the MODY patients (and not required for the development of this form of diabetes).

The prevalence of MODY is estimated to be below 5% of type 2 diabetes patients in most populations studied (10).

III. The Different Subtypes of MODY and Clinical Implications

Molecular genetic studies of MODY families have demonstrated that this condition is not a single entity but is a clinically and genetically heterogeneous disease. Mutations, deletions, or other anomalies in at least six genes are a cause for the majority of the MODY cases (Table 1). The MODY genes encode the enzyme glucokinase (GSK/MODY2) (11) and several transcription factors: hepatocyte nuclear factor-4 α (HNF-4 α /MODY1) (12), hepatocyte nuclear factor-1 α (HNF-1 α /MODY3) (13, 14), insulin promoter factor 1 (IPF1/MODY4) (15), hepatocyte nuclear factor-1 β (HNF-1 β /MODY5) (16), and neurogenic differentiation factor 1 (NeuroD1/ β 2, MODY6) (17). All MODY genes have not yet been discovered, because there are families in which diabetes was shown to cosegregate with markers outside the known MODY loci (18, 19).

Studies from British, French, German, and Spanish family cohorts (20–23) have shown variable prevalence of the different subtypes of MODY between these cohorts. MODY2 may account for 10 to 60% of cases (the most prevalent form in the French and Italian families) and MODY3 from 20 to 65% of cases (the most prevalent form in British families); these differences between the prevalence of MODY2 and MODY3 in French and British populations are likely associated with various ways of ascertainment (self-reported diabetes or new diagnosis of hyperglycemia through a familial survey; recruitment from outpatient clinics), and could not reflect the true difference in their prevalence. The other MODY subtypes are relatively rarer disorders in all family cohorts, whereas additional unknown

TABLE 1. Genetic classification and clinical phenotypes of the MODY subtypes

Locus	Gene name	Gene function	Primary defect	Clinical phenotypes
MODY1 (20q)	<i>HNF4A</i>	Transcription factor (nuclear receptor)	Pancreas/other	Neonatal hyperinsulinism, diabetes (early adulthood)
MODY2 (7p)	<i>GCK</i>	Hexokinase IV	Pancreas/liver	Mild hyperglycemia (in early childhood)
MODY3 (12q)	<i>HNF1A</i>	Transcription factor (homeodomain)	Pancreas/kidney other	Diabetes (early adulthood)
MODY4 (13q)	<i>IPF1</i>	Transcription factor (homeodomain)	Pancreas	Diabetes (pancreas agenesis in homozygote)
MODY5 (17q)	<i>TCF2</i>	Transcription factor (homeodomain)	Kidney/pancreas	Diabetes, RCAD, pancreas hypoplasia
MODY6 (2q)	<i>NEUROD1</i>	Transcription factor (bHLH)	Pancreas	Diabetes (infancy and early adulthood)

The chromosomal localization of each locus is indicated in *parentheses*. RCAD, Renal cysts and diabetes syndrome.

MODY loci (MODY-X) may represent 20 to 50% of the cases (the most prevalent form in German and Spanish families). As indicated above, these contrasting results may be explained by the diverse genetic backgrounds between these populations or may reflect, at least partly, ascertainment bias between the family cohorts that may overlap with polygenic early-onset T2D.

A. MODY2 due to glucokinase mutations

Glucokinase (GCK), also called hexokinase IV or D, is the predominant glucose-phosphorylating enzyme in the liver parenchymal cells and the β -cells of pancreatic islets, both types of cells that have to respond to changes in the blood glucose concentration (24). One major characteristic of GCK is that it has a relatively low affinity for glucose and displays positive cooperativity for this substrate, despite the fact that it is a monomeric enzyme. Furthermore, unlike other hexokinases, it is not inhibited by micromolar, physiological concentrations of glucose 6-phosphate but by a regulatory protein that transduces the effect of fructose 6-phosphate and fructose 1-phosphate. From the numerous studies having evaluated GCK as a candidate gene in MODY patients and families, more than 150 different mutations have been shown to cause MODY2 (25). Studies of the kinetic properties of the mutant GCK proteins have shown that the relative enzymatic activity was impaired, leading to a decrease in the glycolytic flux in pancreatic β -cells (24). This translates *in vivo* as a glucose-sensing defect that is an increase in the blood glucose threshold triggering insulin secretion (26) and a right shift in the dose response curve of glucose-induced insulin secretion (27). In the liver, a decrease in the glycogen synthesis and storage and an increase in gluconeogenesis after standard meals were reported in the MODY2 patients; this defect in the hepatic glucose metabolism contributes to the postprandial hyperglycemia of MODY2 patients (28). Despite these important perturbations in the glucose metabolism, the hyperglycemia associated with GCK mutations is often mild, usually responsive to diet, with fewer than 50% of subjects presenting with overt diabetes. Compared with other subtypes of MODY and late-onset type 2 diabetes, a lower prevalence of microvascular complications (retinopathy and proteinuria) was observed in MODY2 diabetic patients (5). In the fetus, GCK mutations result in reduced birth weight, probably by affecting insulin-mediated fetal growth, whereas

maternal GCK mutations indirectly increase the birth weight by enhancing fetal insulin secretion as a consequence of maternal hyperglycemia during fetal life (29, 30); however, none of these effects persists into adult life (30). More recent studies have demonstrated that a common variant upstream of GCK, located -30 G/A in the β -cell specific promoter, modulate birth weight and fasting glucose levels with a constant effect throughout the lifespan and is associated with gestational diabetes (31), with impaired glucose regulation and a higher prevalence of T2D in patients with coronary artery disease (32).

B. Other MODY forms due to mutations in β -cell expressed transcription factor genes

Both a positional cloning approach and candidate gene studies have led to the identification of five transcription factors as MODY genes: HNF-1 α , HNF-4 α , HNF-1 β , IPF1/PDX1, and NeuroD1/ β 2. Gene-targeting experiments in animals have demonstrated that these islet-expressed genes have a key role in the pancreas fetal development and neogenesis, as well as in the β -cell differentiation and function (33).

1. *HNF1A/TCF1*. Mutations in *HNF1A* account for a great part of the MODY forms linked to a defect in the nuclear transcription factors. More than 150 different mutations located in the promoter or coding sequences of *HNF1A* were found in most of the populations investigated (24). Patients with *HNF1A* mutations develop diabetes after the first decade, and it is preceded by abnormal glucose-induced insulin secretion (34). The penetrance is high, although it is dependent on age, so that the probability of being diagnosed with diabetes increases steadily between 10 and 40 yr of age (20, 24). It is not clear why individuals develop diabetes at diverse ages, or why the severity of β -cell dysfunction differs substantially, whereas insulin secretion deficiency was also reported in nondiabetic *HNF1A* mutation carriers in the absence of insulin resistance (35). In contrast to the usually mild hyperglycemia due to GCK deficiency, MODY3 is a more severe form of diabetes, often evolving toward insulin dependency, and microvascular complications of diabetes are observed in MODY3 as in later onset diabetes (5). HNF-1 α is also expressed in the renal tubular cells, and MODY3 is associated with subtle defects such as a decreased threshold for glycosuria reflecting an impaired expression of glucose

transporter and renal tubular dysfunction (36). Experimental data showed that *HNF1A* mutations located in the transactivation domain of the protein may exhibit a dominant-negative effect on the transactivation potential of HNF-1 α dimers (37), and haploinsufficiency is also likely as another mutational mechanism of *HNF1A* mutations causing MODY because this was described for nonsense-mediated decay of mRNA transcripts of HNF1 α harboring premature termination codons (38). Unlike in humans, heterozygous *HNF1A*+/- mice lacking one copy of HNF-1 α do not give rise to an obvious phenotype. The *HNF1A*-/- deficient mice, although not strictly a model for the human disease, have severe dysfunction of hepatocytes, renal tubular cells, and β -cells, and thus develop diabetes. Detailed studies of β -cell function in these mice have revealed a severe abrogation of glucose-induced insulin secretion (39), providing further evidence for a key role of HNF-1 α in the maintenance of normal β -cell function. This is in part linked to defective islet-cell glycolytic flux and is associated with decreased expression of Glut2 glucose transporter and L-type pyruvate kinase genes (39, 40). Another gene potentially involved in the *HNF-1 α* -deficient secretory defect is collectrin/*TMEM27*, which has been shown to regulate either exocytosis or β -cell growth (41).

2. *HNF4A/Hnf-4 α* . Heterozygous mutations in *HNF4A* are considered a rare cause of MODY compared with *MODY2/GCK* and *MODY3/HNF1A* mutations (24, 42). Clinically, the diabetic phenotype in MODY1 due to *HNF4A* mutations is virtually indistinguishable from that due to *HNF1A* mutations (*MODY3*) (42). This shared phenotype is consistent with a revealed interdependence between HNF-1 α and HNF-4 α forming part of a common regulatory network in the β -cells (43, 44).

HNF-4 α belongs to the steroid/thyroid hormone receptor superfamily. Long-chain fatty acids have been shown to directly modulate the transcriptional activity of HNF-4 α by binding as acyl-CoA thioesters to the ligand binding domain of HNF-4 α (45), and they could contribute to the role of dietary fats in the control of insulin secretion. The target genes of HNF-4 α in the β -cells, which may account for the MODY1 phenotype, have been partially defined in the insulin secretion pathway and in glucose transport and metabolism (46, 47). The genetic interaction between the two transcriptional regulators, HNF-1 α and HNF-4 α , specifically occurring in differentiated pancreatic β -cells, has helped to model some molecular pathogenic events underlying the MODY phenotype (43, 48). HNF4 α controls the expression of HNF-1 α in embryonic endoderm, liver, and pancreatic cells, whereas the HNF-1 α control of HNF4 α is restricted to pancreatic cells and in part to intestinal cells. This latter effect with a cellular specificity is mediated through an alternate promoter of *HNF4A* (known as P2). HNF-1 β and IPF1 may also specifically regulate in the pancreas HNF4 α by a direct binding to the P2 promoter. As *in vivo* biological evidence of this regulation, a nucleotide substitution in the conserved IPF1/Pdx-1 binding site was shown to cosegregate with diabetes in a large MODY family and cause a 3-fold reduction in transcriptional activity (48). Interdependence between HNF-1 α and HNF4 α in a positive crossregulatory loop that occurs specifically in the pancreatic cells and is essential for the differentiated β -cell function helped to explain why the loss of one functional allele

results in insufficient activator concentration required to elicit normal target gene responses in islets (43).

Interestingly, a study of the birth weight and incidence of neonatal hypoglycemia in *HNF1A* and *HNF4A* mutation carriers has shown that *HNF4A* mutations are associated with an increase in birth weight and macrosomia and thus can be viewed as a novel cause of neonatal hypoglycemia (49). This study established a key role for HNF4 α in regulating the *in utero* pancreatic insulin secretion and thus determining the fetal birth weight with an unanticipated feature of the natural history of HNF4 α -deficient diabetes; paradoxically, hyperinsulinemia *in utero* and in the neonatal period can later evolve to decreased insulin secretion and diabetes. Because this is not observed in the *HNF1A* mutation carriers (49), it indicates that during these early stages, HNF4 α plays a role that is independent of HNF-1 α .

3. *TCF2/Hnf-1 β* . Mutations in *TCF2/HNF-1 β* are responsible for early onset diabetes consistent with MODY in several families and for severe kidney disease, which may appear before the impairment of glucose tolerance. The most common phenotype in MODY5 patients is renal cysts and/or particular histological abnormalities showing meganephrons (50); this has been recognized as a discrete clinical syndrome, called RCAD (renal cysts and diabetes syndrome) (50, 51). In addition, internal genital abnormalities have been described in some female carriers (50). Hnf-1 β plays a major role in kidney development and nephron differentiation and is also a critical regulator of a transcriptional network that controls the specification, growth, and differentiation of the embryonic pancreas (44, 52). Hnf-1 β mutations in humans accordingly often cause pancreas hypoplasia (44, 51). Altogether, the most recent studies have demonstrated that point mutations, small deletions/insertions, and large genomic rearrangements of *TCF2* account for most of the cases presenting with a clinical phenotype consistent with MODY5 (53).

4. *IPF1/PDX1*. The pancreatic duodenal homeobox-1 (PDX1) factor is an orphan homeodomain protein whose expression is required for pancreatic development. It is first detected at embryonic day 8.5 in mice, and its expression is gradually down-regulated during development and only later reappears when a marked increase of hormone-positive cells occurs. PDX1 is mostly coexpressed with insulin in the developing β -cell and is required for maintaining its phenotype. Although PDX1 expression is not required for pancreatic determination of the endoderm, it is crucial for the development of both endocrine and exocrine cell types. In mice, targeted inactivation of the gene results in pancreas agenesis by arresting the pancreatic development at the bud stage, and β -cell selective disruption of PDX1 led to the development of diabetes with increasing age (43). PDX1 acts as a major transcriptional regulator of endocrine pancreas-specific genes in adults, such as the preproinsulin, glucose transporter-2 and *GCK* genes in β -cells, and the somatostatin gene in δ -cells.

In humans, a deletion in the coding sequence of the *PDX1* gene was found to cosegregate with MODY in a large kindred presenting a consanguineous link (15). In heterozygous mutation carriers, the phenotypes range from impaired glucose tolerance to overt non-insulin-dependent diabetes. One

child who is homozygous for the mutation was born with pancreatic agenesis and suffers from diabetes as well as exocrine insufficiency. Only a few children were reported with a *PDX1* gene defect associated with pancreatic agenesis.

5. *NeuroD1*. The transcription factor *NeuroD1*/BETA2 is a member of the basic helix-loop-helix transcription factor family and plays an important role in the development of the pancreas and the nervous system. In *NeuroD1* null mice, pancreatic islet morphogenesis is abnormal and hyperglycemia develops, due in part to inadequate expression of the insulin gene. Mutations in *NeuroD1* were shown to cosegregate with the MODY phenotype in a few families (54). The clinical profile of patients with a truncated *NeuroD1* polypeptide is more severe than that of patients with a point mutation. *NeuroD1*, after its heterodimerization with the ubiquitous HLH protein E47, regulates insulin gene expression by binding to a critical E-box motif on the insulin promoter. Deficient binding of *NeuroD1* or binding of a transcriptionally inactive polypeptide to target promoters in pancreatic islets leads to the development of early-onset type 2 diabetes in humans.

C. Impact of MODY genes on pharmacogenetics and pharmacogenomics

Altogether, mutations in *GCK* and *HNF1A* are the cause of the two most prevalent MODY2 and MODY3 subtypes, accounting for around two thirds of all MODY cases, mutations in *HNF4A* and *TCF2/Hnf-1 β* were identified in many dozens of families, and the other defects caused by mutations in *PDX1* and *NEUROD1* are rarer disorders (24, 42). These distinct molecular etiologies may explain a substantial part of the clinical heterogeneity with great differences in the clinical course of the disease. Indeed, heterozygous *GCK* mutations cause fasting hyperglycemia, which is present from birth, is usually responsive to diet, and leads to few complications (20). In contrast, *HNF1 α* and *HNF4 α* mutations are associated with a more severe deterioration in glucose homeostasis, which requires hypoglycemic treatment even at a middle age (34, 35, 42). Physiological and metabolic studies have shown that insulin secretion is initially maintained at normal glucose values but progressively fails in early adulthood and may rise only as the glucose concentration is increased. Therefore, the MODY3 and MODY1 patients appear to be at high risk of developing microvascular and macrovascular complications. Of note, the MODY3 patients with *HNF1 α* mutations are more sensitive to the hypoglycemic effect of sulfonylureas (55), which is consistent with the models of *HNF1 α* deficiency, where the β -cell defect is upstream of the sulfonylurea receptor. Thus, definition of the genetic basis of hyperglycemia may have strong therapeutic implications for the care of the patients. In terms of response to therapy, patients with *HNF-1 β* mutations are more frequently treated with insulin (67%) compared with *HNF1 α* mutation patients (31%) (20), and most MODY5 patients rapidly require insulin treatment. This insulin requirement is quite consistent with a generalized reduction in β -cell mass associated with *HNF1 β* deficiency. This clearly highlights the importance of recognizing the different subtypes of

patients presenting with early-onset diabetes and the benefits of more valuable prognostic and therapeutic strategies.

Interestingly, a validation of the structural and functional models of *GCK* with the putative allosteric activator site as a potential drug target for the treatment of T2D (56) has emerged after the identification of activating mutations within the heterotropic allosteric activator site of human β -cell *GCK*. The so-defined activating mutations are responsible for hyperinsulinism with hypoglycemia of infancy, whereas other mutations causing hyperglycemia are not necessarily kinetically inactivating but may act by other complex mechanisms. A drug discovery process aimed at increasing the activity of *GCK* has led to the production of several compounds that activate the enzyme, so-called GK activators (GKAs) (57). The dual mechanism of action of GKAs in both pancreatic β -cells and liver suggests that these molecules exert their biological actions in T2D patients by improving overall β -cell function coupled with a suppression of hepatic glucose production, with a net effect of decreasing fasting plasma glucose and improving glucose tolerance. Since the discovery of the first orally active GKA (RO0281675), several research groups have reported the identification of novel potent GKAs (57). This is an excellent example of translational research from a complicated system such as the regulation of *GCK* toward the discovery of a new class of therapeutic agents that will be useful in the treatment of T2D.

IV. Other Forms of Monogenic Type 2 Diabetes

In addition to the established MODY genes, other genetic defects have been implicated in familial forms of type 2 diabetes with different phenotypes associated with extrapancreatic anomalies.

A. Diabetes and pancreatic exocrine dysfunction

Two families with diabetes and exocrine pancreatic dysfunction were described with single-base deletions in the carboxyl ester lipase (*CEL*) gene, a major component of pancreatic juice, involved in the duodenal hydrolysis of cholesterol esters. Physiological and *in vitro* functional studies showed that the mutant enzyme was less stable and secreted at a lower rate compared with the wild-type *CEL* protein. These defects are responsible for a similar phenotype with β -cell failure and pancreatic exocrine disease (58) and link diabetes to the impaired function of a lipase expressed in the pancreatic acinar cells. Pancreatic lipomatosis participates as a structural marker in nondiabetic children carrying a *CEL* mutation, which reflects early events in the pathogenesis of the syndrome (59).

B. Diabetes associated with mitochondrial defects (MIDD)

MIDD, a syndrome known as maternally inherited diabetes and deafness, is characterized by the occurrence of neurosensory deafness followed by diabetes mellitus, which usually occurs in the second decade of life (60). Although the original description of MIDD pointed to a 10.4-kb deletion in the mitochondrial genome, other studies have associated an identical phenotype with an A to G transition at base-pair 3243 affecting tRNA (Leu), which is also frequently associated with MELAS

(60, 61). The latter is a syndromic disorder characterized by mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, which is often accompanied by diabetes and deafness (62). The mechanisms underlying the different phenotypic expression (MIDD or MELAS) may be due to heteroplasmy of mitochondrial mutations in different tissues. Based on several association studies, it has been estimated that 1.5% of common diabetes mellitus cases may be caused by the mitochondrial A3243G mutation. Abnormalities in insulin secretion were found in all MIDD subjects that were tested, including those with normal glucose tolerance (63). An impaired glucose-regulated insulin secretion is an early, possible primary defect in carriers of the mutation (60). Several other mitochondrial cytopathies associated with diabetes are caused by point mutations, deletions, or duplications of mitochondrial DNA and characterized by decreased oxidative phosphorylation (60).

C. Wolfram syndrome (WS)

This syndrome (also known as DIDMOAD, the acronym for diabetes insipidus diabetes mellitus, optic atrophy and deafness, which are the main clinical features in WS patients) is a rare progressive neurodegenerative disorder that is inherited in an autosomal recessive manner. Insulin-dependent diabetes mellitus, usually occurring during the first decade of life, and a bilateral progressive optic nerve atrophy are sufficient criteria for the diagnosis, but a wide variety of central nervous system abnormalities can be present.

The WS gene, *WFS1*, was mapped to chromosome 4p16.1 by positional cloning. It encodes an 890-amino acid polypeptide named wolframin, a transmembrane protein located in the endoplasmic reticulum (ER) (64). *WFS1* serves as an ER calcium channel, suggesting that this molecule may have a function in ER homeostasis. *WFS1* is normally up-regulated during insulin secretion, whereas inactivation of *WFS1* in β -cells causes ER stress and β -cell dysfunction. Hence, impaired wolframin function might induce inappropriate apoptotic events, leading to neurodegeneration and loss of pancreatic β -cells. No wolframin aggregates were found in patient cells, suggesting that WS is not a disease of protein aggregation, and *WFS1* mutations rather cause loss-of-function by cellular depletion of wolframin.

D. Genetic anomalies in adult-onset familial diabetes

A mutation in islet brain-1 (IB1), a homologous protein to the c-jun amino-terminal kinase interacting protein 1, which plays a key role in the cellular signaling and regulatory mechanisms of apoptosis, was found to be associated with diabetes in one family (65). The mutant IB1 was found to be unable to prevent apoptosis *in vitro*; thus, IB1 dysfunction may render the β -cells more susceptible to apoptotic stimuli, and may result in decreasing β -cell mass. IB1 is also a transactivator of the islet glucose transporter-2.

Islet-1 is one of the transcription factors that play an important role for the formation of the islet cells, and a nonsense mutation (Q310X) in the *MAPK8IP1* gene, coding for Islet-1, was reported in a Japanese family to be a rare cause of diabetes in isolated families (66).

Krüppel-like factor 11 (KLF11) encodes an SP1 pancreatic

transcription factor that is induced by TGF- β and regulates cell growth in the exocrine pancreas. Sequencing *KLF11* in families enriched for early-onset T2D uncovered two missense mutations that segregated with diabetes in three pedigrees (67). A common polymorphism (Q62R) was also found to be associated with polygenic T2D developing in adulthood (67) and to affect the function of KLF11 *in vitro*, and insulin levels were lower in carriers of the minor allele at Q62R. However, some replication studies in other populations only found a minor effect of the Q62R common variant on diabetes risk. These findings strongly suggest a role for the TGF- β signaling pathway in pancreatic diseases affecting endocrine islets (diabetes) or exocrine cells (cancer).

A *TGM2* heterozygous missense mutation (N333S) located in the active site of the enzyme transglutaminase 2 (TG2) was identified in a family clinically classified as MODY (a 14-yr-old patient and his father who is diabetic and moderately overweight) (68). TG2 is a multifunctional enzyme that catalyzes transamidation reactions or acts as a G protein in intracellular signaling. Mice lacking TG2 activity (*TGM2*^{-/-}) are glucose intolerant and show impairment of insulin secretion, suggesting an important physiological role for TG2 in the pancreatic β -cell (68). Two novel missense mutations in *TGM2* (M330R, I331N) were recently reported to be associated with early-onset type 2 diabetes (69), suggesting a role for TG2 in the pathophysiology of the disease. In this study, gene expression of transglutaminase family genes and localization of TG2 in normal human pancreas have shown that TG2 is the only transglutaminase significantly expressed in the human insulin-secreting β -cell (69). Altogether, these data suggest that a reduced TG2 activity can contribute to disorders of glucose metabolism likely via an impairment in insulin secretion.

V. Relevance of Genes Involved in Monogenic Diabetes to Multifactorial Forms of Type 2 Diabetes

Recent case-control association studies have shown that variants in genes implicated in monogenic and syndromic forms of diabetes may also be involved in susceptibility to more common multifactorial forms of the disease. Indeed, if major mutations (*i.e.*, causing a substantial functional defect and normally rare or absent in the general population) lead to a highly penetrant form of diabetes, it seems plausible that more subtle genetic changes affecting the structure or expression of the gene product might play a role in determining (minor) susceptibility to T2D. Our current understanding of genetic variants influencing T2D supports this hypothesis (Refs. 3 and 24 and Table 2), but common variants in the known MODY genes seem to contribute very modestly to the common forms of type 2 diabetes, as recently assessed in a staged case-control study from multiple clinical samples (70); furthermore, as indicated by the results of the recently published genome-wide association (GWA) studies for T2D (mostly in Caucasian populations; 71–74), the strongest association signals for T2D highlighted by these genome-wide studies do not lie within the gene loci previously known to be implicated in monogenic diabetes phenotypes.

The -30G/A polymorphism in the β -cell-specific promoter of GCK was found to modulate diabetes risk [associ-

TABLE 2. Human genes responsible for monogenic forms of diabetes and associated with increased risk of diabetes in adulthood (from case-control studies of common variants)

Gene name	Monogenic disease (OMIM)	Polygenic type 2 diabetes	Ref.
<i>HNF4A</i>	MODY1 (125850)	Variants at the P2 promoter (MAF > 0.15) OR = 1.15 [1.00–1.30] in Europeans ^a	81, 82
<i>GCK</i>	MODY2 (125851)	Variant –30G/A (β -cell promoter) OR = 1.22 [1.13–1.32] in Europeans	70, 75
<i>TCF1/HNF1A</i>	MODY3 (600496)	G319S, OR = 2.0 in Oji-Cree (heterozygous carriers) OR = 1.17 [1.06–1.30] in Europeans (other variants, MAF > 0.10)	78, 80
<i>TCF2/HNF1β</i>	MODY5 (604284)	Intronic variants (MAF > 0.10) OR = 1.12 [1.07–1.17] in Europeans	70, 85
<i>TIEG2/KLF11</i>	Early-onset T2D (603301)	G62R (MAF > 0.10) OR = 1.29 [1.12–1.49] in Northern-Europeans ^a	67
<i>KCNJ11</i>	PNDM (606176)	E23K (MAF > 0.30) OR = 1.14 [1.10–1.19] in Europeans	90–92, 96
<i>ABCC8</i>	CHI, PNDM, Dominant T2D (256450)	A1369S (MAF > 0.30) OR = 1.14 [1.02–1.28] in Caucasians	91, 92
<i>WFS1</i>	DIDMOAD (22233)	R611H (MAF ~ 0.60), other intronic variants OR = 1.11 [1.08–1.16] in Europeans	88, 96

PNDM, Permanent NDM; CHI, congenital hyperinsulinism of infancy; DIDMOAD, diabetes insipidus, diabetes mellitus, optic atrophy and deafness.

^a There were inconsistencies in replicating some of the initial associations.

ation with an increased risk for the (–30) A-allele] (70); a similar genetic association was also observed with a stronger effect in a French prospective study of a middle-aged general population, along with a significant impact on the modulation of fasting glycemia and on homeostasis model assessment of β -cell function (75). Furthermore, a meta-analysis of previously reported association results for *GCK* (–30A) with type 2 diabetes showed a modest overall effect on disease risk of 1.08 ($P = 0.004$) in mostly European origin populations (70). Of note, private mutations in *HNF-1 α* were identified in African-Americans and Japanese subjects presenting with atypical nonautoimmune diabetes and acute onset (76, 77), and in the Oji-Cree native Canadian population, characterized by a very high risk for developing type 2 diabetes, in which the G319S mutation in *HNF-1 α* was found in approximately 40% of diabetic patients and accelerates the onset of T2D by 7 yr (78). These findings show that, besides *MODY*, *HNF-1 α* mutations can be associated with adult-onset diabetes related to insulin-resistance or obesity. Rare mutations in *HNF4A* and *IPF1* genes were also identified in a number of families with late-onset T2D (79). *IPF1/PDX1* has a dosage-dependent regulatory effect on the expression of β -cell-specific genes and therefore plays a crucial role in the maintenance of euglycemia. As a consequence, common variants in the *IPF1* promoter regulatory sequences that control *IPF1* expression in the β -cell or variants in genes encoding transcription factors known to regulate *IPF1* could contribute to common T2D susceptibility.

More frequent variants at the *HNF1A* and *HNF4A* gene locus may be associated with T2D in different ethnic groups (80–82). Two independent studies, from the Ashkenazim (81) and Finnish (82) populations, have reported significant associations between common variants adjacent to the *HNF4A* P2 promoter and T2D. Interestingly, some of the diabetes-associated variants account for most of the evidence of linkage to chromosome 20q13 reported in these two populations. Consistent with these results, genetic variation near the P2 region of *HNF4A* is associated with T2D in other Danish and UK populations, but not

in French or other Caucasian populations (83), which argues for genetic heterogeneity in *HNF4A* variants susceptibility. The causal variant(s) affecting the expression or function of *HNF4 α* are still unknown and could result in a combination of relative insulin deficiency and defective regulation of the hepatic gluconeogenesis.

A population-based study in Swedish and Finnish cohorts using both *in vitro* and *in vivo* experiments has shown that common variants in and upstream of the *HNF1A* gene influence transcriptional activity and insulin secretion *in vivo*. Some of these variants are associated with a modestly higher risk of diabetes in subsets of elderly overweight individuals (84).

Recent studies having evaluated the genotype-phenotype correlation between the *MODY* genes and the common form of type 2 diabetes have reported that several common variants [minor allele frequency (MAF) > 0.05] in *TCF2/HNF1 β* may contribute to type 2 diabetes risk with yet modest effects [allelic odds ratio (OR) < 1.25; the strongest effect was found for an intronic variant with corrected P values < 0.01 for OR of 1.13] (70, 85). Independently, a GWA scan performed to search for sequence variants conferring risk of prostate cancer demonstrated with replication from eight case-control groups that two intronic variants located in the first and second intron of *TCF2* gene confer protection against type 2 diabetes (OR, 0.91; $P \sim 10^{-7}$) in individuals of European, African, and Asian descent (86). As it was previously known, several epidemiological studies have reported an inverse relationship between T2D and the risk of prostate cancer, and a recent meta-analysis estimated the relative risk of prostate cancer to be 0.84 (95% confidence interval, 0.71–0.92) among diabetic patients (87). Previous explanations of this inverse relationship between T2D and prostate cancer have centered on the impact of the metabolic and hormonal environment in men. However, the protective effect of the *TCF2* single nucleotide polymorphisms (SNPs) against type 2 diabetes is too modest merely to explain their impact on prostate cancer risk by a consequence of an effect on diabetes. The primary functional impact of *TCF2* variants may lie within one or more

metabolic or hormonal pathways (through possibly different mechanisms than the molecular defects involved in MODY5, as discussed above), and incidentally may modulate the risk of developing prostate cancer and T2D throughout the life.

Genetic variation in *WFS1* not only results in a rare syndrome characterized by early-onset non-autoimmune diabetes but is also associated with susceptibility to adult type 2 diabetes (88). In a pooled case-control analysis comprising more than 20,000 individuals, several SNPs in *WFS1* (including a nonsynonymous SNP, R611H) were shown to modulate the diabetes risk [OR ~0.92 for a MAF of ~0.40 (Ref. 88)], with a population attributable fraction of 9% (that could explain 0.3% of the excess familial risk). This recent study provides further evidence that *WFS1*, encoding wolframin that has an essential role in the ER stress response in insulin-producing pancreatic β -cells, contributes to the risk of common type 2 diabetes.

Whereas mutations in the *KCNJ11* and *ABCC8* genes that encode the two subunits (Kir6.2 and SUR1, respectively) of the ATP-sensitive K^+ (K_{ATP}) channel of the pancreatic β -cell have been characterized as a common cause of both permanent and transient NDM (reviewed in Ref. 89), a common polymorphism in *KCNJ11*/ $K_{IR6.2}$, E23K (a glutamate-to-lysine amino acid substitution at position 23), was shown to be associated with an increased risk of developing type 2 diabetes in Caucasian populations (90–92). Large-scale association studies and meta-analyses of this coding variant have confirmed in several populations a modest size effect of the susceptible K23 allele on T2D risk (OR ~1.2); however, because approximately 60% of the population carries at least one K23 allele, it is likely to have a substantial effect on population-attributable risk. A recent association study in a Japanese population and a meta-analysis of East Asian studies confirm the genetic association between SNPs in the *KCNJ11-ABCC8* locus, including the E23K polymorphism, and T2D across multiple racial/ethnic groups (93). Data from *in vitro* functional experiments has indicated that the K23 type of Kir6.2 alters K_{ATP} function by inducing a modest channel overactivity and a subsequent increase in the threshold ATP concentration for insulin release (94). Consistently, in glucose-tolerant subjects, significant associations of the *KCNJ11-K23* allele with reduction in insulin release during an oral glucose tolerance test have been reported (92, 95).

A major lesson learned from monogenic diabetes, where functional mutations cosegregating with early-onset diabetes have been identified, is that it can provide a proof of concept of a pivotal role for a given gene in the establishment and maintenance of adequate β -cell mass and functional capacity. Some regulatory pathways deciphered are shown in Fig. 1. As an example is the discovery of the IPF1-HNFs common regulatory network in β -cells. Whether or not a monogenic diabetes gene also contributes to the genetic risk of multifactorial T2D is another issue that requires larger scale genetic and epidemiological studies and the search of biomarkers for diabetes. As demonstrated by the recent data from the GWA studies in T2D, several other β -cell expressed genes, not previously implicated in the disease, can modulate T2D susceptibility in adulthood. These new etiological pathways have to be established, and the potential pharmaco-

genetic role and clinical relevance of the new gene variants needs to be assessed.

VI. Perspectives in the New Era of Genome-Wide Search for Type 2 Diabetes

Recent advances in T2D genetics have been made with the completion of GWA surveys based on HapMap-selected common SNPs, providing significant evidence in several European populations for at least five new gene regions (*SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A/2B*, *IGF-IIBP2*) involved in the disease (71–74, 96).

Ongoing studies for functional characterization of some of these recently identified genes and extensive epidemiogenetic analyses in general populations and well-powered prospective cohorts promise to greatly speed up the identification of novel confirmed T2D susceptibility genes.

Studying of early-onset T2D and monogenic or syndromic forms of unknown molecular origin will also provide new insights to a better understanding of the cellular events that maintain glucose homeostasis and of their complex interactions and impairments leading to chronic hyperglycemia. Then, a nosological classification of the disease based on primary pathophysiological mechanisms can be made, and more specifically targeted antidiabetic drugs could be designed. Moreover, pharmacogenetic testing might be used in the future to predict for each patient the therapeutic response to different classes of drugs. The practical implications of such novel findings also concern disease risk prediction, by the timely identification of high-risk young people who are offspring of diabetic individuals, with the expectation of a better individualized prevention and obviously the assessment of new putative drug targets.

Given the expected doubling of the worldwide prevalence of diabetes in the next 20 yr, breakthroughs in diabetes care at the very early stages of the disease are needed to reverse these worrying trends in type 2 diabetes occurrence and comorbidities.

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