

Monogenic Diabetes: What It Teaches Us on the Common Forms of Type 1 and Type 2 Diabetes

Yisheng Yang and Lawrence Chan

Division of Endocrinology (Y.Y.), Department of Medicine, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio 44109; and Diabetes and Endocrinology Research Center (L.C.), Division of Diabetes, Endocrinology and Metabolism, Departments of Medicine, Molecular and Cellular Biology, Biochemistry and Molecular Biology, and Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030

To date, more than 30 genes have been linked to monogenic diabetes. Candidate gene and genome-wide association studies have identified > 50 susceptibility loci for common type 1 diabetes (T1D) and approximately 100 susceptibility loci for type 2 diabetes (T2D). About 1–5% of all cases of diabetes result from single-gene mutations and are called monogenic diabetes. Here, we review the pathophysiological basis of the role of monogenic diabetes genes that have also been found to be associated with common T1D and/or T2D. Variants of approximately one-third of monogenic diabetes genes are associated with T2D, but not T1D. Two of the T2D-associated monogenic diabetes genes—potassium inward-rectifying channel, subfamily J, member 11 (*KCNJ11*), which controls glucose-stimulated insulin secretion in the β -cell; and peroxisome proliferator-activated receptor γ (*PPARG*), which impacts multiple tissue targets in relation to inflammation and insulin sensitivity—have been developed as major antidiabetic drug targets. Another monogenic diabetes gene, the preproinsulin gene (*INS*), is unique in that *INS* mutations can cause hyperinsulinemia, hyperproinsulinemia, neonatal diabetes mellitus, one type of maturity-onset diabetes of the young (MODY10), and autoantibody-negative T1D. Dominant heterozygous *INS* mutations are the second most common cause of permanent neonatal diabetes. Moreover, *INS* gene variants are strongly associated with common T1D (type 1a), but inconsistently with T2D. Variants of the monogenic diabetes gene Gli-similar 3 (*GLIS3*) are associated with both T1D and T2D. *GLIS3* is a key transcription factor in insulin production and β -cell differentiation during embryonic development, which perturbation forms the basis of monogenic diabetes as well as its association with T1D. *GLIS3* is also required for compensatory β -cell proliferation in adults; impairment of this function predisposes to T2D. Thus, monogenic forms of diabetes are invaluable “human models” that have contributed to our understanding of the pathophysiological basis of common T1D and T2D. (*Endocrine Reviews* 37: 190–222, 2016)

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I. Introduction

Type 1 diabetes (type 1a; hereafter referred to as T1D) and type 2 diabetes (T2D) are of multifactorial etiology, in which genetic predisposition plays a key role. Monogenic diabetes is relatively rare. Neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young

Abbreviations: *ABCC8*, ATP-binding cassette transporter subfamily C member 8; *CCND2*, cyclin D2; *CHI*, congenital hyperinsulinism; e, embryonic day; ER, endoplasmic reticulum; FBS, Fanconi-Bickel syndrome; FGF, fibroblast growth factor; GCK, glucokinase; GDM, gestational diabetes mellitus; GKR, GCK regulatory protein; *GLIS3*, Gli-similar 3; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; G6PC2, glucose-6-phosphatase, catalytic 2; G6S, glucose-stimulated insulin secretion; GWAS, genome-wide association studies; HFD, high-fat diet; HLA, human leukocyte antigen; HLH, helix-loop-helix; *HNF1A*, hepatocyte nuclear factor 1 homeobox A; IGT, impaired glucose tolerance; *K_{ATP}*, ATP-sensitive potassium; *KCNJ11*, potassium inward-rectifying channel, subfamily J, member 11; KPD, ketosis-prone diabetes; MAF, minor allele frequency; MODY, maturity-onset diabetes of the young; NDH, neonatal diabetes, hypothyroidism; NDM, neonatal diabetes mellitus; PAX4, paired box 4; PDX1, pancreatic and duodenal homeobox 1; PNDM, permanent NDM; *PPARA*, peroxisome proliferator-activated receptor α ; *PPARG*, peroxisome proliferator-activated receptor γ ; RCAD, renal cysts and diabetes; SGLT2, sodium-glucose cotransporter 2; SLC2A2, solute carrier family 2, member 2; SUR1, sulfonylurea receptor 1; T1D, type 1 diabetes; T2D, type 2 diabetes; TH, tyrosine hydroxylase; TNDM, transient NDM; TZD, thiazolidinedione; UPR, unfolded protein response; UTR, untranslated region; VNTR, variable number of tandem repeats; WFS1, Wolfram syndrome 1.

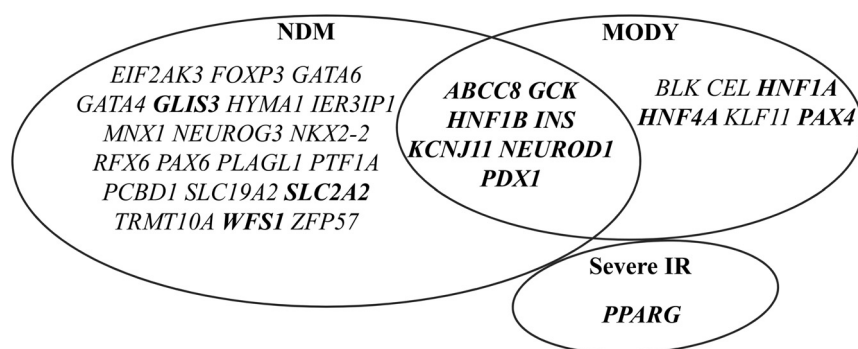
Figure 1.

Figure 1. Monogenic diabetes genes associated with NDM and/or MODY. Over 30 monogenic diabetes genes have been identified to cause NDM or MODY. Mutations in seven of them, including *ABCC8*, *GCK*, *HNF1B*, *INS*, *KCNJ11*, *NEUROD1*, and *PDX1*, may lead to both NDM and MODY. Bolded genes are discussed in this article.

(MODY) are two major forms of monogenic diabetes, which usually result from mutations of genes for transcription factors or other proteins that regulate endocrine pancreas development or function. Mutations in a number of monogenic diabetes genes may cause NDM and MODY (Figure 1). NDM presents within the first 6 months of life and can persist throughout life (called permanent NDM [PNDM]), or it can be transient and disappear during infancy, often reappearing later in life (called transient NDM [TNDM]) (1, 2). In contrast to classic T1D (called common T1D in this article), NDM is only rarely associated with high-risk human leukocyte antigen (HLA) haplotypes or the presence of islet autoimmune antibodies (1, 3); eg, mutations of the NDM gene signal transducer and activator of transcription 3 have recently been reported to be associated with early-onset autoimmune disorders including T1D in rare cases (4). MODY is an early-onset (presenting usually before the age of 25 years) monogenic diabetes caused by mutations in a number of islet-related genes and is inherited in an autosomal dominant manner. Mutations in hepatocyte nuclear factor 1 homeobox A (*HNF1A*) (*HNF1A*-MODY or -MODY3) and glucokinase (*GCK*-MODY or MODY2) underlie the two most common forms of MODY (5, 6). Of note, MODY is a heterogeneous condition. The clinical phenotype can vary substantially among patients with the same MODY genotype, even among members in the same MODY family. The effect of gene-gene and gene-environment (eg, diet and exercise) interactions may underlie the heterogeneities (5).

To date, more than 30 genes have been linked to monogenic diabetes and related syndromes (1, 2, 5). More than 50 and 90 susceptibility loci, respectively, are found to be associated with T1D and T2D (7–11) (Figure 2). In particular, the HLA class II region of the major histocompatibility complex confers major genetic risk for T1D. Transcription factor 7-like

2 (*TCF7L2*) rs7903146 is one of the most robust susceptibility variants for T2D identified to date. Although T1D and T2D share some clinical and pathological similarities, GWAS indicate that their susceptibility loci are mostly distinct, and only a limited number of them have been found to be associated with both T1D and T2D (12–15). These include: *INS*, *GLIS3*, RAS guanyl nucleotide-releasing protein 1 (*RASGRP1*), cordon-bleu WH2 repeat protein (*COBL*), renalase (*RNLS*), and breast cancer antiestrogen resistance 1 (*BCAR1*). Most of the loci associated with T1D and T2D (7–10) will not be discussed further in this article

because they are not known to cause monogenic diabetes. Monogenic diabetes represents unique in vivo models of disordered developmental and functional biology of pancreatic β -cells being played out, not in animals, but in people. Importantly, before the development of GWAS, monogenic diabetes genes provided the genetic landscape toward the identification of new candidate genes for the common forms of T1D and T2D. In the GWAS and post-GWAS era, the different types of monogenic diabetes continue to provide pathophysiological insight for the interpretation of GWAS data. In this context, we will focus on the mechanistic defects that underlie monogenic diabetes genes that have also been found to be associated with common T1D and/or T2D (Table 1 and Figure 2).

II. Monogenic Diabetes Genes Associated With T2D, But Not T1D

GWAS revealed that approximately one-third of monogenic diabetes genes are associated with common T2D, but not T1D. The 12 monogenic diabetes genes in this category are: potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*), ATP-binding cassette transporter subfamily C member 8 (*ABCC8*), *GCK*, solute carrier family 2, member 2 (*SLC2A2*), *HNF1A*, *HNF4A*, *HNF1B*, pancreatic and duodenal homeobox 1 (*PDX1*), paired box 4 (*PAX4*), *NEUROD1/BETA2*, Wolfram syndrome 1 (*WFS1*), and peroxisome proliferator-activated receptor γ (*PPARG*).

A. *KCNJ11* and *ABCC8*

The ATP-sensitive potassium (K_{ATP}) channel is composed of four pore-forming inwardly-rectifying potassium channel subunits (Kir6.2), encoded by *KCNJ11*, and four regulatory sulfonylurea receptor 1 (*SUR1*) subunits, encoded

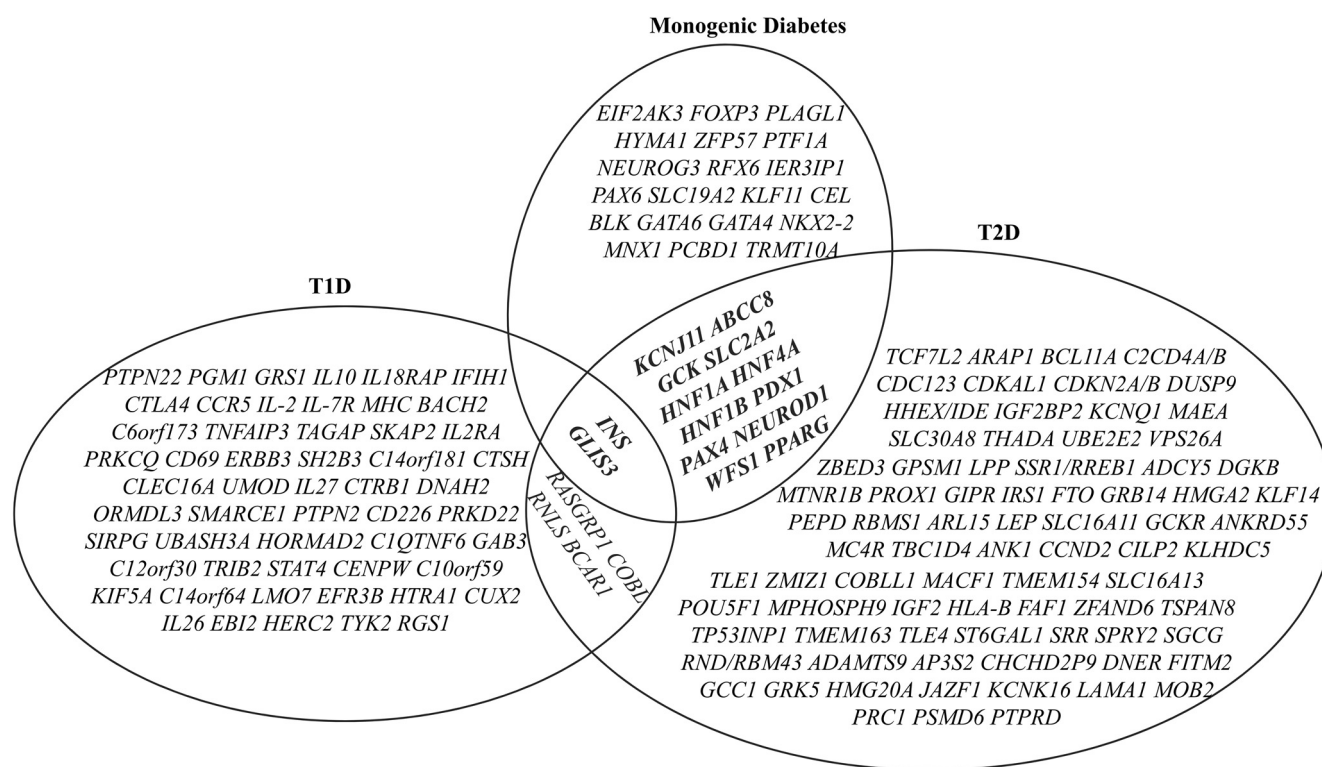
Figure 2.

Figure 2. Venn diagram of intersection between the loci/genes associated with T1D or T2D and known monogenic diabetes. Over 50 susceptibility loci for common T1D and approximately 100 susceptibility loci for T2D have been identified by GWAS and candidate gene association studies. *INS*, *GLIS3*, *RASGRP*, *COBL*, *RNLS*, and *BCAR1* are associated with both T1D and T2D. About one-third of the known monogenic diabetes genes are associated with T2D. *INS* and *GLIS3* are the two known monogenic diabetes genes whose variants are associated with both T1D and T2D.

by *ABCC8*. An exquisitely regulated K_{ATP} channel controls insulin secretion by coupling β -cell metabolism to calcium entry. ATP and MgADP are thought to display opposing roles in closing or opening the K_{ATP} channel. High blood glucose is taken up and metabolized by the β -cell that leads to elevated intracellular ATP level and closure of the K_{ATP} channel. The reduction in K^+ efflux gives rise to membrane depolarization, resulting in opening of the voltage-gated Ca^{2+} channel, triggering electrical activity, Ca^{2+} influx, and insulin secretion (Figure 3A). Inactivating mutations in *KCNJ11* or *ABCC8* result in congenital hyperinsulinism (CHI), whereas activating mutations in either gene that interferes with the ATP sensitivity of the K_{ATP} channel can lead to NDM (16). Monogenic mutations in the K_{ATP} channel components have taught us how insulin secretion is regulated and how insulin secretagogues such as sulfonylureas work.

1. Inactivating mutations in the *KCNJ11* and *ABCC8* genes result in CHI

We will briefly review the molecular basis of CHI because it will shed light on the role of the *KCNJ11* and *ABCC8* genes

in the regulation of insulin secretion. Loss-of-function mutations in the *KCNJ11* and *ABCC8* genes are the most common cause of CHI (17). Most of the disease-causing mutations in the K_{ATP} channel genes are recessively inherited, leading to medically unresponsive CHI, which frequently requires near total pancreatectomy to relieve the recurrent severe hypoglycemia. Mechanistically, these recessive mutations adversely affect the biogenesis and turnover of K_{ATP} channels, resulting in defective trafficking of channels to the plasma membrane and altered open-state frequency (18–20). Increasing numbers of mutations within the nucleotide-binding domain 2, a hotspot for dominantly acting mutations in the *ABCC8* gene, have been identified in CHI patients. These include E1506K, G1479R, R1539Q, L1390R, L1431F, Q1459E, A1508P, A1537V, and R1420H (21–23). An in-frame heterozygous deletion (I284del) in the *KCNJ11* gene (21) and some compound heterozygous mutations in the *ABCC8* gene (24) have also been reported in CHI. These inactivating mutations cause hyperinsulinemia predominately through reduced K_{ATP} channel activity in pancreatic β -cells, which leads to abnormal membrane polarization, activation of voltage-gated cal-

Table 1. Monogenic Diabetes Genes Associated With Common T1D and/or T2D

Gene Name	Major Function	Monogenic Diabetes or Syndromes	Mutations or Variants Associated With Common T1D and/or T2D	Refs.
Monogenic Diabetes Genes Associated With T2D				
<i>KCNJ11</i>	Encodes pore-forming inwardly-rectifying potassium channel subunits (Kir6.2)	PNDM (most common cause) and TNDM, CHI, MODY	E23K	42–46
<i>ABCC8</i>	Encodes regulatory SUR1 subunits	PNDM and TNDM, CHI, MODY	A1369S, 1273AGA, R1420H	46, 47, 52
<i>GCK</i>	A key glucose-phosphorylating enzyme; a glucose sensor	GCK-MODY (MODY2), PNDM, CHI	rs1799884 (G/A), rs4607517 (A/G), 3'UTR SNP, chr7:44184184-G/A	75, 78, 79
<i>SLC2A2</i>	Encodes GLUT2, a high-capacity facilitative glucose transporter	FBS	SNPs rs5393 (AA) and rs5394 (CC) in the promoter region and SNPs rs5400 (T110I) and rs5404 (T198T)	93–100
<i>HNF1A/TCF1</i>	TF; regulator of pancreatic β -cell differentiation	HNF1A-MODY (MODY3), most common cause of MODY, CHI	G319S, c.1522G>A (p.E508K)	114, 118, 119
<i>HNF4A</i>	Key TF for early fetal development	HNF4A MODY (MODY1), CHI	SNPs rs2144908, rs3818247 and rs884614, rs4810424, rs1884613	121–124, 274
<i>HNF1B/TCF2</i>	TF; required for the generation of pancreatic and endocrine progenitors	RCAD syndrome, or MODY5; TNDM and PNDM (rare)	SNP rs757210 A, rs4430796 A, and rs7501939 C	141, 144
<i>PDX1</i>	TF; required for pancreas development, β -cell differentiation and the maintenance of mature β -cell function	PNDM, MODY4	C18R, Q59L, D76N, R197H, G212R, P239Q, InsCCG243, p.Gly218Alafs*12	163–165, 167
<i>PAX4</i>	Islet TF that functions mainly as a transcription repressor	MODY9	R121W, R133W, R37W, rs10229583 G	180, 181, 187
<i>NEUROD1/BETA2</i>	TF; required for the development of the endocrine pancreas; transactivates the <i>INS</i> gene	MODY6 and PNDM	R111L and 206 + C; A45T variant at rs1801262 (inconsistent)	204–208
<i>WFS1</i>	A transmembrane protein; a negative regulator of ER stress	WFS1, sometimes referred to as DIDMOAD	R456 and H611, SNPs at rs10010131, rs6446482; variants rs10010131 G, 1801213 G, and rs734312 A	223–225
<i>PPARG</i>	TF; master regulator of adipogenesis, energy balance, lipid biosynthesis, and insulin sensitivity; cellular target of TZDs	Monogenic diabetes	Pro12Ala variant (rs1801282), SNP at rs4684847	240–243, 250
Monogenic Diabetes Genes Associated With Both Common T1D and T2D				
<i>INS</i>	Predominant glucose-lowering hormone	PNDM (2nd most common cause), TNDM, MODY10	Class I alleles of <i>INS</i> VNTR associated with T1D; Class III alleles of <i>INS</i> VNTR inconsistently associated with T2D	273, 274, 276–281
<i>GLIS3</i>	TF; regulator of islet development, insulin gene transcription, and obesity-induced compensatory β -cell proliferation	Neonatal diabetes syndrome associated with congenital hypothyroidism, and polycystic kidneys	rs7020673 G associated with T1D; rs7034200 A and rs7041847 A associated with T2D	78, 214, 289, 291, 292, 295–308

Abbreviation: TF, transcription factor.

cium channels, and increased Ca^{2+} concentration causing insulin hypersecretion (Figure 3B).

Dominant K_{ATP} channel mutations causing CHI may predispose to the development of diabetes in adulthood. Nonpancreatectomized K_{ATP} -CHI patients eventually enter clinical remission and may progress to diabetes in later life (23–27), whereas those who are treated by partial pancreatectomy often develop late-onset diabetes that may require insulin therapy (17).

Diazoxide is one of the primary medications used to treat CHI (28). In pancreatic β -cells, diazoxide, a K^{+} channel opener, binds to SUR1 subunits to increase K_{ATP} channel activity, promoting K^{+} efflux and cell membrane hyperpolarization to block insulin release. Octreotide (a somatostatin analog) can be used for diazoxide-unrespon-

sive CHI patients (28). The mechanism underlying the inhibition of insulin secretion by octreotide has not been fully elucidated. Octreotide inhibits Ca^{2+} entry into pancreatic β -cells via voltage-dependent calcium channels, leading to suppression of insulin secretion (29, 30). In addition, octreotide may hyperpolarize β -cells by activating K_{ATP} channel and thus inhibits insulin secretion (31).

2. Activating mutations in the *KCNJ11* and *ABCC8* genes lead to PNDM

Gain-of-function mutations in the K_{ATP} channel genes impair ATP binding to the channel, leading to K_{ATP} channel opening, membrane hyperpolarization, impaired insulin release, and NDM (Figure 3C). Activating mutations of *KCNJ11* were first identified over a decade ago in pa-

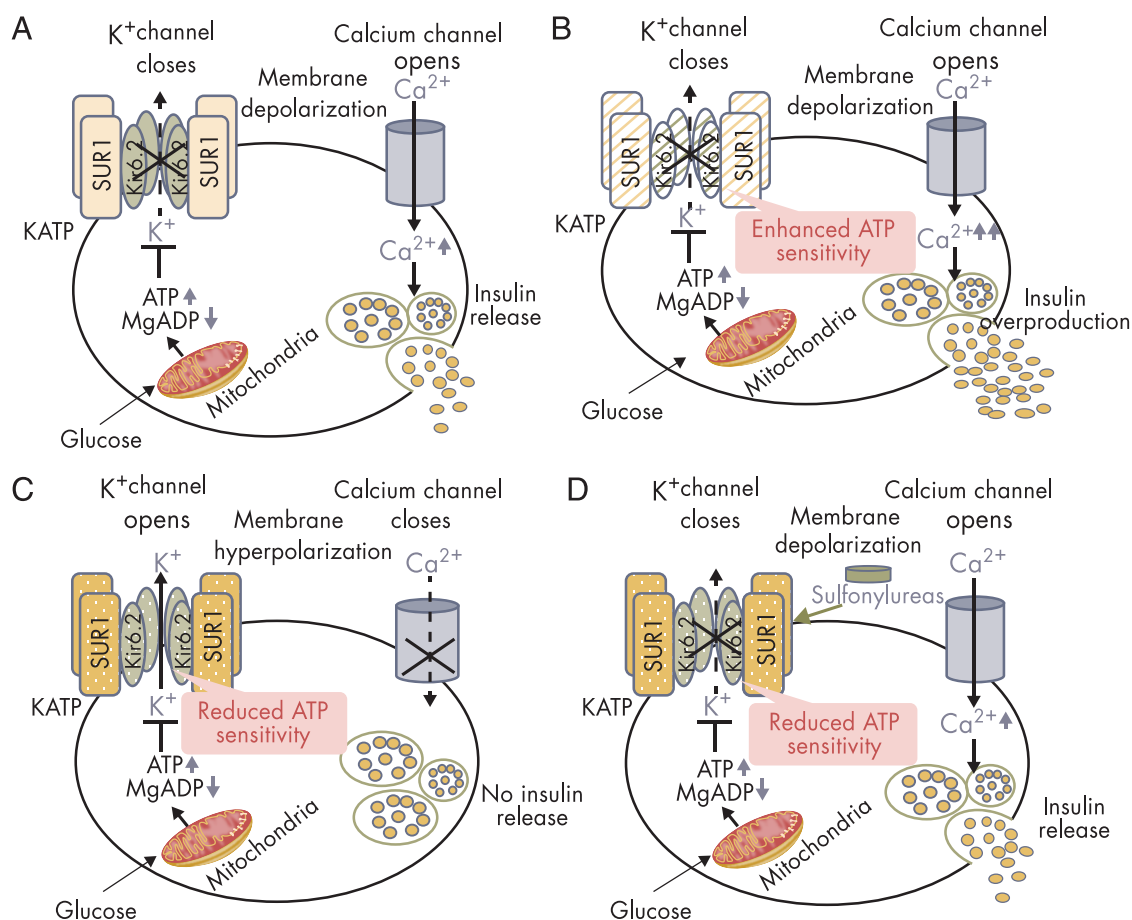
Figure 3.

Figure 3. Insulin secretion in normal and K_{ATP} channel mutant pancreatic β -cells. A, Glucose-stimulated insulin secretion in normal β -cells. The K_{ATP} channel is composed of four Kir6.2 subunits encoded by *KCNJ11* and four SUR1 subunits encoded by *ABCC8*. High glucose in the circulation leads to increased glucose uptake into pancreatic β -cells. Increased intracellular glucose is metabolized via glycolytic and mitochondrial metabolism, leading to an increase in ATP production and a fall in MgADP. This results in K_{ATP} channel closure, membrane depolarization, opening of voltage-gated Ca^{2+} channels, Ca^{2+} influx, and insulin release. B, Insulin overproduction in the β -cell with K_{ATP} channel-inactivating mutations. Loss-of-function mutations in K_{ATP} channel enhances ATP binding to the channel, leading to K_{ATP} channel closure, membrane depolarization, insulin oversecretion and CHI. C, Impaired insulin secretion in the β -cell with K_{ATP} channel activating mutations. Gain-of-function mutations in K_{ATP} channel impair ATP binding to the channel Kir6.2 mutant (shown in olive green, encoded by *KCNJ11*), or enhance the binding of Mg-nucleotide to SUR1 mutant (shown in amber, encoded by *ABCC8*) leading to K_{ATP} channel opening, membrane hyperpolarization, impaired insulin release, and NDM. D, Oral sulfonylureas stimulate insulin secretion in patients with K_{ATP} channel-activating mutations. Sulfonylureas bind to the *ABCC8*-encoded SUR1 subunit of the K_{ATP} channel to effect channel closure independent of ATP and enable insulin secretion.

tients with PNDM and account for approximately 30% of cases (32). Subsequently, gain-of-function mutations of *ABCC8* were reported (33, 34); mutations of these two genes have been identified in > 40% of PNDM patients (35). Mutations in *KCNJ11* and *ABCC8* may also lead to TNDM. More than 100 different mutations in the *KCNJ11* and *ABCC8* genes have been found in patients with PNDM (36). All but one are missense mutations that cause single amino acid substitutions; the only exception to date is an in-frame 15-bp deletion in the *KCNJ11* gene (37). Most of the patients with mutations in the *KCNJ11* and *ABCC8* genes present with isolated neonatal diabetes;

a few patients display severe developmental delay, epilepsy, and NDM (called DEND syndrome) (38). In addition to causing NDM, mutations of *KCNJ11* and *ABCC8* have been recently linked to MODY (39, 40).

Subtle differences in the primary structure of the *ABCC8*-encoded SUR1 protein can produce diametrically opposite phenotypes, as illustrated by the fact that, depending on the specific amino acid substitution, mutations at the same amino acid residue may cause either CHI or NDM. For example, an E1506K substitution in the nucleotide-binding domain 2 of SUR1 leads to CHI (23, 27), whereas two other mutations at the same residue

(E1506D, E1506G) were found to cause NDM (41). K_{ATP} channels are activated by Mg-nucleotides (via SUR1) and blocked by ATP (via Kir6.2). All of these mutations reduce channel activation by MgADP. Different sensitivities to ATP inhibition could be the basis of these opposing clinical phenotypes. For example, E1506D and E1506G mutant K_{ATP} channels display a markedly impaired sensitivity to ATP, resulting in hyperactive channels associated with impaired insulin secretion and PNDM. In contrast, compared to wild-type channels, the E1506K mutant channels are more sensitive to ATP inhibition, producing underactive channels that result in insulin oversecretion and CHI (41).

3. *KCNJ11 and ABCC8 gene variants associated with T2D*

A common variant involving a glutamate (E) to lysine (K) substitution at position 23 (E23K) in *KCNJ11* has been found to be associated with increased risk of T2D (42–46). Moreover, a defect in insulin secretion was found to occur in all euglycemic E23K carriers examined (45, 46). Interestingly, population studies revealed that the *KCNJ11* E23K variant has a strong allelic association with an *ABCC8* coding variant S1369A. It is challenging to clearly decipher which of the two variants is the responsible gene locus. Functional analyses suggested that a combination of the two variants might underlie the increased T2D risk (46, 47). Furthermore, impaired glucose tolerance (IGT) individuals with *KCNJ11* E23K are not as well protected by 1-year metformin treatment in comparison with homozygous E23E IGT individuals who receive the same treatment. A similar relative resistance to metformin-mediated protection was also observed in IGT patients with *ABCC8* S1369A. The authors speculated that the diabetes-protective effect of metformin may interact with the impact of these variants on insulin regulation (47). In vitro experiments indicate that metformin can confer a direct beneficial effect on pancreatic β -cells; this first-line medication for T2D treatment was shown to restore the secretory function in isolated islets that has been impaired by chronic exposure to elevated free fatty acids or glucose (48); it also appears to preserve β -cell viability by inhibiting mitochondrial permeability transition (49).

Laukkanen et al (50) found that the silent 1273AGA variant allele of the *ABCC8* gene was associated with increased risk of T2D. Importantly, this silent polymorphism was in linkage disequilibrium with three promoter polymorphisms (G-2886A, G-1561A, and A-1273G) of the *ABCC8* gene; together they formed a high-risk haplotype conferring a significant 2-fold risk of T2D. Individuals with this high-risk haplotype and the *KCNJ11* E23K allele displayed a 6-fold risk for the conversion to diabetes in IGT patients, whereas the *KCNJ11* E23K vari-

ant alone did not predict conversion to diabetes (50); in fact, it might even be protective (51). Recently, Baier et al (52) reported that *ABCC8* R1420H homozygotes eventually developed diabetes, despite being hyperinsulinemic during infancy. Furthermore, the R1420H variant was associated with higher birth weights and a 2-fold increased risk for T2D in 3.3% of an American Indian population. Their increased birth weights are suggestive of insulin oversecretion due to insulin being a major growth factor in utero. However, the physiological mechanisms underlying the reversal from hyperinsulinemia to diabetes remain elusive. The possible culprits include increased β -cell apoptosis due to elevated intracellular calcium concentration and the accompanying insulin resistance secondary to increased body weight (17, 25, 27).

In a subgroup analysis of the UK Prospective Diabetes Study (UKPDS), Gloyn et al (53) found that the presence of *KCNJ11* E23K did not predict failure to sulfonylurea treatment at 1 year. Subsequently, Sesti et al (54) reported that, compared with *KCNJ11* E23E homozygotes, a higher proportion of E23K carriers failed sulfonylurea-metformin combination therapy. They further showed that islets isolated from E23K carriers displayed a compromised insulin response to glibenclamide stimulation.

4. *Molecular mechanisms and translational significance of mutations or variations in KCNJ11 and ABCC8 and diabetes*

Mechanistically, *KCNJ11* activating mutations associated with PNDM decrease ATP sensitivity by reducing ATP binding to Kir6.2 or prolonging the open state of the channel and indirectly influencing ATP sensitivity (55) (Figure 3C). Most mutations identified to date lie either in the predicted ATP-binding site or in the regions associated with channel opening and closing. Activating mutations in the *KCNJ11* gene decrease the sensitivity of the K_{ATP} channel to ATP, thereby compromising the insulin secretory response. In contrast, mutations in the *ABCC8* gene enhance the binding of Mg-nucleotide to nucleotide-binding domains of SUR1 or alter the intrinsic gating, leading to membrane hyperpolarization and decreased insulin secretion (56).

The details of the mechanism that underlies the association of common variants in the *KCNJ11* and *ABCC8* genes and T2D are still being worked out. *KCNJ11* E23K is thought to exert divergent effects on activatory and inhibitory modulators. It facilitates nucleoside diphosphate-mediated channel opening, whereas it inhibits ATP-triggered channel closure, synergistically causing overactivity of K_{ATP} channels in the pancreatic β -cell and inhibition of insulin release, predisposing to T2D (57). Compared to the wild-type allele, E23K also displays significantly enhanced K_{ATP} activity in response to long-chain acyl coen-

zyme A, leading to impaired insulin and glucagon-like peptide-1 (GLP-1) secretion and increased glucagon release (58). A recent report showed that carriers of the *KCNJ11* variant display reduced Ca^{2+} sensitivity of exocytosis and decreased insulin release (59). As noted above, the *KCNJ11* E23K variant is strongly associated with *ABCC8* S1369A. The K23/A1369 variant was found to exhibit increased K_{ATP} channel MgATPase activity in comparison with the nonrisk E23/S1369 haplotype, providing a plausible mechanism by which the E23K/S1369A haplotype increases susceptibility to T2D (60).

The identification of mutations of *KCNJ11* and *ABCC8* in PNDM patients has important implications for therapy because most of these patients (>90%) can be switched from insulin injections to oral sulfonylureas; patients with K_{ATP} channel defects respond to this class of agents, which enable insulin secretion by binding to the *ABCC8*-encoded SUR1 subunit of the K_{ATP} channel to effect channel closure independent of ATP (61) (Figure 3D). An earlier age at initiation of sulfonylurea treatment is associated with improved response to the therapy in *KCNJ11*-related NDM patients (62).

The therapeutic efficacy of oral sulfonylureas in T2D patients with *KCNJ11* E23K mutation remains controversial. *KCNJ11* E23K carriers were reported to display a marginally inferior therapeutic response in one study (63), whereas another study found that they displayed a better response to sulfonylureas (64). It is important to point out that the use of sulfonylureas did not increase the risk of hypoglycemia in *KCNJ11* E23K carriers with T2D in a third study (65).

B. Glucokinase

The metabolic enzyme GCK is predominantly expressed in hepatocytes and pancreatic β -cells. GCK catalyzes the phosphorylation of glucose to glucose-6-phosphate and is involved in the first step of both glycolysis and glycogen synthesis. In pancreatic β -cells, GCK is induced by glucose and considered as the glucose sensor. Mutations in GCK lead to reduced glycolysis and ATP levels and impaired insulin secretion (5, 6). Homozygous *Gck*-deficient mice die perinatally of severe hyperglycemia, whereas mutant *Gck* heterozygotes develop mild early-onset diabetes resembling GCK-MODY in humans (66–68).

1. GCK mutations underlie MODY2

Heterozygous inactivating mutations in GCK cause GCK-MODY (MODY2), which is characterized by mild fasting hyperglycemia, asymptomatic at birth and often detected later in life during routine screening. Mutations of GCK account for 30–50% of cases of MODY in dif-

ferent populations (6). An inactivating mutation in GCK increases the glucose threshold needed to trigger insulin secretion, although insulin secretion remains regulated with an elevated threshold that responds to postprandial glucose excursions (69). Therefore, MODY2 patients, unlike other forms of diabetes, present with mild fasting hyperglycemia and can be diagnosed at any age (70). Homozygous inactivating GCK mutations lead to PNDM presenting at birth. Although over 600 mutations affecting different parts of the GCK gene have been reported, they are all relatively rare mutations (66). The prevalence of GCK-MODY was found to be 0.5–1% among women with gestational diabetes mellitus (GDM) in recent studies of multiethnic cohorts. It was proposed that a combination of body mass index <25 kg/m² and fasting glucose ≥ 99 mg/dL differentiates GCK-MODY from common GDM (71, 72). Differentiating the two conditions may have therapeutic implications. In contrast to women with simple GDM, GCK-MODY mothers and their offspring have a low prevalence of diabetic complications despite lifetime hyperglycemia; they rarely require pharmacological treatment outside pregnancy (70, 73). It is important to note that activating GCK mutations are another cause of CHI (17, 66), which may presage late-onset diabetes. GCK-CHI causes β -cell replication early on but subsequently leads to extensive β -cell apoptosis associated with DNA double-strand breaks and activation of the tumor suppressor p53. The β -cell membrane depolarization associated with K_{ATP} channel inactivation (like inactivating mutations of the *KCNJ11* and *ABCC8* genes) is thought to mediate this deleterious effect in GCK-CHI patients (74).

2. Variations in the GCK gene and T2D

In a large-scale GWAS and cohort meta-analysis, a common variant rs1799884 G/A of GCK was found to be associated with glycated hemoglobin A1C levels, fasting and 2-hour glucose concentrations, as well as T2D (75). The GCK rs1799884 A allele was inconsistently associated with altered fasting glucose in Chinese populations (76, 77). In another GWAS meta-analysis, GCK rs4607517 A/G was confirmed to be associated with fasting blood glucose levels and T2D (78). In Pima Indians, a 3' untranslated region (UTR) single nucleotide polymorphism (SNP), chr7:44184184-G/A in the GCK gene, is associated with the rate of carbohydrate oxidation post-absorptively, energy expenditure, and T2D risk, which is in agreement with the role of GCK in hepatic glycolysis and energy metabolism. However, this variant was not associated with hepatic glucose production during insulin stimulation, despite a previous report demonstrating that a GCK variant in the promoter region (-258 G/A) was associated with hepatic insulin resistance (79).

3. Molecular mechanisms that underlie the association of variations in the GCK gene and T2D

The activity of GCK can be regulated by glucose-6-phosphatase, catalytic 2 (G6PC2) in the β -cell and GCK regulatory protein (GKRP, or GCKR) in the liver. In the β -cell, G6PC2 catalyzes glucose-6-phosphate dephosphorylation, thereby functionally opposing the action of GCK. Genetic variants of either gene may affect the balance between GCK and G6PC2 activities, resulting in impaired pulsatile insulin secretion, disrupting proper insulin signaling between the pancreas and insulin-sensitive tissues, and predisposing to T2D development (80).

In the liver, the activity and subcellular localization of GCK are allosterically regulated by GKRP. GCK is sequestered to the nucleus as an inactive complex with GKRP at low glucose concentrations. It is rapidly dissociated from the GCK-GKRP complex and translocated to the cytoplasm at high glucose concentrations, which triggers glucose disposal (81, 82). It has been proposed that SNP rs780094 at *GKRP* may perturb the GKRP/GCK system and thus modulate the effect of SNP rs1799884 at *GCK*, resulting in altered glucose metabolism (77). Additional functional studies are needed to prove or disprove this hypothesis.

C. Solute carrier family 2, member 2

The *SLC2A2* gene encodes glucose transporter (GLUT) 2, a high-capacity facilitative glucose transporter expressed predominantly in the liver, kidney, intestine, and pancreatic β -cells. Ablation of *Slc2a2* in mice leads to severe diabetes and lethality usually at 2–3 weeks of age because of an insulin secretion defect (83). It is well established that GLUT2 is the predominant glucose transporter in rodent β -cells. A recent study suggested that GLUT2 may also mediate insulin secretion in human β -cells (84), although GLUT1, not GLUT2, is thought to be the major glucose transporter in human β -cells (85).

1. Mutations in *SLC2A2* lead to Fanconi-Bickel syndrome

Homozygous patients with inactivating mutations of *SLC2A2* develop Fanconi-Bickel syndrome (FBS; also known as glycogen storage disease type XI), characterized by a renal Fanconi syndrome with glycosuria, galactosuria, aminoaciduria, proteinuria and phosphaturia, short stature, rickets, poor growth, hepatomegaly, and galactose intolerance (86). Some FBS patients may present with postprandial hyperglycemia and diabetes or IGT. A large number of homozygous mutations (84, 87–90) or compound heterozygous mutations (91) in the *SLC2A2* gene have been identified to underlie FBS.

Mutations in *SLC2A2* were recently noted to be associated with defective insulin secretion in humans (84). Five

of 104 (5%) NDM patients with unknown etiology (excluding the common genetic causes) were identified to carry homozygous *SLC2A2* mutations. Four of these five patients first presented with isolated diabetes and later developed other features of FBS, suggesting that GLUT2 may play a role in human insulin secretion. Notably, some compound heterozygous mutations in the *SLC2A2* gene, eg, c.457_462delCTTATA (p.153_4delLI) and c.1250C>G (p.P417R), present an unusually mild clinical course, such as modest glycosuria and tubular proteinuria. Some hallmark clinical signs of FBS, like hepatomegaly and short stature, are often absent in these patients (91). Therefore, it would be prudent to include the *SLC2A2* gene for genetic screening in patients with isolated glycosuria.

2. *SLC2A2* gene mutations or variants and T2D

The SNP rs5400 in the *SLC2A2* gene, which causes a GLUT2 T110I substitution, was first reported to be associated with T2D in Pima Native Americans (92); subsequently, other *SLC2A2* gene variants and their association with T2D have been studied extensively, although conflicting conclusions remain. To date, variants of the *SLC2A2* gene are associated with increased risk for T2D in some (93, 94), but not most (95–98), studies. In the Finnish Diabetes Prevention Study, SNPs rs5393 (AA) and rs5394 (CC) in the promoter region as well as SNPs rs5400 (T110I) and rs5404 (GG, T198T) in the exon of the *SLC2A2* gene have been identified to predict the conversion to diabetes in obese subjects with IGT, and rs5393 (AA) increased the risk of T2D by 3-fold. Interestingly, the rs3758947 GG of *ABCC8* presents an additive effect with the rs5393 AA of *SLC2A2* to predict the conversion to diabetes (99), indicating that individuals with risk SNPs in the network of genes regulating insulin secretion (*SLC2A2* and *ABCC8*) are particularly at high risk for T2D.

Kilpeläinen et al (100) found that moderate-to-vigorous physical activity could lower the risk of conversion to T2D in the carriers of the common homozygous genotype of rs5393 (AA), rs5394 (CC), or rs5404 (GG, T198T) of *SLC2A2* and rs3758947 (GG) of *ABCC8*, an observation that implies that improvements in insulin sensitivity by lifestyle changes help preserve the insulin secretory function of β -cells.

3. Molecular mechanisms that underlie the association of mutations or variations in the *SLC2A2* gene and diabetes

In vitro experiments conducted by Michau et al (101) revealed that none of four select FBS-associated *SLC2A2* mutants could transport glucose to a significant level. The G20D and S242R substitution mutants are associated with loss of protein expression at the plasma membrane, whereas the P417L and W444R mutants lose their transport capacity despite adequate membrane targeting, indi-

cating the crucial role of the two amino acids (417Pro and 444Trp) for GLUT2 transport function in humans (101).

A recent report showed no difference in insulin secretion during an oral glucose tolerance test in individuals with or without the risk allele at *SLC2A2* rs5400 (T110I), suggesting that neither β -cell mass nor insulin secretion is significantly affected (102). In agreement with this, this GLUT2 T110I variant displays similar kinetics for glucose transport as wild-type GLUT2 (101). Additionally, this variant is in strong linkage disequilibrium with two other variants (SNPs rs5406 and rs6785803) located in the promoter region of the *SLC2A2* gene (103), which raises the possibility that the functional consequence of the rs5400 (T110I) variant could be related to the difference in the transcription of the *SLC2A2* gene, rather than the effect of the gene product of variant rs5400, ie, GLUT2 T110I itself. Interestingly, the variant rs5400 (T110I) is associated with habitual consumption of sugars (104), which may reflect glucose sensing in the portal vein (105) and/or the hypothalamus (106), the two organs that also harbor GLUT2-dependent glucose sensors. Although GLUT2 has been identified in the paraventricular nucleus, lateral hypothalamic area, and arcuate nucleus, it is unclear whether the high K_m of GLUT2 would allow the putative transporter to function normally in these regions of the brain with normal blood-brain barrier because of the local low glucose concentrations in these brain regions (104). In contrast, GLUT2 is likely operative in parts of the brain that lack a blood-brain barrier, ie, where the transporter is exposed to physiological levels of circulating blood glucose. Indeed, the circumventricular organ, area postrema, is one such brain area that has also been found to harbor *SLC2A2* mRNA (107). These observations suggest that a GLUT2-mediated glucose-sensing mechanism could regulate food intake in select parts of the brain and thus be associated with the risk of T2D.

D. *HNF1A* and *HNF4A*

HNF1A, also known as transcription factor 1 (TCF1), is first expressed in the yolk sac and in the liver bud. Later on to adulthood, *HNF1A* is expressed throughout organogenesis of the liver, kidney and pancreas. *Hnf1a*-deficient mice develop hepatic dysfunction, phenylketonuria, and renal Fanconi syndrome. A fraction of the mice lacking *Hnf1a* die shortly after weaning due to a progressive wasting syndrome (108). Mice with *Hnf1a* ablation also develop diabetes with a profound defect in glucose or arginine-stimulated insulin secretion (109).

HNF4A is first expressed in the primary endoderm in mice at embryonic day 4.5 (e4.5) and is restricted to the visceral endoderm from e5.5 to e8.5. Thereafter, it is expressed in the liver diverticulum, the hindgut, the meso-

nephric tubules of the kidney, and the developing pancreas, stomach, and intestine (110). *Hnf4a*-deficient mice display defective gastrulation and die around e9 (111). In hepatocytes, *HNF4A* controls the transcription of *HNF1A*, whereas in pancreatic islets and exocrine cells, *HNF1A* controls the transcription of *HNF4A* through an alternate tissue-specific *HNF4A* promoter (112).

1. Mutations in *HNF1A* and *HNF4A* lead to *MODY3* and *MODY1*, respectively

Mutations in the *HNF4A* gene lead to the first subtype of *MODY* identified (*HNF4A*-*MODY* [*MODY1*]), whereas mutations in the *HNF1A* gene cause *HNF1A*-*MODY* (*MODY3*). These two types of *MODY* display very similar clinical characteristics. The patients develop young-onset diabetes in the second to fourth decade without features of insulin resistance or β -cell autoimmunity. Pancreatic β -cell dysfunction can be observed before the onset of diabetes in the carriers with *HNF1A* mutations. Glycosuria due to a low renal threshold for glucose is observed in *HNF1A*-*MODY* patients, and in nondiabetic *HNF1A* mutant carriers, but not in *HNF4A*-*MODY* patients (113). Interestingly, inactivating mutations in *HNF1A* and *HNF4A* can cause CHI associated with increased body weight in early life, which may improve with age (114). Both *HNF1A* and *HNF4A* *MODY* patients respond to low-dose sulfonylureas (12.5% or less of the maximum licensed dose) (5, 6).

Mutations in *HNF1A* (*MODY3*) are the most common cause of *MODY*, which underlie 52% of monogenic diabetes in a large UK series (115). Interestingly, although patients display inherent β -cell defects, they develop diabetes relatively late in life—63% at age 25 years and 94% at age 50 (116). The reason that *MODY3* presents relatively late in life is caused by the capacity of *HNF1A* to control the transcription of sodium-glucose cotransporter 2 (*SGLT2*), a renal glycosuria threshold-controlling gene. Therefore, individuals with *HNF1A* mutations display a drastically decreased expression of *SGLT2*, thereby reducing glucose reabsorption through the proximal tubule (117). This defective *HNF1A*-mediated down-regulation of *SGLT2* helps maintain relative euglycemia in *MODY3* individuals before the appearance of overt hyperglycemia and diagnosis of diabetes much later in life; ie, *HNF1A* mutations function like *SGLT2* inhibitors, and the belated appearance of overt diabetes in affected individuals could have predicted the development of this new class of hypoglycemic agent for the treatment of diabetes.

2. *HNF1A* gene variants and T2D

A private mutation (G319S) in *HNF1A* has been reported in Canadian Oji-Cree populations to be associated

with early-onset T2D, lower body mass, and a higher post-challenge plasma glucose (118). Using whole-exome sequencing, MacArthur and colleagues (119) identified a single low-frequency variant (c.1522G>A [p.E508K]) in *HNF1A*, which is associated with T2D prevalence in Latino populations. The variant allele p.E508K is located in the HNF1A transactivation domain. Functional studies revealed that, despite the preservation of its DNA binding activity, the p.E508K variant protein displays compromised transactivation activities on the promoters of *SLC2A2* and *HNF4A* in β -cells. Of note, a recent report showed that *HNF1A* variant (rs2650000) predisposes to latent autoimmune diabetes in adults and adult-onset T1D (120).

3. HNF4A gene variants and T2D

Multiple SNPs in the alternate upstream promoter (P2) region of *HNF4A* have been found to be associated with increased risk of T2D. Initial studies showed that SNPs at rs2144908, rs3818247, and rs884614 in the P2 region of the *HNF4A* gene were associated with T2D risk in Finnish (121) and Ashkenazi (122) populations. Subsequently, Weedon et al (123) reported that the risk haplotype of rs4810424 and rs2144908 in the P2 region of the *HNF4A* gene was associated with T2D in UK populations in both case-control and family-based studies. Recently, Barroso et al (124) found that *HNF4A* P2 SNPs rs1884613 and rs2144908 were associated with T2D in the Ashkenazi, but not in UK, populations. These findings suggest that P2 SNPs in the *HNF4A* gene confer varying risk effects in different populations.

4. Molecular mechanisms and pathophysiology that underlie the association of mutations in the HNF1A and HNF4A genes and diabetes

To dissect the molecular mechanisms underlying MODY3, Bjorkhaug et al (125) investigated the functional properties of *HNF1A* mutations. They reported that two mutant HNF1A proteins (R171X and R263C) manifest reduced or absent DNA binding activity. Five mutants (R131W, R171X, P379fsdelCT, S445fsdelAG, and Q466X) display defective nuclear translocation. Most of the MODY3-associated mutants exhibit reduced transactivational activity. These loss-of-function *HNF1A* mutants underlie the β -cell dysfunction in MODY3 (125). Recently, Nowak et al (126) reported that circulating ghrelin levels were higher in *HNF1A*-MODY patients than those in common T1D or T2D patients. *Hnf1a*-deficient mice develop diabetes caused by a defect in glucose-stimulated insulin secretion (GSIS) (109). It is intriguing that a recent study showed that serum ghrelin levels were also increased in *Hnf1a*-deficient mice, and treatment with

a ghrelin receptor antagonist restored glucose homeostasis in *Hnf1a*-null mice (127). Ghrelin suppresses glucose-induced insulin secretion, but not basal insulin secretion. It counteracts cAMP-protein kinase A signaling, a well-established pathway of GSIS, by interacting with the GH secretagogue receptor GHS-R1a on β -cells. The suppression of the cAMP pathway results in activation of delayed outward K^+ (K_v) channels and inhibition of Ca^{2+} signaling, causing decreased insulin release (128).

In mammals, the *HNF4A* gene encodes up to nine distinct isoforms, resulting from the use of alternate promoters and alternative splicing. Promoter P1 initiates transcripts that contain exon 1A (isoforms A1–A6) encoding activation function 1 (AF-1) domain, whereas promoter P2 initiates transcripts that contain exon 1D (isoforms A7–A9) lacking AF-1. In pancreatic β -cells, the P1 promoter exhibits stronger transcriptional activities than the P2 promoter (129). Pancreatic β -cell-specific *Hnf4a* deletion leads to hyperinsulinemia in fasted and fed mice but paradoxically is also associated with IGT. *Hnf4a* mutant β -cells exhibit a defective response to stimulation by glucose and sulfonylureas. Experiments in mice showed that the expression of the potassium channel subunit Kir6.2 (encoded by *KCNJ11*), a downstream target of *Hnf4a*, is reduced by 60% in *Hnf4a* mutant β -cells (130).

Studies in rodents further showed that both maternal suboptimal nutrition and aging lead to progressive epigenetic silencing at the enhancer region in the *Hnf4a* gene, disrupting the P2 promoter-enhancer interaction and resulting in a permanent reduction in *Hnf4a* expression (131). It is unclear whether the variants in *HNF4A* predispose to T2D via a similar mechanism in people.

E. Hepatocyte nuclear factor 1 homeobox B

HNF1B, also known as transcription factor 2 (TCF2), is first expressed in the visceral endoderm at the onset of gastrulation. Later on to adulthood, it is expressed throughout organogenesis of the liver, kidney and pancreas (132). In mice, HNF1B-positive progenitors were shown to be equally capable of giving rise to pancreatic duct, acinar, and endocrine cells from e11.5 to e13.5. Global *HNF1B*-deficient mice die soon after implantation (132, 133). Pancreatic β -cell-specific (*RIP-Cre*) *Hnf1b* deletion resulted in IGT with reduced insulin secretion (134). HNF1B is required for the proliferation and survival of pancreatic multipotent progenitor cells. *Hnf1b* deficiency in pancreatic progenitors leads to severe pancreatic hypoplasia and perinatal lethality (135). HNF1B is also a key regulator of duct morphogenesis, acinar cell differentiation, and maintenance of acinar cell identity. It is indispensable for the generation of endocrine precursors, likely by directly regulating the pancreatic islet lineage-defining transcription

factor neurogenin 3 (*Neurog3*, or *Ngn3*) expression (135). The sequential activation of *Hnf1b*, *Hnf6*, and *Pdx1* is believed to direct the differentiation of endodermal cells into pancreatic progenitors (136).

1. Mutations in HNF1B lead to RCAD syndrome, or MODY5

In addition to causing PNDM or TNDM in very rare cases (137), heterozygous mutations in *HNF1B* cause renal cysts and diabetes (RCAD syndrome, or MODY5). *HNF1B* whole-gene deletions account for approximately 50% of MODY5 cases. To date, more than 50 missense mutations or deletions have been identified in MODY5 patients. Various phenotypes related to these mutations have been described, including urogenital malformations, hyperuricemia, young-onset gout, and pancreatic hypoplasia or atrophy. In a literature meta-analysis, renal cysts and diabetes occurred in 89.6 and 45% of the patients with RCAD syndrome, respectively. However, the concurrence of renal cysts and diabetes was observed in only 27.5% of the patients, which could delay the clinical diagnosis and timely genetic testing (138). Patients with *HNF1B* mutations display abnormal β -cell development and reduced insulin secretion (135, 136) that is usually resistant to sulfonylureas; most of them require early insulin therapy (139, 140).

2. HNF1B gene variants and T2D

Winckler et al (141) found that SNP rs757210 A in intron 2 of *HNF1B* showed a strong association with T2D in multiple populations. Epidemiological studies have demonstrated an inverse association between T2D and the risk of prostate cancer (142, 143). In accordance with this finding, Gudmundsson et al (144) found that a common variant rs4430796 A in *HNF1B* was positively associated with prostate cancer and negatively associated with T2D risk. It has been proposed that with time, metabolic status in T2D patients might switch from hyperinsulinemia to endogenous insulin deficiency, thus alleviating the pro-oncogenic effect of insulin in the prostate.

3. Molecular mechanisms and pathophysiology that underlie the association of mutations in the HNF1B gene and diabetes

HNF1A and HNF1B share a highly conserved DNA-binding domain and a more divergent C-terminal transactivation domain. HNF1B may act either as a homodimer or as a heterodimer with HNF1A (145). Diverse mechanisms have been uncovered that may underlie the development of *HNF1B*-MODY. For example, frameshift mutations R112fsdel (an 8-bp deletion in exon 2) or P472fsins (an 8-bp insertion in the exon 7) in the *HNF1B* gene were found to lead to severe pancreatic hypoplasia

with underdeveloped and disorganized acini in human fetuses. The *HNF1B* R112fsdel mutation causes a frameshift and a truncated protein lacking part of the POU-specific domain (POU_S), which is essential for DNA binding specificity, and the entire POU homeodomain (POU_H), as well as the C-terminal transactivation domain, whereas the *HNF1B* P472fsins mutation leads to a premature stop codon and the insertion of 35 novel amino acids at the C-terminus of the transactivation domain. Functional studies showed that the truncated R112fsdel protein, retaining the N-terminal dimerization domain, functions as a weak dominant-negative mutant, through the formation of nonfunctional heterodimers with wild-type HNF1B protein. In contrast, the P472fsins mutant exhibits a decreased transactivation capacity, whereas it retains the normal DNA binding activity; however, it does not interfere with the function of the wild-type HNF1B protein (146).

GLUT2, a potential direct target of HNF1B (147), was undetectable in islet β -cells of human fetuses with R112fsdel or P472fsins mutation (146). Similarly, overexpression of the *HNF1B* P159L mutant (disrupting its DNA binding domain) led to significantly reduced expression of GLUT2 in Min6 mouse insulinoma cells (148). As discussed earlier, *Slc2a2*-deficient mice develop severe diabetes and lethality with impaired glucose sensing by pancreatic β -cells (83). Forced overexpression of a naturally occurring dominant-negative form of human *HNF1A* (P291fsinsC) disrupts the formation of homo- and heterodimers between wild-type HNF1A and HNF1B, leading to reduced expression of GLUT2 and E-cadherin (149). In addition, β -catenin and E-cadherin expression was drastically reduced in the islet and acinar compartments of human fetuses with R112fsdel or P472fsins mutation. Wnt/ β -catenin is required for acinar lineage specification and differentiation (150–152). These findings suggest that perturbation in the Wnt/ β -catenin signaling pathway may underlie the severe pancreas hypoplasia frequently observed in *HNF1B* mutant individuals; early loss of GLUT2 in β -cells may cause early-onset diabetes in MODY5 patients (146).

F. Pancreatic and duodenal homeobox 1

PDX1 (also known as insulin promoter factor 1 [IPF1]) is a homeodomain transcription factor expressed throughout the pancreatic epithelium at e8.5 in mice; from e15.5 onward, its expression becomes mainly restricted to β -cells and a small subpopulation of δ and PP (pancreatic polypeptide) cells (153). PDX1 is essential for pancreas development, β -cell differentiation, and the maintenance of mature β -cell function by regulating the expression of key islet-specific genes such as *Ngn3*, insulin, *Gck*, and

Slc2a2 (153–155). Mice lacking *Pdx1* fail to form a pancreas (156). Pancreatic β -cell-specific *Pdx1* deficiency in mice leads to reduced expression of insulin and *Slc2a2*, causing maturity-onset diabetes (155). A large fraction of *Pdx1*-deleted β -cells rapidly acquires ultrastructural and physiological features of α -cells, suggesting that *Pdx1* maintains β -cell identity and function via repressing an α -cell lineage (157). Mutations or variants in the *PDX1* gene cause PNDM and MODY4 and are also linked to common T2D and ketosis-prone diabetes (KPD).

1. *PDX1* mutations underlie PNDM and MODY4

Stoffers et al (158) first reported that a homozygous single cytosine deletion within codon 63 (Pro63fsdelC) of the human *PDX1* gene was responsible for a previously described PNDM syndrome that is also associated with pancreatic exocrine insufficiency (159). Two substitution mutants, E164D and E178K in the human *PDX1* gene, also individually lead to PNDM and pancreatic exocrine insufficiency (160), whereas the hypomorphic mutation (E178G) in *PDX1* is responsible for PNDM but is not associated with clinical signs of exocrine insufficiency (161). In the first family pedigree, Stoffers et al (162) further identified that the heterozygous Pro63fsdelC mutation in *PDX1* causes MODY4. Family members developed diabetes in six generations, with an average age at onset of 35 years (range, 17 to 67 years). Six of eight affected heterozygotes, lacking ketosis or other indications of severe insulin deficiency, were treated with diet or oral hypoglycemic agents. Notably, patients afflicted with *PDX1* mutations (eg, D76N) may concurrently carry other MODY gene mutations (eg, S315fsinsA in *HNF1 α* /MODY3). Not surprisingly, carriers of mutations in both genes (*PDX1* and *HNF1 α*) display more severe insulin deficiency than those who carry the mutation in only one of the two genes (163).

2. Mutations or variations in the *PDX1* gene and T2D

Shortly after *PDX1* mutations were identified in patients with PNDM and MODY4, other mutations in the *PDX1* gene were also found to be linked to common T2D. Candidate gene association studies showed that *PDX1* substitution mutations (C18R, Q59L, D76N, R197H, G212R, and P239Q) and an in-frame proline insertion (InsCCG243) predispose to common T2D (163–165). Of note, approximately 5% of the examined T2D patients and control nondiabetic individuals carried low-frequency *PDX1* variants that were not associated with diabetic phenotype, suggesting that *PDX1* mutations or variants are a very rare cause of diabetes (166). Consistent with this observation, whole-genome sequencing of 2630 Icelanders showed that a novel rare (0.20%) frameshift

variant (p.Gly218Alafs*12) in *PDX1* is associated with high risk of T2D (167). Furthermore, the same study observed seven previously reported variants (six missense variants and one in-frame insertion) in *PDX1*, but none were associated with diabetes (167). In addition, *PDX1* variants have also been linked to KPD (see Section II.G for details).

3. Molecular mechanisms that underlie the association of mutations in the *PDX1* gene and diabetes

As noted above, *PDX1* variants associated with enhanced T2D risk are rare, despite the fact that *PDX1* mutations cause PNDM and MODY4. Pro63fsdelC point deletion in *PDX1* leads to a frame shift, causing a premature truncated protein with 59 aberrant codons that is lacking transactivation domain at its C terminus. The mutant protein fails to transactivate the *INS* gene transcription, leading to PNDM (158). The C-terminal domain of *PDX1* is required to maintain all endocrine lineages in the pancreas. Expression of a single C-terminal truncated form of *PDX1* results in mild hyperglycemia at birth and progresses to overt diabetes by the down-regulation of *Ngn3* (154). Schwitzgebel et al (160) reported that *PDX1* E178K displayed reduced transactivation activity on the *INS* promoter due to a decrease in *PDX1* steady-state protein levels resulting from impaired protein stability, whereas substitution variant *PDX1* E178G displays reduced transactivation activity via an unclear mechanism, leading to PNDM (161).

A number of *PDX1* mutations (eg, C18R, Q59L, D76N, R197H, and InsCCG243) lead to reduced binding of the mutant protein to the *INS* gene promoter and decreased *INS* gene transcription in response to hyperglycemia in pancreatic β -cells, which may underlie the substantial defect in insulin secretion detected in these patients (163–165). D76N and Q59L mutations in *PDX1* have also been linked to decreased GSIS in nondiabetic subjects (164).

In mice, *Pdx1* haplodeficiency enhances β -cell susceptibility to endoplasmic reticulum (ER) stress-associated apoptosis and leads to a failure of β -cell compensation for high-fat diet (HFD)-induced insulin resistance (168). Mitochondrial dysfunction is an important contributor to β -cell failure, insulin resistance, and diabetes (169, 170). Mitochondrial autophagy or mitophagy is required for the selective elimination of dysfunctional or damaged mitochondria to maintain cellular respiration. Recently, *Pdx1* has been shown to direct autophagosome-lysosome fusion during mitophagy and regulate mitochondrial function in pancreatic β -cells (171). Although it has not been directly examined, it is possible that these mechanisms may also

underlie the association of *PDX1* mutations/variants with diabetes.

G. Paired box 4

PAX4, a paired-homeodomain transcription factor, functions mainly as a transcription repressor (172). *Pax4* mRNA is initially detected in the ventral spinal cord and pancreatic bud at e9.5 in mice; its expression is later restricted to pancreatic β - and δ -cells, reaching a maximal level at e13.5 to e15.5, and thereafter declining to low levels. PAX4 is also found to be expressed in adult rodent and human islets (173). *Pax4*-deficient mice develop severe hyperglycemia and die within 2 days of birth. The β -cells are replaced by a proportional increase in glucagon-positive α -cells; somatostatin-expressing δ -cells are also missing in *Pax4*-deficient mice. Thus, *Pax4* deficiency is characterized by a favoring of an α -cell fate at the expense of β -/ δ -cell lineages (174). The aristaless-related homeobox-encoding gene, *Arx*, and *Pax4* are coexpressed in the same proendocrine cell during pancreas genesis. *Arx*-deficient mice develop early-onset hypoglycemia, dehydration, and die 2 days after birth. In the absence of *Arx*, endocrine progenitor cells assume β -/ δ -cell destinies (175). At the molecular level, ARX and PAX4 directly bind to the respective promoter or enhancer and drastically repress each other's transcription (176).

1. Mutations in PAX4 lead to MODY9

To determine whether PAX4 mutations contribute to MODY in the Thai population, Plengvidhya et al (177) screened PAX4 coding sequences in 46 MODY probands who did not have mutations in other known MODY genes. They identified two possible pathogenic mutations of PAX4, R164W and IVS7–1G>A (a G to A substitution at splice acceptor of intron 7), in patients with MODY (PAX4-MODY, or MODY9, a very rare type of MODY), but not in nondiabetic controls and healthy subjects. Subsequently, PAX4 R192H (178) and a 39-base heterozygous deletion in exon 3 (C.374–412 del 39) in PAX4 (179) have also been reported in MODY9 patients.

2. PAX4 gene mutations or variants and T2D and KPD

In a Japanese population, a missense mutation of PAX4 R121W was found to be associated with T2D. The R121W mutation was located in the C terminus of the paired domain and was thought to affect its transcriptional activity due to a lack of DNA binding (180). In a GWAS meta-analysis, Ma et al (181) reported that the rs10229583 G risk variant near PAX4 was associated with elevated fasting glucose, impaired β -cell function, and early-onset T2D in a Chinese population. In newly diagnosed T2D patients, PAX4 variant rs6467136 corre-

lated with a positive therapeutic response to rosiglitazone, but not repaglinide. PAX4 variant rs6467136 GA+AA carriers exhibited greater responses to rosiglitazone therapy than GG homozygotes, with greater decrement of 2-hour glucose level and amelioration of insulin resistance as well as higher cumulative attainment rates of target fasting and 2-hour glucose levels (182).

In addition to the association of PAX4 variants with T2D, one candidate gene association study (183) and a linkage analysis (184) reported that PAX4 variants including +1,168 C/A of PAX4 (rs712701) were associated with T1D, but other studies failed to find an association (185, 186), which suggests that PAX4 variants are unlikely to play an important role in the development of T1D.

Mauvais-Jarvis et al (187) first reported that PAX4 homozygous R133W and heterozygous R37W mutations may be associated with KPD. KPD is a heterogeneous group of atypical diabetic syndromes characterized by recurrent severe β -cell dysfunction and a variable clinical course (188, 189). KPD patients can be classified into four subgroups, as defined by: 1) the presence or absence of autoantibodies (that are associated with common T1D), ie, A+ or A–; and 2) the presence or absence of β -cell function, ie, β + or β –. The A- β subgroup of KPD patients, characterized by β -cell failure without evidence of autoimmunity, often has a strong family history of diabetes (188, 189). Balasubramanyam and colleagues (190) systematically sequenced seven genes associated with monogenic diabetes in an A- β patient subgroup and found that about 30% of them harbor variants of *HNF1A*, *PDX1*, or *PAX4* genes, suggesting that these variants may underlie the β -cell dysfunction in a fraction of patients with A- β KPD.

3. Molecular mechanisms and pathophysiology that underlie the association of mutations in the PAX4 gene and diabetes

Our knowledge of the molecular basis of PAX4 mutations causing diabetes remains incomplete. PAX4 predominantly represses the glucagon promoter activity in α -cells and weakly inhibits insulin promoter activity in β -cells (172). PAX4 mutations are located either in the paired domain (R37W), in the homeodomain (R164W), or between the paired domain and homeodomain (R133W). These mutations impair its transcriptional repressor activity by interfering with its capacity to bind DNA, or the binding specificity or functional stability, or its interaction with other proteins. PAX4 mutants fail to repress glucagon transcription, leading to hyperglucagonemia (187). PAX4 mutations may cause insulin deficiency, possibly through the disruption of β -cell develop-

ment or impairment of GSIS in β -cells. Some *PAX4* mutations (eg, R121W, IVS7-1G>A) seem to increase the susceptibility of β -cells to apoptosis upon cytokine or high glucose exposure (177, 191). Conversely, forced expression of wild-type *PAX4* has been shown to protect cytokine-induced β -cell death in isolated human islets (191). In general, most MODY patients are treated with sulfonylureas, metformin, or insulin (5). A few recent studies have also documented the efficacy of GLP-1 receptor agonists (192, 193) and dipeptidyl peptidase-IV inhibitors (194, 195) in these patients. Although it has not been directly studied, it is possible that the GLP-1 receptor agonists and dipeptidyl peptidase-IV inhibitors, through their glucagon-inhibiting actions (196), are especially efficacious in the treatment of patients with *PAX4* mutations.

H. NEUROD1/BETA2

The basic helix-loop-helix (HLH) transcription factor NEUROD1, also called BETA2, plays a crucial role in pancreatic β -cell maturation and maintenance. NEUROD1 is detected in the mouse embryo as early as e9.5 in glucagon-positive cells and is mostly restricted to β -cells at birth. *Neurod1*-deficient mice fail to develop mature islets due to enhanced apoptosis, leading to NDM and lethality within the first few days of life (197). Pancreatic β -cell-specific *Neurod1*-deficient mice exhibit severe glucose intolerance with greatly reduced insulin secretion. Islets lacking *Neurod1* respond poorly to glucose and display a glucose metabolic profile similar to immature β -cells, characterized by increased expression of glycolytic genes, elevated levels of lactate dehydrogenase and basal oxygen consumption, and overexpression of neuropeptide Y. In sum, NEUROD1 is required for the development and maintenance of fully functional mature β -cells (198).

1. Mutations in the NEUROD1 gene lead to MODY6 and PNDM

Heterozygous loss-of-function mutations in *NEUROD1* produce a very rare type of MODY (*NEUROD1*-MODY, or MODY6), with six families reported to date. A missense mutation E110K in *NEUROD1* was first reported in an Icelandic MODY6 family (199). Subsequently, missense mutations S159P, H241Q, and R103P in *NEUROD1* were identified in Chinese (200), Czech (201), and Polish (202) MODY6 families, respectively.

Recently, Rubio-Cabezas et al (203) reported that two recessive homozygous mutations in *NEUROD1*, a single base pair duplication (c.364dupG) and a 2-bp CT deletion (c.427_428del), led to a syndrome of PNDM and neurological abnormalities. Both mutations introduced a frame-

shift to produce a premature truncated protein lacking the activation domain at the C terminus.

2. NEUROD1 gene variants and T2D

Malecki et al (204) reported that a missense mutation R111L and a cytosine residue insertion (206 +C) in the *NEUROD1* gene were associated with the risk of T2D. A number of studies showed that a common A45T variant at rs1801262 in *NEUROD1* was inconsistently associated with T2D (204–208). Recent meta-analyses revealed that this polymorphism is associated with T2D in European descent Caucasians, but not in individuals of Chinese and Japanese descent, or others of East Asian descent (207). Of note, the A45T variant in *NEUROD1* is associated with T1D in several small population studies (208–210), but not in a larger population study (211).

3. Molecular mechanisms that underlie mutations in the NEUROD1 gene and diabetes

NEUROD1 forms a heterodimer with the ubiquitous HLH protein E47 to transactivate insulin gene expression by binding to a critical E-box motif on the promoter (212), synergistically with MAFA, PDX1 (213), and GLIS3 (214). The mutation R111L in the *NEUROD1* gene is located in the proximal basic portion of the basic HLH domain, which mediates DNA binding. This mutation abolishes E-box binding activity of NEUROD1 and drastically compromises insulin gene transcription in pancreatic β -cells. The 206 +C insert mutation produces a frameshift and synthesis of a nonsense peptide from amino acid 205 to 242, followed by a stop codon. The mutant peptide has lost its C-terminal transactivation domain, which normally enables interaction with the coactivators cAMP response element-binding protein and p300. Thus, these NEUROD1 mutants impair DNA binding and/or the transactivation activity on the *INS* gene as well as other target genes in pancreatic β -cells leading to T2D (204).

I. Wolfram syndrome 1

WFS1 encodes a 100-kDa transmembrane glycoprotein that is localized in the ER and secretory granules. Unfolded protein response (UPR) is a cellular stress response induced by the accumulation of unfolded or misfolded proteins within the ER lumen. *WFS1* is a component of the inositol requiring 1 and PKR-like ER kinase UPR signaling pathway and is important in the maintenance of ER homeostasis. The maintenance of ER integrity by PKR-like ER kinase is crucial to normal β -cell function because large amounts of insulin are produced by these cells (215). *WFS1* has been implicated in the activation of the UPR to mitigate ER stress (216). This ER protein is induced by ER stress and during glucose or potassium

chloride-stimulated insulin secretion in β -cells. *Wfs1*-deficient β -cells display increased susceptibility to ER stress-mediated apoptosis (217).

1. Mutations in *WFS1* lead to Wolfram syndrome 1

Recessive mutations in the *WFS1* gene cause pancreatic β -cell death, resulting in a monogenic form of diabetes known as Wolfram syndrome 1 (WFS1), which is sometimes referred to as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). It is noteworthy that, in certain populations, eg, a Lebanese population, patients with some *WFS1* mutations may present with isolated early-onset diabetes, contributing to a substantial proportion of patients who are often mislabeled as having “T1D” (218). There is currently no effective treatment for the syndrome, which usually ends in premature death. With respect to the optic atrophy, a recent report showed that average retinal thickness is significantly lower in WFS1 patients, compared with age-matched T1D patients and healthy individuals. Moreover, a strong negative correlation exists between average retinal thickness and both age at examination and duration of diabetes in WFS1 patients. It has therefore been proposed that retinal thinning is a marker of disease progression in these patients (219). To date, over 180 mutations in the *WFS1* gene, most commonly in exon 8, have been identified (220). A WFS1-like syndrome, WFS2, is caused by homozygous mutation in the *CDGSH* iron sulfur domain 2 (*CISD2*) gene. *CISD2* encodes a highly conserved zinc-finger protein, ER intermembrane small (ERIS), which plays a crucial role in calcium homeostasis (221). WFS1 and WFS2 share some common clinical features such as diabetes mellitus, hearing loss, and optic atrophy or neuropathy. They also display distinct characteristics, eg, diabetes insipidus is a specific feature for WFS1, whereas defective platelet aggregation resulting in bleeding peptic ulcer appears to be specific for WFS2 (222).

2. *WFS1* gene variants and T2D

Minton et al (223) reported the first evidence that variation in the *WFS1* gene may influence susceptibility to T2D. In a parent-offspring trios study, R456 and H611 in *WFS1* were found to be overtransmitted to affected offspring from heterozygous parents in diabetic families. In a further cohort study, the H611 allele and the R456-H611 haplotype were present more frequently in T2D individuals than in control subjects.

After genotyping 1536 SNPs in 84 genes regulating pancreatic β -cell development, function, and survival, Sandhu et al (224) found that rs10010131 (minor allele frequency [MAF] = 40%) and rs6446482 (MAF = 41%) in the *WFS1* gene were strongly associated with T2D

risk in UK and other populations. The frequency at the rs10010131 risk allele is 60%, and it was estimated that the population attributable fraction of rs10010131 is 9%, explaining 0.3% of the excess familial risk of T2D.

Cheurfa et al (225) examined the association of allelic variations in the *WFS1* gene with insulin secretion and risk of T2D in the prospective Data from Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study. They found that the three variants rs10010131 G, 1801213 G, and rs734312 A were significantly associated with plasma glucose, glycated hemoglobin A1C levels, and insulin secretion at baseline and throughout the study in individuals with T2D or at risk of developing diabetes, but not in those who remained euglycemic at the end of the follow-up. Carriers of the combined GGA haplotype for these SNPs had a 26% increased risk for developing diabetes compared with carriers of the ACG haplotype. These associations between the three variants and T2D were replicated in a large case-control, cross-sectional study. These findings suggested that variants of the *WFS1* gene affect insulin secretion and are associated with an increased risk of T2D. However, variants of *WFS1* including rs10010131G were found not to be associated with T2D in a well-designed fine-mapping study, raising the argument that low frequency variants in *WFS1* may or may not have significant impact on T2D risk in the examined populations (226).

Awata et al (227) reported that variant R456H in the *WFS1* gene was associated with an increased risk of common T1D in a small candidate gene association study, which needs validation in larger populations.

3. Molecular mechanisms and pathophysiology that underlie the association of mutations in the *WFS1* gene and diabetes

In WFS1 patients, loss-of-function mutations in the *WFS1* gene lead to deficiency of wolframin protein and an inadequate activation of the UPR in response to accumulation of unfolded proteins within the ER lumen, which induces ER stress and results in apoptotic cell death. These mechanisms are believed to underlie progressive neurodegeneration and endocrine dysfunction in these patients (216, 228). Interestingly, ER stress-mediated diabetes in WFS1 was diagnosed earlier in life than the common type of autoimmune-mediated T1D. *WFS1* mutations induce ER stress, which in turn mediates the decline of β -cell mass and diabetes in WFS1 patients. Poor glycemic control-induced oxidative stress is thought to further aggravate the progression of neurodegeneration in this disease (216). The development of therapeutic measures that alleviate ER stress and oxidative stress could benefit WFS1 patients. Calpain, a family member of calcium-dependent,

nonlysosomal cysteine proteases, may be a plausible therapeutic target. This enzyme is thought to be a mechanistic link between the ER and β -cell death in WFS1 (229). Loss-of-function mutations of *WFS1* increase cytoplasmic calcium levels, leading to calpain activation, which causes ER stress-induced β -cell death (230). Treatment with the ryanodine receptor inhibitor dantrolene was shown to reduce calcium leakage from the ER to cytosol, lowering cytosolic calcium levels and suppressing calpain activation; it also prevents cell death in pancreatic β -cells and neural progenitor cells. The protective effect of dantrolene suggests that modulating calcium levels by suppressing calpain activation could be one approach to treat WFS1 and other diseases associated with excess ER stress (229).

In addition to its role in the UPR, WFS1 may have other β -cell-specific functions. WFS1 localizes not only to the ER but also to secretory granules in pancreatic β -cells. Compared with wild-type β -cells, a 32% reduction in granular acidification was observed in *Wfs1*-deficient β -cells (231). This aberration may account for the impaired proinsulin processing and an increased circulating proinsulin level in *Wfs1*-null β -cells. Electron microscopy showed that *Wfs1* deficiency leads to a reduction in plasma membrane-attached secretory granules in the β -cell, indicating that WFS1 may play a role in the intracellular distribution of secretory granules, especially the docking of insulin granules to the plasma membrane. These perturbations may cause the profoundly impaired GSIS in *Wfs1*-deficient mice, providing new insights into the molecular basis of β -cell dysfunction in WFS1 patients (231).

J. Peroxisome proliferator-activated receptor γ

The *PPARG* gene, predominantly expressed in white and brown adipose tissue, is a master regulator of adipogenesis as well as a potent modulator of whole-body energy balance, lipid biosynthesis, and insulin sensitivity (232). *PPARG* exists in two splice isoforms, *PPARG1* and *PPARG2*, with the latter carrying an additional 30 amino acids at its N terminus. *PPARG* is a nuclear hormone receptor and a target of thiazolidinediones (TZDs), a commonly used class of antidiabetic medication despite concerns on side effects of weight gain, fluid retention, bone loss, and heart failure. *PPARG* activation by TZDs leads to a marked improvement of whole-body insulin sensitivity and glucose metabolism (232). Recently, fibroblast growth factor (FGF) 21 and FGF1 are thought to act locally in adipose tissue to mediate the pharmacological actions as well as the side effects of TZDs (233, 234). *Fgf21*-deficient mice are resistant to the insulin-sensitizing effects of TZDs as well as the associated weight gain and fluid retention (234). In contrast, FGF21 administration in mice

produces strong antidiabetic effects along with bone loss (235). In addition, obesity can activate cyclin-dependent kinase 5 in adipose tissue, resulting in the phosphorylation of *PPARG* at serine 273. This modification underlies the dysregulation of a number of genes associated with obesity and insulin resistance in adipose tissue. *PPARG* ligands such as TZDs can block this phosphorylation and confer their antidiabetic therapeutic effects (236, 237).

1. Mutations in *PPARG* lead to severe insulin resistance and diabetes

Barroso et al (238) first reported the identification of two heterozygous mutations, P467L and V290M, in the ligand-binding domain of *PPARG* in three subjects with severe insulin resistance who presented with diabetes and hypertension at an unusually early age. Although these mutations are uncommon, detected in just three of 85 severely insulin-resistant individuals and none in 314 controls, they represent a unique model of monogenic diabetes through decreased insulin sensitivity, without overtly defective β -cell function.

2. *PPARG* gene variants and T2D

Several variants in the *PPARG* gene have been identified, with the P12A variant (rs1801282), first identified by Yen et al (239), being the most extensively examined in epidemiological studies. Ethnic heterogeneity has been observed between the *PPARG* P12A and the magnitude of the association with T2D (240–242). In a large meta-analysis that involved 32 849 T2D cases and 47 456 controls, which included a population-based cohort, case-control, cross-sectional, and GWAS analyses, Gouda et al (243) found that the *PPARG* P12A polymorphism was associated with a reduction in T2D risk, with a combined overall odds ratio of 0.86.

Of note, *PPARG* SNP rs1801282 (P12A C>G) was found to be associated with T1D in one report (244) but not in another (245), suggesting that this T2D locus may or may not play a role in T1D genetic susceptibility.

3. Molecular mechanisms and pathophysiology that underlie the association of mutations or variations in the *PPARG* gene and diabetes

The P467L mutation discussed above (238) lies in an amphipathic α -helix at the C terminus of the *PPARG* ligand-binding domain, a motif that is critical for mediating ligand-dependent transactivation and coactivator recruitment. The mutant displays a severely impaired binding capacity to its ligand and coactivator. The V290M receptor mutation is located proximally within the ligand-binding domain. Both *PPARG* mutants inhibit wild-type receptor function in a dominant-negative manner, which

may lead to silencing of basal gene transcription (238). Notably, a recent study highlights that motif-altering SNPs in target genes of *PPARG* cause differential *PPARG* binding to the DNA, modulating the recruitment of co-operating factors including CCAAT/enhancer binding protein, and thus determine individual disease risk and the response to TZD treatment (246).

Peroxisome proliferator-activated receptor α (*PPARA*) is abundantly expressed in the liver, heart, and muscle, where it plays important roles in the regulation of fatty acid oxidation, lipoprotein metabolism, and glucose homeostasis (247). In the Quebec family study, Bossé et al (248) examined the interactions and combined effects of *PPARG2* A12 and *PPARA* V162 on glucose and insulin homeostasis. Carriers of the *PPARA* V162 allele were found to display higher insulin and C-peptide levels in response to a glucose challenge. The *PPARG2* A12 allele reduced plasma insulin or C-peptide levels only on a *PPARA* V162 genetic background. The *PPARG2* A12 allele appeared to attenuate the deleterious effect of the *PPARA* V162 allele and improve insulin sensitivity (248), an observation that is consistent with the fact that obese subjects carrying the *PPARG2* A12 allele exhibited greater insulin sensitivity as measured by euglycemic-hyperinsulinemic clamp (249).

Recently, Claussnitzer et al (250) identified the T2D risk SNP rs4684847 as a cis-regulatory variant located at 6.5 kb upstream of the *PPARG2*-specific promoter. Functional studies revealed that paired related homeobox 1 (*PRRX1*) may act as a repressor of *PPARG2* via its enhanced binding at the rs4684847 C risk allele. Consistent with the role of *PPARG2* for insulin sensitivity rather than insulin secretion, this enhanced binding activity was observed only in insulin target cells (adipocytes, hepatocytes, and myocytes), but not in pancreatic β -cells or kidney cells. These findings support the interpretation that the rs4684847 C risk allele-mediated enhanced binding of *PRRX1* represses the expression of *PPARG2*, leading to reduced insulin sensitivity and impaired glucose homeostasis.

III. Monogenic Diabetes Genes Associated With Both T1D and T2D

Among the list of monogenic diabetes genes, variants of the human preproinsulin gene (*INS*) are strongly associated with common T1D, but inconsistently with T2D. Interestingly, GWAS and meta-analyses showed that variants of *GLIS3*, a NDM gene, are associated with susceptibility to both common T1D and T2D.

A. Preproinsulin gene, *INS*

INS is unique among monogenic diabetes genes in that *INS* mutations can cause hyperinsulinemia, hyperproinsulinemia, NDM, *MODY10*, as well as autoantibody-negative T1D (type 1b) (Figure 4). Moreover, variants of the *INS* gene are also strongly associated with common T1D (type 1a), but inconsistently with T2D.

1. Mutations in the *INS* gene lead to hyperinsulinemia and hyperproinsulinemia

Mutations of the *INS* gene that produce structurally defective insulins can cause hyperinsulinemia and late-onset diabetes (Figure 4). These mutated insulins display drastically reduced bioactivity and receptor binding capacity, and often prolonged half-life (251). For example, the *INS* mutations F49L (252), F48S (253, 254), and V92L (255) have been identified in such patients. It is important to note that not all individuals who harbor heterozygous *INS* gene mutations necessarily develop diabetes because affected individuals who produce both normal and mutant insulins may compensate for the defect by overproducing the normal insulin. In addition, other factors such as aging, body weight gain, and insulin resistance may also play a role.

Insulin gene mutations affecting the conversion of proinsulin to insulin cause hyperproinsulinemia with or without mild diabetes. Mutations at the junction of C-peptide and α -chain (R89H, R89L, R89P; Figure 4) (251) disrupt the cleavage site of the prohormone convertase 2, and the mutated insulins can be cleaved only at the junction of C-peptide and β -chain by prohormone convertase 1/3. Another mutation at β -chain (H34D) was also shown to cause hyperproinsulinemia via an unclear mechanism. H34D proinsulin has a 4- to 5-fold higher receptor binding activity than wild type, and it has been suggested that it may bind to insulin receptors in the trans-Golgi and be secreted constitutively (256, 257).

2. Mutations in the *INS* gene lead to PNDM, *MODY10*, and type 1b diabetes

In 2007, Støy et al (258) first reported that mutations of the *INS* gene are a novel cause of PNDM. They identified 10 heterozygous mutations in *INS* among 16 PNDM families. These patients develop diabetes at a median age of 9 weeks, usually with diabetic ketoacidosis or severe hyperglycemia that needs immediate insulin therapy. To date, heterozygous autosomal dominantly inherited mutations in the *INS* gene are a common cause of PNDM (~12%), second only to mutations in *KCNJ11* (35). These dominant heterozygous *INS* mutations lead to preproinsulin misfolding and accumulation in the ER of the β -cell,

[illegible]

Molven et al (268) extended the phenotype of the *INS* gene mutations to include rare cases of MODY (MODY10) and type 1b diabetes. They reported the *INS*

mutation c.137G>A (R46Q) in a MODY10 family and the *INS* mutation c.163C>T (R55C) in a type 1b diabetes family who presented with ketoacidosis and insulin dependency. The R46Q mutation disrupts a critical hydrogen bond formation, which impairs the stability of the insulin molecule. The R55C substitution is thought to perturb insulin biosynthesis via the introduction of an unpaired cysteine, as noted in the Akita mouse harboring a C96Y mutation in the *ins2* gene (269, 270), or it may affect proteolytic processing of proinsulin to insulin (268). It is significant that the C96Y mutation has also been found in rare patients with PNDM (271). A novel heterozygous single nucleotide deletion (c.233delA) leading to a frameshift mutation (Q78fs) in the *INS* gene was recently identified in a MODY family. This mutation produces an aberrant “proinsulin” that is devoid of the native structures of C-peptide and α -chain (261).

Although most of the diabetogenic mutations in the *INS* gene occur in a dominant heterozygous manner, Garin et al (272) identified 10 different recessive *INS* mutations that cause PNDM or TNDM by interfering with the efficiency of insulin biosynthesis. These include four homozygous mutations involving the coding region: c.184C > T (p.Q62X), c.3G > T (p.0?), c.3G > A (p.0?), and a deletion (c.-370-? 186+?del); five homozygous mutations in the promoter or 3' UTR regions: c.-331C > A, c.-331C > G, c.-218A > C, and c.-366_-343del, and c.*59A > G; and one compound heterozygote for two regulatory region mutations, c.-331C > G and c.-332C > G. Interestingly, patients with recessive *INS* mutations were diagnosed earlier (median, 1 week vs 10 weeks) and presented with a lower birth weight (−3.2 vs −2.0 SD score) than those with dominant heterozygous *INS* mutations. A plausible explanation of these observations is that two distinct disease mechanisms are involved in pathogenesis. In babies with recessive *INS* mutations, disrupted insulin synthesis occurs as soon as the β -cell starts to produce insulin during early fetal development. In contrast, in patients with dominant heterozygous *INS* mutations, the mutant preproinsulin misfolds and accumulates in the ER of the β -cell, causing increasingly severe ER stress that with time ultimately disrupts insulin production by the β -cell (267).

3. *INS* gene variants associated with T1D and possible mechanisms

Prior to GWAS, the *INS* gene on chromosome 11p15 was one of a few loci identified to be associated with susceptibility to T1D (273). The genetic risk conferred by the *INS* locus maps to a DNA region with a variable number of tandem repeats (VNTRs) of a 14- to 15-bp sequence approximately 0.5 kb upstream of the *INS* gene. The class

I alleles of *INS* VNTR (26 to 63 repeats, frequency ~70% in Caucasians) are associated with T1D, whereas the class III alleles (140 to more than 200 repeats, frequency ~30% in Caucasians) seem to confer protection against T1D. Although these classes of VNTR alleles have little effect on insulin transcript levels in the pancreas, class I alleles are associated with lower levels of insulin mRNA and protein in the thymus, which may compromise negative selection and allow more autoreactive T cells to escape into the periphery, increasing susceptibility to T1D, whereas the higher insulin levels associated with class III alleles may enhance negative selection for autoreactive T cells, protecting against T1D (274). In support of this hypothesis, recent GWAS and other studies highlight *INS* as the second strongest risk locus (right after HLA) for T1D (273), insulin and its precursors being major initiating autoantigens in human T1D (275). It is unclear whether any missense mutation in the *INS* gene underlies common T1D, although the *INS* mutation c.163C>T (R55C) has been linked to type 1b diabetes (268).

4. *INS* gene variants associated with T2D

Although the class III alleles of *INS* VNTR may render protection against T1D, association studies suggested that they are inconsistently associated with the risk of T2D, probably due to population admixture (276–281). In Caucasians, class III *INS* VNTR appeared to confer a modest increase in risk of T2D (276), but the observation could not be replicated in a large family-based association study (279). The latter study did, however, report a marked excess transmission of class III *INS* VNTR from fathers to diabetic probands, suggesting the potential contribution of imprinted genes in the risk of T2D. In the Pima population, significant linkage disequilibrium was observed between *INS* VNTR (−23*Hph*1, an A/T SNP within the *Hph*1 restriction endonuclease site) and birth weight, but not T2D (280).

Notably, one large-scale meta-analysis showed that tyrosine hydroxylase (*TH*)-*INS* variant (rs10770141), a T1D risk allele, is protective for T2D. This variant, different from *INS* VNTR, is located in the promoter region of the *TH* gene and 11 kb upstream of the *INS* gene. *TH*-*INS* variant regulates the expression of *TH*, but not *INS* (282). The mechanism underlying the association between this variant of *TH* and diabetes has not been investigated.

5. Molecular mechanisms and pathophysiology that underlie *INS* mutations and diabetes

Heterozygous dominant mutations of the *INS* gene have been identified within all regions of the preproinsulin molecule including the signal peptide, C-peptide, and flanking cleavage sites (Figure 4) (283). The mutations

within the signal peptide region likely impair one or more of the earliest events of proinsulin biosynthesis, including completion of translocation, excision of the signal peptide, initiation of β -chain folding, and disulfide bond formation (283). For example, R6C and R6H mutations in the *INS* gene lead to loss of the N-terminal positive charge of the 24-amino acid signal peptide, which fails to be fully translocated across the ER membrane and accumulate in a juxtanuclear cytoplasmic compartment, inducing ER stress and β -cell death (284). The preproinsulin A24D mutation that affects the last signal peptide residue likely disrupts normal signal peptide cleavage and interferes with downstream proinsulin folding and trafficking (265), leading to PNDM.

Proper disulfide pairing is a key event that determines whether a proinsulin molecule can achieve its native folded structure. Proinsulin contains six cysteine residues that form three evolutionarily conserved disulfide bonds: B7-A7, B19-A20, and A6-A11 (Figure 4). Many *INS* mutations introduce or eliminate a cysteine residue in the polypeptide chain, producing unpaired cysteine residues, which may alter or disrupt normal proinsulin disulfide pairing (283). For example, the mutations C43G and C96Y in the *INS* gene disrupt normal disulfide bonds at B19-A20 and A7-B7, respectively. The mutations R89C and G90C introduce an additional unpaired cysteine residue at the α -chain-C-peptide cleavage site (258). It is noteworthy that some mutations, such as G32S, G32R, and G47V, do not change proinsulin cysteine content, but may still disrupt the normal proinsulin folding, an observation that may be related to the fact that most of these mutations involve evolutionarily highly conserved residues (258). These mutations in the *INS* gene may lead to proinsulin misfolding and accumulation in the ER of the β -cell and may cause ER stress, β -cell apoptosis, and diabetes. Autophagy is a physiological process that maintains cellular homeostasis via clearance of misfolded proteins and damaged organelles (285). Accumulation of excessive amounts of misfolded proinsulin molecules per se, eg, in *Akita* mice, can stimulate autophagy by inhibiting mammalian target of rapamycin complex 1, alleviates ER stress, and partially prevents β -cell apoptosis. Treatment of female diabetic *Akita* mice with rapamycin (mammalian target of rapamycin complex 1 inhibitor) improves diabetes and further down-regulates β -cell apoptosis (286). These findings suggest that augmentation of autophagy may be a novel therapeutic approach for this type of diabetes. The challenge would be to find agents that are safe and efficacious in alleviating the excess ER stress in the β -cell.

Dominant-negative inhibition of wild-type proinsulin trafficking appears to be a feature of many of the *INS*

mutants that cause PNDM (287). Forced expression of mouse proinsulin mutants with either cysteine residue substitution (C96Y) or noncysteine residue substitution (H29D or L35P), all known to be associated with human PNDM (Figure 4), inhibits the production of mature human insulin in the rat INS-1-derived 832/13 β -cell line, which coexpresses wild-type human insulin. On the other hand, it is noteworthy that the simultaneous introduction of missense substitutions that replace all six cysteine residues of proinsulin fails to repress the secretion of coexpressed wild-type human insulin. This suggests that pathways for proinsulin folding/processing are complicated; cysteine residues (paired or unpaired) in the *INS* mutants play a critical role in causing intracellular entrapment of coexpressed wild-type proinsulin, disrupting insulin production (287). In addition, *INS* mutants associated with PNDM facilitate the wild-type proinsulin to recruit into non-native disulfide-linked protein complexes in a cell line and in pancreatic islets of *Akita* mice (269, 270), which leads to disruption of normal folding of wild-type proinsulin. Although the C96Y mutation affects only one copy of the *Ins2* gene, leaving one normal *Ins2* gene and two normal *Ins1* genes intact in these animals, β -cells from *Akita* mice display severe ER stress, accompanied by failure of GSIS, culminating in diabetes at an early age (269, 270). As noted earlier, heterozygous C96Y mutation was also found to cause PNDM in humans (271). Thus, it has been proposed that perturbation of the disulfide-coupled folding pathway of wild-type proinsulin initiates the molecular pathogenesis of PNDM associated with *INS* mutations (287).

In addition to *INS* mutations that cause proinsulin misfolding and severe ER stress that cripples the insulin production machinery of the β -cell, recessive *INS* mutations can also cause decreased insulin biosynthesis and diabetes via other mechanisms (272). These include absent or altered translation because of coding-sequence deletions or mutations, reduced insulin transcripts because of mutations in the promoter, or increased insulin mRNA instability. A few examples of *INS* mutations that impair insulin production directly include: two point mutations (c.3G > A and c.3G > T) at the translation initiation codon that abolish the native translation initiation for the preproinsulin protein; a 3' UTR mutation (c.*59A > G) that abolishes the polyadenylation signal and potentially impairs mRNA stability; a 24-bp deletion (c.-366_-343del) in the *INS* promoter region that disrupts the promoter evolutionary conserved C1 and E1 elements, which are involved in the binding of MAFA and NEUROD1 to the *INS* promoter, respectively (288); and the CC dinucleotide mutations, c.-331(C > G, C > A) and c.-332C > G, that abolish a canonical binding motif for a key *INS*

transactivator protein GLIS3 (214, 272, 289) (see discussion in the next section), producing up to 90% reduction in the *INS* promoter transcriptional activity.

B. Gli-similar 3

GLIS3, a member of the Krüppel-like family of transcription factors, is predominantly expressed in pancreatic β -cells, thyroid, and kidney (290, 291). Interestingly, *GLIS3* is a NDM gene that is also associated with the susceptibility of both common T1D and T2D, as identified by GWAS and large-scale meta-analyses that include multiple populations.

1. Mutations in the *GLIS3* gene lead to monogenic diabetes-related syndromes

About a decade ago, Senée et al (291) first reported that mutations in the *GLIS3* gene cause a previously described rare syndrome characterized by PNDM, congenital hypothyroidism, polycystic kidneys, and in some cases, also with intrauterine growth retardation, facial anomalies, congenital glaucoma, and hepatic fibrosis. Six individuals from three families were affected. In one family (with neonatal diabetes, hypothyroidism [NDH]), they identified a homozygous insertion (2067insC) in *GLIS3* leading to a frameshift and a truncated protein. In two other families with an incomplete syndrome, affected individuals harbor homozygous large fragment (426 and 149 Kb) deletions affecting the 5' UTR of the *GLIS3* gene. Recently, additional patients carrying homozygous partial *GLIS3* gene deletions or mutations have been reported, most presenting with NDH as well as renal cysts and liver disease (292–294). It is noteworthy that Dimitri et al (293) reported a patient with compound heterozygous mutations in *GLIS3* (p.Arg589Trp/exons 1–11 del) presenting with NDM, but not congenital hypothyroidism or renal cysts, who survived to adulthood.

2. *GLIS3* gene variants and T1D

Barrett et al (295) first identified the association between a *GLIS3* variant and common T1D in a report that combined a new GWAS and a meta-analysis of two prior studies that involved a total of 7514 T1D patients and 9045 control individuals. They found that the region of strong linkage disequilibrium at chromosome 9p24.2 with a MAF of 50.2% harbors only a single gene, *GLIS3*. The risk allele rs7020673 G was strongly associated with susceptibility to T1D in GWAS, case-control, and families analyses. This association was replicated recently in Pakistani T1D patients (296).

In another recent study, Winkler et al (297) found that the inclusion of 40 non-HLA gene SNPs could significantly improve the prediction accuracy of T1D, compared

to that provided by HLA alone. Furthermore, they identified that HLA plus nine SNPs including the one from *GLIS3* could achieve similar prediction accuracy as the total SNP set for T1D. They proposed a weighted risk model with selected SNPs that could be considered for recruitment of at-risk infants into studies of the natural history or disease prevention for T1D.

3. *GLIS3* gene variants and T2D

Shortly after the report that the *GLIS3* variant was strongly associated with common T1D (295), Dupuis et al (78) identified the association between a variation in *GLIS3* and common T2D, which has been subsequently extensively examined in epidemiological studies among different populations.

In meta-analyses involving 46 186 nondiabetic participants in 21 GWAS and follow-up studies, Dupuis et al (78) identified the *GLIS3* variant (rs7034200 A) as one of nine newly identified loci associated with fasting glucose in T2D trait, but not associated with body mass index, blood pressure, or lipid profile in participants of European descent. These findings were replicated in Danes (298), Chinese (299, 300), South Asians (301), and East Asians (302). Boesgaard et al (298) found that *GLIS3* variant rs7034200 A was associated with reduced glucose-stimulated β -cell function in middle-aged Danish people. Barker et al (303) reported that *GLIS3* variant rs7034200 was associated with fasting blood glucose levels in healthy children and adolescents of European origin. *GLIS3* variant rs7034200 carriers showed impaired β -cell function, as indicated by homeostasis model assessment. Additionally, variant rs7041847 A in *GLIS3* is associated with susceptibility to T2D in East Asians (302, 304).

4. Molecular mechanisms and pathophysiology that underlie the association of *GLIS3* mutations or variations and diabetes

The gene association studies in humans are tantalizing. However, the underlying mechanisms were largely unknown until *Glis3* global and β -cell-specific knockout mice were generated. Early studies in vitro identified a *GLIS3* response element in the insulin gene promoter and revealed that *GLIS3* physically and functionally interacts with PDX1, MAFA, and NEUROD1 to control insulin gene transcription (214). Moreover, the direct binding of *GLIS3* to the insulin promoter is required for the interaction of PDX1, MAFA, and NEUROD1 with the promoter (305), indicating that *GLIS3* plays a pivotal role in forming a transactivator complex to control insulin transcription. In agreement with these in vitro findings, Yang et al (306) found that tamoxifen-mediated β -cell-specific inactivation of *Glis3* in adult mice down-regulates insulin ex-

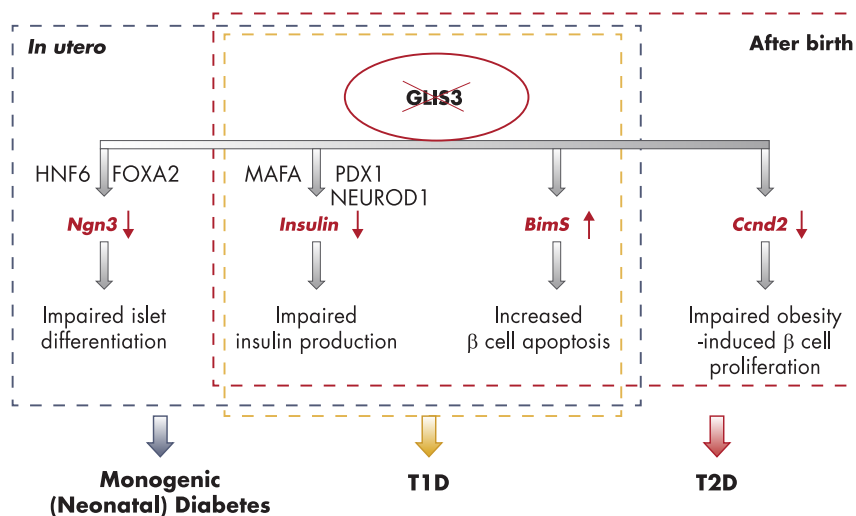
Figure 5.

Figure 5. Multifaceted role of GLIS3 in diabetes. In utero, GLIS3 controls islet differentiation by transactivating *Ngn3*, synergistically with HNF6 and forkhead box A2 (FOXA2, also known as HNF3B or transcription factor 3B [TCF-3B]). Loss-of-function mutations or ablation of *Glis3* cause impaired islet differentiation and NDM. After birth, GLIS3 predominantly controls insulin gene transcription, cooperating with MAFA, PDX1, and NEUROD1. GLIS3 is also required for obesity-induced β -cell proliferation and compensatory β -cell mass expansion by transactivating *Ccnd2*. In addition, GLIS3 plays a protective role for β -cell survival, possibly by regulating *BimS*. Therefore, impairment of GLIS3 function also plays a key role in the development of T1D and T2D. This figure summarizes the pathways by which ablation, loss-of-function mutations, or functional impairment of *GLIS3* cause NDM, T1D, and T2D. Pathways in the blue rectangle take place in the developing pancreas in utero and underlie monogenic NDM; pathways in the yellow square and the red rectangle pertain to the postnatal β -cell and contribute to the development of T1D and T2D, respectively.

pression, leading to fulminant diabetes and death. Thus, both in vitro and in vivo data demonstrated that GLIS3 is a potent transactivator of the insulin gene.

To gain insight into the role of GLIS3 in monogenic diabetes, three groups independently generated *Glis3*-deficient mice (289, 307, 308). Recapitulating the phenotype of NDH patients with *GLIS3* mutations (291), *Glis3*-null mice died with severe hyperglycemia and ketoacidosis within the first days of life. The mice also developed hypothyroidism and polycystic kidney, whereas exocrine development was unaffected. Mechanistically, GLIS3 was shown to control fetal islet differentiation, synergistically with HNF6 and forkhead box A2 (FOXA2), via direct transactivation of *Ngn3*, the endocrine lineage-defining transcription factor (308).

Consistent with an autosomal recessive inheritance observed in humans, heterozygous *Glis3*-mutant mice remained euglycemic while on regular chow diet. However, when they were challenged with a HFD, adult mice developed diabetes because of impaired compensatory β -cell proliferation and mass expansion. It has been shown that GLIS3 controls β -cell proliferation in response to HFD feeding partly by direct regulation of

cyclin D2 (*Ccnd2*) mRNA expression (306). *CCND2* is essential for postnatal pancreatic β -cell growth (309, 310) and compensatory mass expansion in response to insulin resistance (311). Interestingly, recent GWAS identified that the variant rs11063069 G in *CCND2* confers susceptibility risk to T2D (312), whereas the variant rs76895963 G in *CCND2* reduces the risk of T2D by half and is correlated with increased *CCND2* expression (167).

GLIS3 may also protect pancreatic β -cells against apoptosis. Proinflammatory cytokines, particularly IL-1 β and interferon- γ (313), and the saturated nonesterified fatty acid palmitate (314), may contribute to β -cell loss in T1D and T2D, respectively. Nogueira et al (315) reported that *Glis3* knockdown in INS-1 cells increased basal and inflammatory cytokine (IL-1 β + interferon- γ)- or palmitate-induced β -cell apoptosis. They suggested that reduced *Glis3* expression might modulate the alternative splicing of the proapoptotic BH3-only protein Bim, promoting

the expression of the prodeath variant *BimS* and β -cell death.

These data from cell lines and mouse models provide the mechanistic basis for the genetic associations of the *GLIS3* gene and NDM (291), common T1D (295, 296), and T2D (78, 298–304) (Figure 5). GLIS3 may underlie all three forms of diabetes by potentially controlling insulin gene transcription and likely β -cell survival. The homozygous insertion (2067insC) in *GLIS3* identified in an NDH family (291) leads to a frameshift and a truncated protein that lacks the C-terminal transactivation domain (290), which is required to activate both *NGN3* (308) and *INS* (214, 305, 306) gene transcription. This serious developmental deficiency causes severely abnormal β -cell development in utero and marked impairment in insulin production at birth, culminating in PNDM. In addition to causing PNDM (289, 291, 307, 308), *GLIS3* was also found by GWAS to be linked to common T1D (295, 296), probably through its action on insulin gene transcription and β -cell survival. Finally, GWAS showed that the *GLIS3* locus is also linked to T2D (78, 298–304). Studies in adult mouse models suggest that GLIS3 plays a critical role in compensatory obesity-induced β -cell proliferation via the

regulation of *Ccnd2* transcription (306). Of note, the effects of the susceptibility gene variants examined in isolation on the risk of T1D or T2D are typically modest, often making it a challenge to decipher such subtle effects by current functional assays (10). The precise mechanisms underlying the *GLIS3* variants and diabetes remain to be fully elucidated.

IV. Concluding Remarks

In the past few decades, an increasing number of genes have been linked to monogenic diabetes and related syndromes. GWAS have markedly expanded the repertoire of susceptibility loci associated with common T1D or T2D. Although T1D and T2D share overlap in select clinical and pathological features, the susceptibility loci identified by GWAS indicate that the genetic basis for the two common types of diabetes is mostly distinct (7–15) (Figure 2). In agreement with this premise, candidate gene-association studies and GWAS showed that, to date, at least 12 monogenic diabetes genes are associated only with T2D, but not T1D; the *INS* locus appears to be an exception in that it is strongly associated with T1D but is inconsistently associated with T2D. *GLIS3* is a developmental transcription factor gene that was shown to underlie a rare kind of monogenic PNDM. It is unique that GWAS showed that variants of *GLIS3* are associated with both common T1D and T2D in different populations. Not unexpectedly, the T1D and T2D *GLIS3* variants are unique and do not overlap, likely because they confer their diabetogenic effects via different mechanisms.

The monogenic forms of diabetes offer excellent models to unravel the developmental biology of pancreatic β -cells and the role of the implicated genes in the regulation of β -cell function. Information gained from these studies also facilitates the interpretation of GWAS data for common T1D and T2D. Because more and more rare variants are being identified in diabetic patients with advanced sequencing technologies, special caution needs to be taken to avoid ascertainment bias, overinterpretation, and misidentification of risk variants for common forms of diabetes (264). A number of rare mutations of late-onset MODY genes (eg, *PDX1*) have been reported to be variants associated with common T2D, blurring the boundary between the two diabetes syndromes. Differentiating between an incompletely penetrant MODY mutation from a rare T2D variant is often difficult and can be a matter of semantics (264, 316).

Most of the T2D risk variants in islet transcription factors are enriched in clustered islet enhancers in human islet cells where they interact functionally with the epigenome.

Individual variants may display disrupted islet enhancer activity, which may be an important mechanism for the genetic predisposition of T2D (317, 318). It remains a challenge to translate our knowledge from research in the monogenic diabetes genes into effective forms of treatment. Because many of these have been shown to occur in T1D or T2D, we are hopeful that future research into these genes will provide new insights into disease pathogenesis and treatment target identification, not only for the rare monogenic disorders, but also for the worldwide epidemic of T1D and T2D.

Acknowledgments

Address all correspondence and requests for reprints to: Yisheng Yang, Division of Endocrinology, Department of Medicine, MetroHealth Medical Center, Case Western Reserve University, 2500 Metrohealth Drive, Cleveland, OH 44109. E-mail: yisheng.yang@case.edu. Or Lawrence Chan, Division of Diabetes, Endocrinology and Metabolism, Departments of Medicine and Molecular & Cellular Biology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030. E-mail: lchan@bcm.edu.

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