MONOGENIC DIABETES

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ABSTRACT

At least 10% of diabetes cannot be attributed to the most common forms, Type 1 or Type 2 diabetes. Maturity-Onset Diabetes of Young (MODY) can be diagnosed in (non-obese) patients with diabetes at a young age, often less than 25 years, who have a strong autosomal dominant family history of diabetes. Patients are generally heterozygous for the different mutations as the homozygous conditions result often in permanent neonatal diabetes. The genetic defects behind MODY and neonatal diabetes cause impaired insulin synthesis or secretion or a reduced beta cell mass due to mutations in genes that are important for beta cell biology. Currently there are more than 10 genes associated with these disorders, and more genes are likely to be identified.

GENETIC DEFECTS OF BETA-CELL FUNCTION

Table 1. Genetic Defects of Beta-Cell Development and Function				
HNF-1 alpha -diabetes				
Glucokinase diabetes				
HNF-4 alpha diabetes				
Pdx1 diabetes				
HNF-1 beta diabetes				
NeuroD1 diabetes				
KLF11 diabetes				
CEL diabetes				
Pax4 diabetes				
Insulin diabetes				
BLK diabetes				
ABCC8 gene/ Sur1 diabetes				
KJCN11 gene/ Kir6.2 diabetes				
Neonatal diabetes (permanent or transient)				

AUTOSOMAL DOMINANT DISEASE

Historically, before the current epidemic of teenage T2DM (1,2), many patients diagnosed with T2DM or T1DM were found to have a form of diabetes with a strong family history of diabetes, which was labeled Maturity-Onset Diabetes of Young (MODY) in 1965. Although some of them phenotypically resemble T2DM, these individuals are not typically obese and have onset of disease at a young age, generally less than 25 years. Inheritance of the diabetes in these individuals is autosomal dominant with up to 85-95% penetrance. Patients are generally heterozygous for the different mutations as the homozygous conditions result often in permanent neonatal diabetes. The genetic defects cause impaired insulin synthesis or secretion or a reduced beta cell mass due to mutations in genes that are important for beta cell biology (3). Currently there are at least 13 genes associated with this disorder, although more genes are likely to be identified in the future (4). Instead of MODY the specific genetic defects are included in the names of the monogenic forms.

Hepatocyte Nuclear Factor (HNF-4A) Diabetes (Formerly MODY 1)

This is the first MODY to be described. HNF-4 α belongs to the nuclear receptor superfamily of transcription factors and is found in the liver, intestine, kidney, and pancreatic islets. Although it binds DNA as a zinc finger motif there is no defined ligand. It is involved in the regulation of genes required for glucose transport and metabolism (5,6). Patients with HNF4- α diabetes are seldom diagnosed before adolescence. A diagnostic clue can be low triglycerides (0.5- 0.8 mmol/l) (7,8) and the patient may also have been LGA as a newborn and have had a neonatal hyperinsulinemic hypoglycemia (9). Fasting plasma glucose can be quite normal for several years although postprandial glucose and HbA1c is high. Eventually HNF-4A patients require either oral hypoglycemic agents or insulin treatment. Exocrine pancreatic insufficiency can be present.

Glucokinase (GCK) Diabetes (Formerly MODY 2)

Heterozygous inactivating mutations in glucokinase cause defects in function (10,11,12,13). This glycolytic enzyme has a low affinity for glucose and controls the rate-limiting step of glucose metabolism. It is referred to as the glucose sensor of the β -cell as it controls glucose-mediated insulin release. More than 60 different mutations have been described and all ethnic groups can be affected. The clinical disease manifests as mild fasting hyperglycemia with onset during infancy but high postprandial glucose levels are very rare even later in life. Severe hyperglycemia and vascular complications are rare in GCK diabetes (14). Treatment consists basically of dietary (avoiding large quantities of carbohydrate) and lifestyle interventions. Homozygotic inactivating GCK mutations lead to permanent neonatal diabetes (15).

HNF-1A Diabetes (Formerly MODY 3)

Mutations in HNF-1A are a common cause of MODY (6,16). HNF-1A is part of the homeodomaincontaining superfamily of transcription factors. It has a DNA binding motif, and is involved in the genetic control of development and its expression is partly controlled by HNF-4-alpha (17,18). HNF-1A is expressed in the liver, kidney, intestine, and pancreatic islets (19). Over 90 different mutations have been identified and these occur in all ethnic groups, though it is more common in those of European origin (20). Similar to (HNF-4A) diabetes, fasting plasma glucose can be quite normal for several years although postprandial glucose and HbA1c is high. Glucosuria is often part of the clinical presentation, and diabetic complications are often present. Besides diet intervention, most patients will do well on sulfonylurea treatment.

Pdx1 (a.k.a. Insulin Promotor Factor IPF-1) Diabetes (Formerly MODY4)

Only a few families have been identified with this disorder (21). Pdx1 is a homeodomain-containing transcription factor that is expressed in the endoderm already before the pancreatic anlage is identifiable (22). It regulates the development of beta and delta cells (23) and therefore it is not surprising that homozygotic or two different heterozygotic mutations lead to pancreatic agenesis and neonatal diabetes (24,25) while single heterozygotic mutations associate with beta cell dysfunction and type 2 like diabetes (21,26). The average age at diagnosis is 35 years (variation between 16-76 years), yet not all mutation carriers develop diabetes (27).

HNF-1-Beta Diabetes (Formerly MODY 5)

This form of diabetes is caused by heterozygotic mutations in *TCF2* gene encoding HNF-1beta, and is characterized by progressive non-diabetic renal dysfunction of variable severity, pancreatic atrophy and genital abnormalities (28,29). It is also called RCAD i.e. renal cysts and diabetes. HNF-1beta is expressed in the liver, kidney, intestine, stomach, lung, ovary and pancreatic islets (30). Recently, complete deletion of HNF-1b and 17q12 microdeletion syndrome have been considered to be the same genetic disorder (31). Half of the carriers develop diabetes and are usually treated with insulin because of pancreatic atrophy.

Neuro D1 Diabetes (Formerly MODY6)

NeuroD1 (Beta2) is a basic-loop-helic transcription factor involved in pancreatic and neuronal development. Interestingly, heterozygotic Neuro D1 mutation leads to diabetes at the age of 20-40 years (32,33) while mutations in both alleles result in neonatal diabetes with neurological abnormalities and learning disabilities (34).

KLF11 Diabetes (Formerly MODY7)

Krüppel-like factor (KLF)-11 is a zinc-finger transcription factor and in-regulates transcription of Pdx1 and insulin genes (35,36). Mutations of KLF-11 result in a type 2-like diabetes.

CEL Diabetes (Formerly MODY8)

Carboxy ester lipase (CEL) is expressed in pancreatic acinar cells and its mutations result in pancreatic atrophy, fibrosis and lipomatosis together with exocrine insufficiency and later also endocrine dysfunction and diabetes (37). Patients usually need insulin treatment and pancreatic enzyme replacement therapy.

Pax4 Diabetes (Formerly MODY9)

Pax4 is a crucial transcription factor of pancreatic beta and delta cells (38), and its deletion in mouse models leads to lack of beta and delta cells and death from diabetes soon after birth. In

humans, Pax4 gene mutations have been detected in only a few patients with a phenotype similar to type 2 diabetes and it has also been associated with ketosis-prone diabetes (39,40).

Insulin Diabetes (Formerly MODY10)

Over 25 mutations have been reported in the preproinsulin gene leading to diabetes at various ages (41-43). The treatment is generally insulin although some patients manage with metformin or diet intervention. Interestingly, only a few patients develop late-complications.

BLK Diabetes (Formerly MODY11)

Mutations in the B-lymphocyte kinase (BLK) have been reported to cause a dominantly inherited diabetes in three families (44). BLK is a nonreceptor tyrosine-kinase of the *src* family of proto-oncogenes and it regulates insulin synthesis and secretion in beta cells through transcription factors Pdx1 and Nkx6.1.

ABCC8 Gene/ SUR1 Diabetes (Formerly MODY12)

SUR1 is encoded by the *ABCC8* gene and it is a part of the K-ATP-channel (45). Its activating homo- and heterozygous mutations cause neonatal diabetes, but heterozygous mutations can also cause MODY in patients whose clinical features are similar to those with HNF1A/4A diabetes (46). The correct molecular diagnosis is important as the patients can be treated with sulfonylureas.

KJCN11 gene/ Kir6.2 Diabetes (Formerly MODY13)

Kir6.2 is encoded by *KJCN11* gene and it is a part of the K-ATP-channel (45). Similar to SUR1, its activating homozygous mutations cause neonatal diabetes, but heterozygous mutation has been associated with a large spectrum of diabetes phenotypes in a French family and was not totally penetrant (47). The age at diagnosis varied from childhood to adulthood and the treatment from diet to OHA or insulin.

Table 2. MODY Characteristics						
MODY type	Frequency (% from MODYs)	Age at diagnosis (y)	Hyperglycemia			
GKC	15-20	newborn or older	Mild			
HNF-4A	5	From puberty	Progressive			
HNF-1A	almost 60	From puberty	Progressive			
HNF-1B	2	> 20	Progressive			
Pdx1	< 1	> 35	Progressive			

Ins	2	Infant to adult	Varies
CEL	< 1	> 30	N.A
NeuroD	< 1	20-30	Progressive
KLF11	< 1	20-30	Variable
Pax4	< 1	> 20	Progressive
Kir6.2	< 1	From early puberty to adulthood	Variable
SUR1	< 1	From early puberty to adulthood	Variable

Table 2. MODY Characteristics					
MODY Types	Complications	Other Features	Treatment		
GKC	Very rare	Mild hyperglycemia already from newborn, homozygote: PNDM	Diet		
HNF-4A	as T1D	Neonatal hyperinsulinemia, LGA, low triglycerides	OHA or insulin		
HNF-1A	as T1D	reduced renal glucose threshold	OHA or insulin		
HNF-1B	as T1D	Renal anomalies, renal insufficiency, pancreatic hypoplasia, genital anomalies	OHA or insulin		
Pdx1	NA	Homozygote: pancreatic agenesis	Diet or OHA or insulin		
Ins	Mild but can be as T1D	Can also present as PNDM	Diet or OHA or insulin		
CEL	NA	Exocrine insufficiency, lipomatosis	OHA or insulin		
NeuroD	NA	Homozygote: PNDM and neurological abnormalities	OHA or insulin		
KLF11	NA	NA.	OHA or insulin		
Pax4	NA	NA.	Diet or OHA or insulin		
Kir6.2	NA	Homozygote: neonatal diabetes	Diet or OHA or insulin		
SUR1	NA	Homozygote: permanent neonatal diabetes; heterozygote: transient neonatal diabetes	OHA (sulfonylurea)		

Permanent and Transient Neonatal Diabetes

Neonatal diabetes (NDM) is a diabetes that manifests during the first six months of life and it can be divided into permanent (PNDM) and transient (TNDM) forms. In this age group the most likely etiology is monogenic instead of autoimmune, and the diabetes can present either as isolated or a part of a syndrome (48-51). The incidence of NDM is estimated to be 1: 260000 (52). Recently, Flanagan et al. reported from a cohort of 147 of PNDM patients from consanguineous pedigrees that 75% had mutations in non-transcription factor genes (ABCC8 11%, EIF2AK3 40%, GCK 17%, INS 16%, KCNJ11 8%, SLC19A2 5%, SLC2A2 2%), and 7.5% in developmentally important pancreatic transcription factors (PDX1, PTF1A, GLIS3, RFX6, NEUROD1, NKX2.2, MNX1) (53). Furthermore, mutations in other pancreatic transcription factor genes (PAX6, NEUROG3, GATA4, GATA6, STAT3, FOXP3) have been identified in patients with neonatal diabetes (54-60). It is important to get the exact molecular diagnosis behind NDM since the patients can be treated life-long with sulfonylureas instead of insulin in case of SUR1 or Kir6.2 mutations (38). Most of TNDM is caused by abnormalities of an imprinted locus on chromosome 6q24 that results in the overexpression of the paternally expressed gene. Approximately 5% of these cases are due to recessive ZFP57 mutations, causing hypomethylation at the TNDM locus and other maternally imprinted loci (e.g. PEG3/ZIM2 and GRB10) and 25% are caused by mutations in either KJCN11 or ABCC8 genes (61).



Figure 1. Mutation in genes governing beta cell development and function reduce beta cell mass and impair insulin secretion resulting in diabetes (modified from Folias & Hebrok, Nat Rev Endocrinol 2014) (62).

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