U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Naylor R, Knight Johnson A, del Gaudio D. Maturity-Onset Diabetes of the Young Overview. 2018 May 24. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Maturity-Onset Diabetes of the Young Overview

Synonym: MODY Overview

Rochelle Naylor, MD,[1] Amy Knight Johnson, MS, CGC,[2] and Daniela del Gaudio, PhD[2]

Created: May 24, 2018.

Summary

The purpose of this overview is to increase the awareness of clinicians regarding maturity-onset diabetes of the young (MODY) and its genetic causes and management.

The following are the goals of this overview:

Goal 1

Describe the clinical characteristics of MODY.

Goal 2

Review the genetic causes of MODY.

Goal 3

Provide an evaluation strategy to identify the genetic cause of MODY in a proband (when possible).

Goal 4

Inform (when possible) medical management of MODY based on genetic cause.

Goal 5

Inform risk assessment and surveillance of at-risk relatives for early detection and treatment of MODY.

1. Clinical Characteristics of MODY

Maturity-onset diabetes of the young (MODY) is a group of inherited disorders of non-autoimmune diabetes mellitus which usually present in adolescence or young adulthood.

Author Affiliations: 1 Departments of Pediatrics and Medicine University of Chicago Chicago, Illinois; Email: rnaylor@bsd.uchicago.edu. 2 Department of Human Genetics University of Chicago Chicago, Illinois; Email: aknightjohnson@bsd.uchicago.edu; Email: ddelgaudio@bsd.uchicago.edu.

A clinical diagnosis of MODY can be suspected in individuals with:

- Early-onset diabetes in adolescence or young adulthood (typically age <35 years);
- Features atypical for type 1 diabetes mellitus including the following:
  - Absence of pancreatic islet autoantibodies [McDonald et al 2011a]
  - Evidence of endogenous insulin production beyond the honeymoon period (i.e., 3-5 years after the onset of diabetes)
  - Measurable C-peptide in the presence of hyperglycemia (C-peptide ≥0.60 ng/mL or 0.2 nmol/L) [Besser et al 2011, Ludvigsson et al 2012]
  - Low insulin requirement for treatment (i.e., <0.5 U/kg/d)
  - Lack of ketoacidosis when insulin is omitted from treatment
- Features atypical for type 2 diabetes mellitus including the following:
  - Onset of diabetes before age 45 years
  - Lack of significant obesity
  - Lack of acanthosis nigricans
  - Normal triglyceride levels and/or normal or elevated high-density lipoprotein cholesterol (HDL-C)
- Mild, stable fasting hyperglycemia that does not progress or respond appreciably to pharmacologic therapy
- Extreme sensitivity to sulfonylureas
- Extrapancreatic features (e.g., renal, hepatic, gastrointestinal)
- A personal history or family history of neonatal diabetes or neonatal hypoglycemia
- A family history of diabetes consistent with autosomal dominant inheritance that contrasts with type 1 diabetes and type 2 diabetes in the following ways:
  - Type 1 diabetes can run in families but is often sporadic: only 2%-6% of individuals with type 1 diabetes have an affected parent [Harjutsalo et al 2010].
  - Type 2 diabetes often runs in families: shared risk alleles and shared environment can lead to occurrence of type 2 diabetes in multiple family members. Family history that helps distinguish between type 2 diabetes and MODY are onset of diabetes after age 45 years in association with obesity (type 2 diabetes) versus onset of diabetes before age 35 years and lack of obesity (MODY).

Note: (1) A clinical prediction tool that can be used to calculate an individual's probability of having MODY also provides a rational approach to molecular genetic testing [Shields et al 2012, Thomas et al 2016]. This tool (click here), which applies only to individuals younger than age 35 years, was developed in a cohort of white Europeans. (2) Genetic risk scores have been developed to distinguish type 1 diabetes from monogenic diabetes and from type 2 diabetes. To date these scores have been studied in fairly homogeneous (i.e., white European) populations [Patel et al 2016].

Prevalence of MODY. Although estimates of prevalence vary by country, between children and adults, and by method of ascertainment, MODY is thought to account for at least 1%-3% of all diabetes [Shields et al 2010, Pihoker et al 2013, Shepherd et al 2016].

The prevalence of MODY in racial and ethnic minorities may be underrepresented as many individuals with MODY remain undiagnosed [Shields et al 2010] and studies to date have largely involved white populations.

2. Genetic Causes of MODY

To date it has been proposed that pathogenic variants in at least 14 genes cause MODY. The genes and associated clinical features are summarized in Table 1.

The four most common causes of MODY are the following:

- *GCK*-MODY (MODY2) and *HNF1A*-MODY (MODY3), each accounting for 30%-60% of all MODY. The prevalence of *GCK*-MODY has been estimated at 1:1,000 individuals [Chakera et al 2014]; however, among all causes of MODY, the prevalence of *GCK*-MODY is higher in some countries (United States, Germany, Italy, France, and Spain) [Estalella et al 2007, Schober et al 2009, Carmody et al 2016] most likely due to biased ascertainment of children compared to adults.
- *HNF4A*-MODY (MODY1) and *HNF1B*-MODY (MODY5), together accounting for about 10% of all MODY

Approximately 20% of all MODY has been attributed to pathogenic variants in ten other genes – some of which were designated before the availability of large-scale genetic testing and thus may be incorrectly associated with MODY. Molecular genetic testing of large numbers of individuals with possible MODY as well as other investigations (e.g., functional studies and/or segregation of variants with the disease) are needed to determine the significance of variants previously inferred to be pathogenic based on other methods.

A portion of MODY may be caused by pathogenic variants in yet-to-be-identified genes or complex molecular alterations in the known MODY-related genes that were not detected by previous genetic testing methods [Ellard et al 2008].

Table 1. Maturity-Onset Diabetes of the Young (MODY): Genes and Associated Clinical Features

Gene (Locus Name)	% of All MODY	Clinical Features	Frequency of Microvascular Complications	References / Selected OMIM Links
ABCC8 [1, 2] (MODY12)	<1%	Similar to *HNF1A*- & *HNF4A*-MODY [3]	Unknown	Bowman et al [2012] / 600509
APPL1 (MODY14)	<1% [4]	Overweight/obesity in some	Unknown	Prudente et al [2015] / 616511
BLK (MODY11)	<1% [5]	Overweight/obesity in some	Unknown	Kim et al [2004], Borowiec et al [2009] / 613375
CEL (MODY8)	<1% [6]	• Pancreatic atrophy → exocrine pancreatic insufficiency • Fibrosis & lipomatosis → diabetes	Unknown	Raeder et al [2006], Johansson et al [2011] / 609812
GCK (MODY2)	30%-50% [7, 8]	• Stable, mild fasting hyperglycemia at birth • Typically asymptomatic; diagnosis often incidental	Rare [9]	Froguel et al [1993], Pearson et al [2001] / 125851
HNF1A [3] (MODY3)	30%-65% [7, 10, 11]	• Transient neonatal hyperinsulinemic hypoglycemia in some • Progressive insulin secretory defect • OGTT frequently needed to make an early diagnosis • Renal glycosuria	Common [12]	Stride et al [2005] / 600496
HNF1B (MODY5)	<5% [13]	• IUGR • Renal anomalies • Urogenital tract anomalies • Pancreatic hypoplasia	Common [12]	Montoli et al [2002], Bellanné-Chantelot et al [2004], Ulinski et al [2006], Faguer et al [2011] / 137920

Table 1. continued from previous page.

Gene (Locus Name)	% of All MODY	Clinical Features	Frequency of Microvascular Complications	References / Selected OMIM Links
HNF4A [2] (MODY1)	5%-10% [14]	• Birth weight >800 g above normal • Transient neonatal hyperinsulinemic hypoglycemia common [15] • Progressive insulin secretory defect	Common [12]	Fajans et al [2001], Pearson et al [2005], Pearson et al [2007], Shields et al [2010] / 125850
INS [1] (MODY10)	<1%		Unknown	Edghill et al [2008a], Meur et al [2010] / 613370
KCNJ11 [1, 2] (MODY13)	<1%	Similar to *HNF1A*-MODY & *HNF4A*-MODY [3]	Unknown	Bonnefond et al [2012], Liu et al [2013] / 616329
KLF11 (MODY7)	<1% [5]		Unknown	Neve et al [2005], Fernandez-Zapico et al [2009] / 610508
NEUROD1 (MODY6)	<1% [5]	Overweight/obesity in some	Unknown	Malecki et al [1999], Kristinsson et al [2001] / 606394
PAX4 (MODY9)	<1% [5]		Unknown	Mauvais-Jarvis et al [2004], Plengvidhya et al [2007] / 612225
PDX1 [1] (MODY4)	1% [5]	Overweight/obesity in some	Unknown	Wright et al [1993], Stoffers et al [1997], Fajans et al [2010] / 606392

IUGR = intrauterine growth restriction; OGTT = oral glucose tolerance test

1. Pathogenic variants in this gene are also associated with permanent neonatal diabetes mellitus.

2. Pathogenic variants in this gene are also associated with familial hyperinsulinism.

3. Should be considered in patients responsive to sulfonylurea who test negative for *HNF1A*-MODY and *HNF4A*-MODY

4. Two *APPL1* loss-of-function variants reported

5. Some variants in *BLK*, *KLF11*, *NEUROD1*, *PAX4*, and *PDX1* reported in the Human Gene Mutation Database (HGMD) as pathogenic are present in the Genome Aggregation Database (gnomAD) at population frequencies that are not consistent with their potential clinical significance. Additional studies are necessary to better understand the association of variants in these genes with MODY.

6. One individual had a large *CEL* deletion (429 nucleotides) [Ellard et al 2013].

7. Depending on the population studied

8. ~1.8% of *GCK*-MODY is associated with whole-gene or exon deletions [Garin et al 2008].

9. Steele et al [2014]

10. Frayling et al [1997], Costa et al [2000], Gragnoli et al [2001], Xu et al [2005], Pihoker et al [2013]

11. ~1.2% of *HNF1A*-MODY is associated with whole-gene or exon deletions [Colclough et al 2013].

12. Related to overall glycemic control [Bacon et al 2016a, Bacon et al 2016b]

13. ~33% of *HNF1B*-MODY is associated with whole-gene or exon deletions [Bellanné-Chantelot et al 2005].

14. ~1.9% of *HNF4A*-MODY is associated with whole-gene or exon deletions [Colclough et al 2013].

15. Individuals with *HNF4A*-MODY may also have reduced levels of lipoprotein A1, lipoprotein A2, and HDL cholesterol and increased levels of LDL-cholesterol, similar to the lipid profiles seen in type 2 diabetes mellitus [Pearson et al 2005].

***GCK*-MODY (MODY2)** is characterized by mild, stable fasting hyperglycemia (5.5-8.0 mmol/L; 99-144 mg/dL) present at birth. Beta-cell function shows minimal deterioration with increasing age (as in the general population). Affected individuals are generally asymptomatic and the hyperglycemia is often discovered during

routine medical examinations, such as in pregnancy or family screening when MODY is suspected. Diabetes-related complications are extremely uncommon.

***HNF1A*-MODY (MODY3)** is associated with onset of diabetes in late adolescence or early adulthood. Typically in childhood or early adolescence, glucose tolerance is normal [Lorini et al 2009]. However, prior to developing overt diabetes, *HNF1A* heterozygotes have marked progressive β-cell dysfunction, increased insulin sensitivity, and glycosuria [Stride et al 2005]. Oral glucose tolerance tests in early stages tend to show a very large glucose increment, usually >90 mg/dL [Stride & Hattersley 2002].

Penetrance in *HNF1A*-MODY is high: 63% of affected individuals develop diabetes by age 25 years, 78.6% by age 35 years, and 95.5% by age 55 years [Shepherd et al 2001].

***HNF1B*-MODY (MODY5, or renal cysts and diabetes [RCAD] syndrome)** is a multisystem disorder in which renal involvement is more common than diabetes. Renal manifestations can include structural defects evident at birth and later-onset functional defects.

Of the renal structural defects, the most common are renal cysts, which can be evident prenatally as isolated bilateral hyperechogenic kidneys [Decramer et al 2007]); postnatally the majority of affected individuals have normal-size or small kidneys with hyperechogenicity and/or renal cysts [Heidet et al 2010]. Other structural abnormalities can include absence of a kidney and renal hypoplasia.

Renal functional defects include renal magnesium wasting, which can lead to life-threatening hypomagnesemia, and hyperuricemia, which can manifest as early-onset gout.

Early-onset diabetes mellitus is the most common extrarenal manifestation and usually presents after the identification of childhood-onset renal disease. The mean age of onset of diabetes is 24 years [Chen et al 2010], but ranges from the neonatal period [Edghill et al 2006b] to late middle age [Edghill et al 2006a].

Additional findings can include pancreatic atrophy, genital tract abnormalities in females, abnormal liver function, and primary hyperparathyroidism [Montoli et al 2002, Bellanné-Chantelot et al 2004, Ferrè et al 2013].

HNF1B pathogenic variants include single-nucleotide variants as well as intragenic deletions. In addition, a heterozygous contiguous deletion comprising at least 1.2 Mb at chromosome 17q12 that includes all of *HNF1B* and at least seven (and as many as 14) contiguous genes accounts for approximately 50% of genetic alterations in adults with *HNF1B*-MODY [Bellanné-Chantelot et al 2005, Edghill et al 2008b]. Those with the 17q12 recurrent deletion syndrome may have neurologic features including autism spectrum disorder (ASD) and cognitive impairment [Raile et al 2009, Clissold et al 2015] that are not caused by *HNF1B* haploinsufficiency [Clissold et al 2016].

***HNF4A*-MODY (MODY1).** A dual phenotype is observed in *HNF4A*-MODY: some individuals have transient hyperinsulinemic hypoglycemia in the neonatal period, followed later by diabetes in late adolescence or adulthood. The nature and timing of the transition remain poorly defined [Bacon et al 2016a].

3. Evaluation Strategy to Identify the Genetic Cause of MODY in a Proband

Establishing a specific genetic cause of MODY in an individual whose clinical findings suggest MODY (see Clinical Characteristics) can aid in management of the proband, genetic counseling of family members, and medical surveillance of at-risk family members [Rubio-Cabezas et al 2014].

Establishing the specific genetic cause of MODY usually involves a medical history, family history, physical examination, diabetes-related laboratory testing, and molecular genetic testing.

Medical history. In MODY, diabetes onset is most often in adolescence or young adulthood (age <35 years). Other relevant medical history, such as birth history or complications and other medical problems, varies by genetic cause (Table 1). A history of developmental renal disease, particularly cystic renal disease, should prompt suspicion of *HNF1B*-MODY.

Family history. A three-generation family history should be obtained, with attention to relatives with diabetes mellitus and documentation of relevant findings (e.g., age at onset of diabetes, body habitus at onset, insulin independence) either through direct examination or review of medical records, including results of any molecular genetic testing. As heterozygous pathogenic variants in *HNF1B* can cause renal disease in isolation and diabetes in isolation, a family history of multiple individuals with renal disease and others with diabetes should also raise consideration of *HNF1B*-MODY.

Physical examination. Although MODY is typically characterized by and compatible with normal weight or mildly overweight status, obesity does occur in some of the uncommon genetic causes of MODY. Furthermore, obesity can coexist with any type of MODY. In one study at least 4.5% of obese and overweight adolescents enrolled in a clinical trial to treat type 2 diabetes had MODY (mostly *HNF4A*-MODY, *GCK*-MODY, or *HNF1A*-MODY) [Kleinberger et al 2018]. Since MODY does not protect one from being overweight, MODY may occur together with insulin resistance.

Other than findings consistent with gout (suggestive of *HNF1B*-MODY), no findings on physical examination can distinguish one cause of MODY from others.

Laboratory testing

- In *GCK*-MODY, the levels of serum glucose and hemoglobin A1c (HbA1c) can help with diagnosis because they will fall within the following expected ranges:
  - **Fasting serum glucose.** Typical range 99-144 mg/dL (5.49-7.99 mmol/L) [Ellard et al 2008]
  - **HbA1c.** Typical range 5.6%-7.3% (38-56 mmol/mol) at age ≤40 years and 5.9%-7.6% (41-60 mmol/mol) at age >40 years [Steele et al 2013]
- High-sensitivity C-reactive protein (hsCRP) is useful as values are lower in *HNF1A*-MODY (i.e., <0.75 mg/L) than in other forms of diabetes [McDonald et al 2011b, Thanabalasingham et al 2011].

Molecular genetic testing approaches to determine the associated MODY gene can include a combination of **gene-targeted testing** (serial singe-gene or multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis or exome sequencing), depending on the phenotype.

Single-gene testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because of the clinical and genetic heterogeneity of MODY, the genetic cause of MODY in a person with the distinctive clinical findings described in Table 1 could be established by single-gene (or serial single-gene) testing (see Option 1), whereas those with a phenotype indistinguishable from other genetic causes of MODY are more likely to be diagnosed using a multigene panel (see Option 2). If the genetic cause is not identified using clinically available testing or if the individual has additional clinical features, comprehensive genomic testing (see Option 3) may be considered.

Option 1

When the phenotypic and laboratory findings are consistent with one or more genetic causes of MODY (Table 1), molecular genetic testing approaches to define the genetic cause can include **serial single-gene testing**, use of a **multigene panel**, and/or **CMA**.

Serial single-gene testing. Sequence analysis of the most likely genes is performed first. If no pathogenic variant is found, gene-targeted deletion/duplication analysis to detect exon-sized deletions could be considered,

especially for those genes (*CEL*, *GCK*, *HNF1A*, *HNF1B*, and *HNF4A)* in which whole-gene or multiexon deletions have been identified.

Option 2

A MODY multigene panel that includes the 14 known MODY-related genes and other genes of interest is most likely to identify the genetic cause of MODY at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype [Ellard et al 2013, Alkorta-Aranburu et al 2016]. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some custom laboratory-designed multigene panels may include genes not associated with MODY but possibly associated with other types of monogenic diabetes; other custom laboratory-designed panels may not include the genes that rarely cause MODY. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that include genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. Note: Given that whole-gene and/or multiexon deletions have been identified in *GCK*, *HNF1A*, *HNF1B*, and *HNF4A* (Table 1), a multigene panel that also includes deletion/duplication analysis is recommended.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Chromosomal microarray analysis (CMA) using oligonucleotide comparative genomic hybridization (CGH) or single-nucleotide polymorphism (SNP) arrays may be considered in the following cases:

- In individuals with distinguishing phenotypic features suggestive of a contiguous gene deletion, such as the 17q12 recurrent deletion syndrome, which is associated with a 1.2-Mb (megabase) or larger deletion that includes *HNF1B*
- To estimate the breakpoints and size of a whole-gene deletion detected by gene-targeted deletion/duplication analysis

Option 3

Exome sequencing does not require the clinician to determine which gene is likely causative. Furthermore, it may be possible to reanalyze existing exome sequencing data for MODY-related genes not included in the multigene panel used to test a given patient.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Management of MODY Based on Genetic Cause

Table 2. MODY: Management by Genetic Cause

Gene	Pathophysiology	Treatment				References
		None	Diet	OAD	Insulin	
ABCC8	ATP-sensitive potassium channel dysfunction			Sulfonylureas		Bowman et al [2012]
APPL1	Insulin secretion defect		X	X	X	Prudente et al [2015]

Table 2. continued from previous page.

Gene	Pathophysiology	Treatment				References
		None	Diet	OAD	Insulin	
BLK	Insulin secretion defect		X	X	X	Borowiec et al [2009]
CEL	Pancreatic endocrine & exocrine dysfunction			X	X	Raeder et al [2006]
GCK	β-cell dysfunction (glucose-sensing defect)	Except possibly in pregnancy [1]				Stride et al [2014], Chakera et al [2015]
HNF1A	β-cell dysfunction; mainly insulin secretory defect			Low-dose sulfonylureas or meglitinides; GLP-1 agonists also used	May be required [2]	Shepherd et al [2003], Tuomi et al [2006], Østoft et al [2014], Bacon et al [2016b]
HNF1B	β-cell dysfunction			A minority respond to sulfonylureas.	Commonly needed	Dubois-Laforgue et al [2017]
HNF4A	β-cell dysfunction (mainly insulin secretory defect)			Sensitive to sulfonylureas		Pearson et al [2005]
INS	β-cell dysfunction		X	X	X [3]	Molven et al [2008], Boesgaard et al [2010]
KCNJ11	ATP-sensitive potassium channel dysfunction		X	Sulfonylureas	X	Bonnefond et al [2012], Liu et al [2013]
KLF11	Decreased glucose sensitivity of β-cells			X	X	Neve et al [2005]
NEUROD1	β-cell dysfunction		X	X	X	Malecki et al [1999], Kristinsson et al [2001]
PAX4	β-cell dysfunction		X	X	X	Mauvais-Jarvis et al [2004], Plengvidhya et al [2007]
PDX1	β-cell dysfunction		X	X	X	Clocquet et al [2000], Fajans et al [2010]

GLP-1 = glucagon-like peptide-1; OAD = oral antidiabetic agents

1. Depending on genotype of the fetus (see Table 3) [Spyer et al 2001]

2. Patients with *HNF1A*-MODY and diabetes of several years' duration may continue to require insulin.

3. May require only small doses of insulin

***GCK*-MODY** is associated with mild, stably increased fasting blood sugars and HbA1c ranging from 5.6% to 7.6% [Steele et al 2013]. Insulin secretion and regulation are fully intact. Comparison of cohorts with *GCK*-MODY on treatment versus on no treatment does not show significant differences in HbA1c. Moreover, studies have shown that discontinuing pharmacologic therapy does not alter HbA1c [Stride et al 2014]. For this reason, *GCK*-MODY in isolation (i.e., without co-occurrence of type 1 or type 2 diabetes or pregnancy) does not require pharmacologic therapy [Chakera et al 2015].

At the level of glycemic control observed in *GCK*-MODY, long-term complications are rare. In a cross-sectional study of long-term complications in adults with *GCK*-MODY (mean age 48.6 years), only the prevalence of non-proliferative (also known as background) retinopathy was increased compared to healthy controls [Steele et al 2014]. Thus, it would be reasonable to screen annually for retinopathy in older individuals with *GCK*-MODY;

however, annual screening for other microvascular and macrovascular complications typically associated with diabetes appears to be low-yield.

The co-occurrence of type 1 or type 2 diabetes. Treatment is dictated by the type of co-occurring diabetes. Clinicians should continue to account for the increased set point for glucose-stimulated insulin secretion as well as lower threshold for counter-regulation seen in *GCK*-MODY by setting the HbA1c treatment goal within the expected range for *GCK*-MODY [Uday et al 2014].

Pregnancy in a woman with *GCK*-MODY. Insulin may be required; recommendations for treatment are based on the known or inferred fetal genotype [Spyer et al 2001, Chakera et al 2015] (Table 3).

Fetal genotype:

- **Known.** Genotyping the fetus solely for prenatal management is not recommended due to the risks associated with invasive prenatal testing; however, when such testing is performed for other indications, determining if the fetus has inherited the maternal *GCK* pathogenic variant is helpful.
- **Inferred**. Using abdominal circumference measurements obtained on second trimester ultrasound examination, it is assumed that a fetal abdominal circumference >75th centile indicates that the fetus has not inherited the maternal *GCK* pathogenic variant [Chakera et al 2015].

Fetal outcome:

- If the fetus has inherited the maternal GCK pathogenic variant, the fetus will produce normal amounts of insulin and grow normally. Current recommendations do not support use of insulin in the mother.
- If the fetus has not inherited the maternal GCK pathogenic variant, the fetus will respond to maternal hyperglycemia with excess insulin production resulting in excess growth. While current recommendations are to treat the mother with insulin to decrease the risk of macrosomia, data to support these recommendations are limited.
- Note: While more data currently support fetal genotype-based treatment, some advocate treating all women with GCK-MODY with insulin early in pregnancy [Bacon et al 2015]. Additional studies on pregnancy management and outcomes are warranted.

Additional considerations:

- Glycemic excursions are difficult to manage with insulin in GCK-MODY as exogenous insulin will suppress endogenous insulin secretion and counter-regulation occurs at a lower blood glucose value [Guenat et al 2000]. High doses of insulin may be required [Bacon et al 2015, Chakera et al 2015, Hattersley & Patel 2017].
- If the fetus inherits a GCK pathogenic variant from the father or has a de novo GCK pathogenic variant, the fetus will have decreased insulin secretion leading to lower birth weight.

Table 3. Influence of Parental and Fetal Genotype on Fetal Growth and Recommended Management of the Mother during a Pregnancy at Risk for *GCK*-MODY

Source of *GCK* Pathogenic Variant	Fetal Growth and Recommended Management during Pregnancy: *GCK* Variant Present in Fetus? [1]			
	Yes		No	
	Fetal growth	Treatment	Fetal growth [2]	Treatment [3]
Mother	Normal	None	Birth weight >700 g compared to normal (i.e., fetus with maternal *GCK* variant)	Insulin is recommended (dose required to ↓ mother's fasting glucose is > replacement dose). Consider delivery at 38 wks' gestation when abdominal circumference >75th %ile.

Table 3. continued from previous page.

Source of *GCK* Pathogenic Variant	Fetal Growth and Recommended Management during Pregnancy: *GCK* Variant Present in Fetus? [1]			
	Yes		No	
	Fetal growth	Treatment	Fetal growth [2]	Treatment [3]
Father (or *de novo*)	Restricted: birth weight 400 g < normal	None	Normal	None

1. When the fetal genotype is not known, it can be inferred from abdominal circumference on second trimester fetal ultrasound.
2. Assessed by second-trimester ultrasound [Spyer et al [2001]
3. Chakera et al [2015], Colom & Corcoy [2010]

***HNF1A*-MODY.** The first-line therapy is low dose sulfonylureas which act downstream of the genetic defect and increase insulin secretion via a glucose-independent mechanism [Bacon et al 2016b].

Patients with *HNF1A*-MODY previously misdiagnosed with type 1 diabetes and treated with insulin may be able to discontinue insulin therapy and start treatment with sulfonylureas without the risk of ketoacidosis [Shepherd et al 2003]. Transition from insulin to sulfonylureas is often associated with a decrease in HbA1c which is associated with decreased diabetes-related complications [Bacon et al 2016b]. These observations plus the low cost of sulfonylureas make them particularly appropriate for treatment of *HNF1A*-MODY.

In the US, glyburide is the most commonly used sulfonylurea for *HNF1A*-MODY. Starting doses should be low and insulin doses may need to be lowered or discontinued to avoid hypoglycemia.

Because individuals with *HNF1A*-MODY have normal or even increased insulin sensitivity, sulfonylureas can (even at low doses) cause hypoglycemia, which may limit their use in some patients. In such cases, treatment with meglitinides (which act on the same receptor as sulfonylureas, but with decreased binding affinity and decreased duration of action) can be considered. Studies showed that in *HNF1A*-MODY nateglinide caused lower postprandial glucose levels and reduced the risk of hypoglycemia compared to the sulfonylurea glibenclamide [Tuomi et al 2006]. GLP-1 agonists have also been effective in treating *HNF1A*-MODY. The glucose-lowering effect of liraglutide and risk of hypoglycemia are less than those of the sulfonylurea glimepiride [Østoft et al 2014].

Over time the glycemic control of sulfonylureas may deteriorate in individuals with *HNF1A*-MODY, especially those who are obese [Bacon et al 2016b]. The best augmentative therapy is unclear; GLP-1 agonists and insulin therapy are appropriate options.

Because of the increased risk of cardiovascular disease (despite the accompanying elevated levels of HDL and low levels of high-sensitivity C- reactive protein (hsCRP), persons with *HNF1A*-MODY should be treated with statin therapy by age 40 years [Steele et al 2010].

Hyperglycemia during pregnancy in a woman with *HNF1A*-MODY can be managed with sulfonylureas or insulin and result in normal-size infants. However, there are concerns regarding placental transfer of sulfonylureas. Of note, a meta-analysis showed increased risk of macrosomia and neonatal hypoglycemia in pregnancies treated with glyburide compared to insulin [Poolsup et al 2014].

Of note, the background risk for birth defects in the general population is approximately 3%-4%. Women who have pre-pregnancy insulin-dependent diabetes are at increased risk of having a child with a birth defect (~6%-8% risk). Women with non-insulin dependent diabetes prior to pregnancy are also at risk greater than the general population of having a baby with a birth defect; however, their risk is less than that of women who have insulin-dependent diabetes prior to pregnancy.

Appropriate glycemic control during pregnancy may reduce (though does not eliminate) the risk of having a child with a birth defect and also decrease the risk of having a child with neonatal diabetes-related complications

(e.g., macrosomia, hypoglycemia, and electrolyte abnormalities). In a meta-analysis by Silva et al [2012] the rate of birth defects was not significantly different between women who took an oral hypoglycemic (including glyburide) and women who required insulin to treat diabetes during pregnancy. Given the risks to the fetus associated with diabetes during pregnancy, aggressive treatment of chronic maternal hyperglycemia is recommended.

To screen for fetal birth defects in pregnant women with diabetes, prenatal high-resolution ultrasound with fetal echocardiogram is recommended; referral to a maternal-fetal medicine specialist may also be considered.

See MotherToBaby for more information on the use of medications during pregnancy [Silva et al 2012].

***HNF1B*-MODY.** Despite significant homology between the transcription factors HNF1A and HNF1B, *HNF1B*-MODY does not show the same sensitivity to sulfonylureas as *HNF1A*-MODY. Insulin sensitivity to endogenous glucose is decreased even though peripheral insulin sensitivity is normal [Brackenridge et al 2006]. While some individuals with *HNF1B*-MODY respond to oral medications, including sulfonylureas, insulin therapy is often required [Brackenridge et al 2006, Dubois-Laforgue et al 2017].

***HNF4A*-MODY.** As with *HNF1A*-MODY, sulfonylureas are the established first-line treatment for *HNF4A*-MODY [Pearson et al 2005]. It is reasonable to assume that individuals with *HNF4A*-MODY (like those with *HNF1A*-MODY) may respond to meglitinides and GLP-1 agonists; however, no formal data support this assumption.

Other. Data on treatment outcomes of MODY of rare causes are unavailable and, thus, treatment relies on clinical judgment. Reported treatment of individuals is found in Table 2.

5. Risk Assessment and Surveillance of At-Risk Relatives for Early Detection and Treatment of MODY

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

The advantages of early clarification of the genetic status of asymptomatic family members at risk for MODY:

- Routine surveillance to identify hyperglycemia enables prompt and appropriate treatment based on the type of MODY (Table 2).
- For those at increased risk, early intervention reduces the long-term risk of hyperglycemia-related microvascular and macrovascular complications [Bacon et al 2016a, Bacon et al 2016b].
- Families with individuals with MODY as well as the much more common type 1 and type 2 diabetes [Uday et al 2014] can be assured that each individual will receive the appropriate surveillance and therapy for his/her diagnosis.

Studies have shown that family members at risk for MODY are generally in favor of early predictive genetic testing [Liljeström et al 2007, Bosma et al 2015].

Mode of Inheritance

Maturity-onset diabetes of the young (MODY) is generally inherited in an autosomal dominant manner. *De novo* pathogenic variants do occur.

Note: Biallelic pathogenic variants in *PDX1* are associated with pancreatic agenesis, and biallelic pathogenic variants in *GCK* are associated with permanent neonatal diabetes. Autosomal recessive inheritance of *PDX1*-related pancreatic agenesis and *GCK*-related permanent neonatal diabetes are not addressed in this *GeneReview*; see Permanent Neonatal Diabetes for more information on these phenotypes and recurrence risks.

Risk to Family Members

Table 4. Risk Assessment of Family Members of a Proband with Maturity-Onset Diabetes of the Young (MODY)

Family Members	Clinical & Genetic Status Possibilities	Evaluation of Apparently Asymptomatic Family Member: MODY-Related Pathogenic Variant Identified in Proband?	
		Yes	No
Parents of proband	• Affected & heterozygous for MODY-related pathogenic or likely pathogenic variant OR • Apparently asymptomatic & heterozygous due to reduced penetrance or variable expressivity OR • Not heterozygous because either: ◦ Pathogenic or likely pathogenic variant was *de novo* in proband [1, 2] ◦ Parental germline mosaicism	Molecular genetic testing • If familial pathogenic or likely pathogenic variant is identified, surveillance for early manifestations of MODY (see Management) • If familial pathogenic or likely pathogenic variant is not identified, monitoring consistent w/standard of care for general population	Surveillance for early manifestations of MODY (see Management)
Sibs of proband	• If one parent of the proband is affected/heterozygous: 50% risk to sibs of inheriting variant / being at risk for MODY • If the proband has a known MODY-related pathogenic variant that is not detectable in leukocyte DNA of either parent: ~1% recurrence risk to sibs due to the theoretic possibility of parental germline mosaicism [3]		
Offspring of proband	50% chance of inheriting the MODY-related pathogenic or likely pathogenic variant		
Other family members	If a parent is heterozygous for a MODY-related pathogenic variant, his/her family members may be at risk.		

1. The proportion of cases caused by a *de novo* pathogenic variant is unknown for the majority of MODY-related genes. In 17q12 recurrent deletion syndrome (associated with MODY5), 70% of affected individuals have a *de novo* genetic alteration. A limited number of case reports describe de *novo* variants in *GCK, HNF1A*, and *HNF4A*; based on one small study, the *de novo* rate for these genes may approach 7% [Stanik et al 2014].
2. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.
3. Rahbari et al [2016]

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Diabetes Association**
  Phone: 800-DIABETES (800-342-2383)
  Email: AskADA@diabetes.org
  diabetes.org
- **Diabetes Genes**
  Providing information for patients and professionals on research and clinical care in genetic types of diabetes.
  United Kingdom
  diabetesgenes.org
- **Diabetes UK**
  United Kingdom
  Phone: 0345 123 2399
  Email: helpline@diabetes.org.uk
  www.diabetes.org.uk
- **International Society for Pediatric and Adolescent Diabetes (ISPAD)**
  Phone: +49 (0)30 24603-210
  Email: secretariat@ispad.org
  ispad.org

References

Published Guidelines / Policy Statements

ABMG Board of Directors. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. Genet Med. 2015;17:68–9. PubMed PMID: 25356965.

Literature Cited

Alkorta-Aranburu G, Sukhanova M, Carmody D, Hoffman T, Wysinger L, Keller-Ramey J, Li Z, Johnson AK, Kobiernicki F, Botes S, Fitzpatrick C, Das S, Del Gaudio D. Improved molecular diagnosis of patients with neonatal diabetes using a combined next-generation sequencing and MS-MLPA approach. J Pediatr Endocrinol Metab. 2016; 2016;29:523–31. PubMed PMID: 26894574.

Bacon S, Kyithar MP, Condron EM, Vizzard N, Burke M, Byrne MM. Prolonged episodes of hypoglycaemia in HNF4A-MODY mutation carriers with IGT. Evidence of persistent hyperinsulinism into early adulthood. Acta Diabetol. 2016a;53:965–72. PubMed PMID: 27552834.

Bacon S, Kyithar MP, Rizvi SR, Donnelly E, Mccarthy A, Burke M, Colclough K, Ellard S, Byrne MM. Successful maintenance on sulphonylurea therapy and low diabetes complication rates in a HNF1A-MODY cohort. Diabet Med. 2016b;33:976–84. PubMed PMID: 26479152.

Bacon S, Schmid J, McCarthy A, Edwards J, Fleming A, Kinsley B, Firth R, Byrne B, Gavin C, Byrne MM. The clinical management of hyperglycemia in pregnancy complicated by maturity-onset diabetes of the young. Am J Obstet Gynecol. 2015;213:236.e1–7. PubMed PMID: 25935773.

Bellanné-Chantelot C, Chauveau D, Gautier JF, Dubois-Laforgue D, Clauin S, Beaufils S, Wilhelm JM, Boitard C, Noël LH, Velho G, Timsit J. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med. 2004;140:510–7. PubMed PMID: 15068978.

Bellanné-Chantelot C, Clauin S, Chauveau D, Collin P, Daumont M, Douillard C, Dubois-Laforgue D, Dusselier L, Gautier JF, Jadoul M, Laloi-Michelin M, Jacquesson L, Larger E, Louis J, Nicolino M, Subra JF, Wilhem JM, Young J, Velho G, Timsit J. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. Diabetes. 2005;54:3126–32. PubMed PMID: 16249435.

Besser RE, Ludvigsson J, Jones AG, McDonald TJ, Shields BM, Knight BA, Hattersley AT. Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with type 1 diabetes. Diabetes Care. 2011;34:607–9. PubMed PMID: 21285386.

Boesgaard TW, Pruhova S, Andersson EA, Cinek O, Obermannova B, Lauenborg J, Damm P, Bergholdt R, Pociot F, Pisinger C, Barbetti F, Lebl J, Pedersen O, Hansen T. Further evidence that mutations in INS can be a rare cause of maturity-onset diabetes of the young (MODY). BMC Med Genet. 2010;11:42. PubMed PMID: 20226046.

Bonnefond A, Philippe J, Durand E, Dechaume A, Huyvaert M, Montagne L, Marre M, Balkau B, Fajardy I, Vambergue A, Vatin V, Delplanque J, Le Guilcher D, De Graeve F, Lecoeur C, Sand O, Vaxillaire M, Froguel P. Whole-exome sequencing and high throughput genotyping identified KCNJ11 as the thirteenth MODY gene. PLoS One. 2012;7:e37423. PubMed PMID: 22701567.

Borowiec M, Liew CW, Thompson R, Boonyasrisawat W, Hu J, Mlynarski WM, El Khattabi I, Kim SH, Marselli L, Rich SS, Krolewski AS, Bonner-Weir S, Sharma A, Sale M, Mychaleckyj JC, Kulkarni RN, Doria A. Mutations at the BLK locus linked to maturity onset diabetes of the young and beta-cell dysfunction. Proc Natl Acad Sci U S A. 2009;106:14460–5. PubMed PMID: 19667185.

Bosma AR, Rigter T, Weinreich SS, Cornel MC, Henneman L. A genetic diagnosis of maturity-onset diabetes of the young (MODY): experiences of patients and family members. Diabet Med. 2015;32:1385–92. PubMed PMID: 25763774.

Bowman P, Flanagan SE, Edghill EL, Damhuis A, Shepherd MH, Paisey R, Hattersley AT, Ellard S. Heterozygous ABCC8 mutations are a cause of MODY. Diabetologia. 2012;55:123–7. PubMed PMID: 21989597.

Brackenridge A, Pearson ER, Shojaee-Moradie F, Hattersley AT, Russell-Jones D, Umpleby AM. Contrasting insulin sensitivity of endogenous glucose production rate in subjects with hepatocyte nuclear factor-1beta and -1alpha mutations. Diabetes. 2006;55:405–11. PubMed PMID: 16443774.

Carmody D, Naylor RN, Bell CD, Berry S, Montgomery JT, Tadie EC, Hwang JL, Greeley SA, Philipson LH. GCK-MODY in the US National Monogenic Diabetes Registry: frequently misdiagnosed and unnecessarily treated. Acta Diabetol. 2016;53:703–8. PubMed PMID: 27106716.

Chakera AJ, Spyer G, Vincent N, Ellard S, Hattersley AT, Dunne FP. The 0.1% of the population with glucokinase monogenic diabetes can be recognized by clinical characteristics in pregnancy: the Atlantic Diabetes in Pregnancy cohort. Diabetes Care. 2014;37:1230–6. PubMed PMID: 24550216.

Chakera AJ, Steele AM, Gloyn AL, Shepherd MH, Shields B, Ellard S, Hattersley AT. Recognition and management of individuals with hyperglycemia because of a heterozygous glucokinase mutation. Diabetes Care. 2015;38:1383–92. PubMed PMID: 26106223.

Chen YZ, Gao Q, Zhao XZ, Chen YZ, Bennett CL, Xiong XS, Mei CL, Shi YQ, Chen XM. Systematic review of TCF2 anomalies in renal cysts and diabetes syndrome/maturity onset diabetes of the young type 5. Chin Med J (Engl). 2010;123:3326–33. PubMed PMID: 21163139.

Clissold RL, Hamilton AJ, Hattersley AT, Ellard S, Bingham C. HNF1B-associated renal and extra-renal disease-an expanding clinical spectrum. Nat Rev Nephrol. 2015;11:102–12. PubMed PMID: 25536396.

Clissold RL, Shaw-Smith C, Turnpenny P, Bunce B, Bockenhauer D, Kerecuk L, Waller S, Bowman P, Ford T, Ellard S, Hattersley AT, Bingham C. Chromosome 17q12 microdeletions but not intragenic HNF1B mutations link developmental kidney disease and psychiatric disorder. Kidney Int. 2016;90:203–11. PubMed PMID: 27234567.

Clocquet AR, Egan JM, Stoffers DA, Muller DC, Wideman L, Chin GA, Clarke WL, Hanks JB, Habener JF, Elahi D. Impaired insulin secretion and increased insulin sensitivity in familial maturity-onset diabetes of the young 4 (insulin promoter factor 1 gene). Diabetes. 2000;49:1856–64. PubMed PMID: 11078452.

Colclough K, Bellanné-Chantelot C, Saint-Martin C, Flanagan SE, Ellard S. Mutations in the genes encoding the transcription factors hepatocyte nuclear factor 1 alpha and 4 alpha in maturity-onset diabetes of the young and hyperinsulinemic hypoglycemia. Hum Mutat. 2013;34:669–85. PubMed PMID: 23348805.

Colom C, Corcoy R. Maturity onset diabetes of the young and pregnancy. Best Pract Res Clin Endocrinol Metab. 2010;24:605–15. PubMed PMID: 20832739.

Costa A, Bescos M, Velho G, Chevre J, Vidal J, Sesmilo G, Bellanné-Chantelot C, Froguel P, Casamitjana R, Rivera-Fillat F, Gomis R, Conget I. Genetic and clinical characterisation of maturity-onset diabetes of the young in Spanish families. Eur J Endocrinol. 2000;142:380–6. PubMed PMID: 10754480.

Decramer S, Parant O, Beaufils S, Clauin S, Guillou C, Kessler S, Aziza J, Bandin F, Schanstra JP, Bellanné-Chantelot C. Anomalies of the TCF2 gene are the main cause of fetal bilateral hyperechogenic kidneys. J Am Soc Nephrol. 2007;18:923–33. PubMed PMID: 17267738.

Dubois-Laforgue D, Cornu E, Saint-Martin C, Coste J, Bellanné-Chantelot C, Timsit J, et al. Diabetes, associated clinical spectrum, long-term prognosis and genotype/phenotype correlations in 201 adult patients with hepatocyte nuclear factor 1 B (HNF1B) molecular defects. Diabetes Care. 2017;40:1436–43. PubMed PMID: 28420700.

Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. J Med Genet. 2006a;43:84–90. PubMed PMID: 15930087.

Edghill EL, Bingham C, Slingerland AS, Minton JA, Noordam C, Ellard S, Hattersley AT. Hepatocyte nuclear factor-1 beta mutations cause neonatal diabetes and intrauterine growth retardation: support for a critical role of HNF-1beta in human pancreatic development. Diabet Med. 2006b;23:1301–6. PubMed PMID: 17116179.

Edghill EL, Flanagan SE, Patch AM, Boustred C, Parrish A, Shields B, Shepherd MH, Hussain K, Kapoor RR, Malecki M, Macdonald MJ, Stoy J, Steiner DF, Philipson LH, Bell GI. Neonatal Diabetes International Collaborative G, Hattersley AT, Ellard S. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. Diabetes. 2008a;57:1034–42. PubMed PMID: 18162506.

Edghill EL, Oram RA, Owens M, Stals KL, Harries LW, Hattersley AT, Ellard S, Bingham C. Hepatocyte nuclear factor-1beta gene deletions--a common cause of renal disease. Nephrol Dial Transplant. 2008b;23:627–35. PubMed PMID: 17971380.

Ellard S, Bellanné-Chantelot C, Hattersley AT, et al. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. Diabetologia. 2008;51:546–53. PubMed PMID: 18297260.

Ellard S, Lango Allen H, De Franco E, Flanagan SE, Hysenaj G, Colclough K, Houghton JA, Shepherd M, Hattersley AT, Weedon MN, Caswell R. Improved genetic testing for monogenic diabetes using targeted next-generation sequencing. Diabetologia. 2013;56:1958–63. PubMed PMID: 23771172.

Estalella I, Rica I, Perez De Nanclares G, Bilbao JR, Vazquez JA, San Pedro JI, Busturia MA, Castano L, Spanish MG. Mutations in GCK and HNF-1alpha explain the majority of cases with clinical diagnosis of MODY in Spain. Clin Endocrinol (Oxf). 2007;67:538–46. PubMed PMID: 17573900.

Faguer S, Decramer S, Chassaing N, Bellanné-Chantelot C, Calvas P, Beaufils S, Bessenay L, Lengele JP, Dahan K, Ronco P, Devuyst O, Chauveau D. Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. Kidney Int. 2011;80:768–76. PubMed PMID: 21775974.

Fajans SS, Bell GI, Paz VP, Below JE, Cox NJ, Martin C, Thomas IH, Chen M. Obesity and hyperinsulinemia in a family with pancreatic agenesis and MODY caused by the IPF1 mutation Pro63fsX60. Transl Res. 2010;156:7–14. PubMed PMID: 20621032.

Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. N Engl J Med. 2001;345:971–80. PubMed PMID: 11575290.

Fernandez-Zapico ME, Van Velkinburgh JC, Gutierrez-Aguilar R, Neve B, Froguel P, Urrutia R, Stein R. MODY7 gene, KLF11, is a novel p300-dependent regulator of Pdx-1 (MODY4) transcription in pancreatic islet beta cells. J Biol Chem. 2009;284:36482–90. PubMed PMID: 19843526.

Ferrè S, Bongers EM, Sonneveld R, Cornelissen EA, Van Der Vlag J, Van Boekel GA, Wetzels JF, Hoenderop JG, Bindels RJ, Nijenhuis T. Early development of hyperparathyroidism due to loss of PTH transcriptional repression in patients with HNF1beta mutations? J Clin Endocrinol Metab. 2013;98:4089–96. PubMed PMID: 23979948.

Frayling TM, Bulamn MP, Ellard S, Appleton M, Dronsfield MJ, Mackie AD, Baird JD, Kaisaki PJ, Yamagata K, Bell GI, Bain SC, Hattersley AT. Mutations in the hepatocyte nuclear factor-1alpha gene are a common cause of maturity-onset diabetes of the young in the U.K. Diabetes. 1997;46:720–5. PubMed PMID: 9075818.

Froguel P, Zouali H, Vionnet N, Velho G, Vaxillaire M, Sun F, Lesage S, Stoffel M, Takeda J, Passa P, et al. Familial hyperglycemia due to mutations in glucokinase. Definition of a subtype of diabetes mellitus. N Engl J Med. 1993;328:697–702. PubMed PMID: 8433729.

Garin I, Rica I, Estalella I, Oyarzabal M, Rodriguez-Rigual M, San Pedro JI, Perez-Nanclares G, Fernandez-Rebollo E, Busturia MA, Castano L, Perez De Nanclares G, Spanish MG. Haploinsufficiency at GCK gene is not a frequent event in MODY2 patients. Clin Endocrinol (Oxf). 2008;68:873–8. PubMed PMID: 18248649.

Gragnoli C, Cockburn BN, Chiaramonte F, Gorini A, Marietti G, Marozzi G, Signorini AM. Early-onset Type II diabetes mellitus in Italian families due to mutations in the genes encoding hepatic nuclear factor 1 alpha and glucokinase. Diabetologia. 2001;44:1326–9. PubMed PMID: 11692182.

Guenat E, Seematter G, Philippe J, Temler E, Jequier E, Tappy L. Counterregulatory responses to hypoglycemia in patients with glucokinase gene mutations. Diabetes Metab. 2000;26:377–84. PubMed PMID: 11119017.

Harjutsalo V, Lammi N, Karvonen M, Groop PH. Age at onset of type 1 diabetes in parents and recurrence risk in offspring. Diabetes. 2010;59:210–4. PubMed PMID: 19833881.

Hattersley AT, Patel KA. Precision diabetes: learning from monogenic diabetes. Diabetologia. 2017;60:769–77. PubMed PMID: 28314945.

Heidet L, Decramer S, Pawtowski A, Moriniere V, Bandin F, Knebelmann B, Lebre AS, Faguer S, Guigonis V, Antignac C, Salomon R. Spectrum of HNF1B mutations in a large cohort of patients who harbor renal diseases. Clin J Am Soc Nephrol. 2010;5:1079–90. PubMed PMID: 20378641.

Johansson BB, Torsvik J, Bjorkhaug L, Vesterhus M, Ragvin A, Tjora E, Fjeld K, Hoem D, Johansson S, Raeder H, Lindquist S, Hernell O, Cnop M, Saraste J, Flatmark T, Molven A, Njolstad PR. Diabetes and pancreatic exocrine dysfunction due to mutations in the carboxyl ester lipase gene-maturity onset diabetes of the young (CEL-MODY): a protein misfolding disease. J Biol Chem. 2011;286:34593–605. PubMed PMID: 21784842.

Kim SH, Ma X, Weremowicz S, Ercolino T, Powers C, Mlynarski W, Bashan KA, Warram JH, Mychaleckyj J, Rich SS, Krolewski AS, Doria A. Identification of a locus for maturity-onset diabetes of the young on chromosome 8p23. Diabetes. 2004;53:1375–84. PubMed PMID: 15111509.

Kleinberger JW, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, Linder B, Shuldiner AR, Tollefson S, White NH, Pollin TI. Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. Genet Med. 2018;20:583–90. PubMed PMID: 29758564.

Kristinsson SY, Thorolfsdottir ET, Talseth B, Steingrimsson E, Thorsson AV, Helgason T, Hreidarsson AB, Arngrimsson R. MODY in Iceland is associated with mutations in HNF-1alpha and a novel mutation in NeuroD1. Diabetologia. 2001;44:2098–103. PubMed PMID: 11719843.

Liljeström B, Tuomi T, Isomaa B, Sarelin L, Aktan-Collan K, Kääriäinen H. Adolescents at risk for MODY3 diabetes prefer genetic testing before adulthood. Diabetes Care. 2007;30:1571–3. PubMed PMID: 17351287.

Liu L, Nagashima K, Yasuda T, Liu Y, Hu HR, He G, Feng B, Zhao M, Zhuang L, Zheng T, Friedman TC, Xiang K. Mutations in KCNJ11 are associated with the development of autosomal dominant, early-onset type 2 diabetes. Diabetologia. 2013;56:2609–18. PubMed PMID: 24018988.

Lorini R, Klersy C, D'annunzio G, Massa O, Minuto N, Iafusco D, Bellanné-Chantelot C, Frongia AP, Toni S, Meschi F, Cerutti F, Barbetti F, et al. Maturity-onset diabetes of the young in children with incidental hyperglycemia: a multicenter Italian study of 172 families. Diabetes Care. 2009;32:1864–6. PubMed PMID: 19564454.

Ludvigsson J, Carlsson A, Forsander G, Ivarsson S, Kockum I, Lernmark A, Lindblad B, Marcus C, Samuelsson U. C-peptide in the classification of diabetes in children and adolescents. Pediatr Diabetes. 2012;13:45–50. PubMed PMID: 21910810.

Malecki MT, Jhala US, Antonellis A, Fields L, Doria A, Orban T, Saad M, Warram JH, Montminy M, Krolewski AS. Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus. Nat Genet. 1999;23:323–8. PubMed PMID: 10545951.

Mauvais-Jarvis F, Smith SB, Le May C, Leal SM, Gautier JF, Molokhia M, Riveline JP, Rajan AS, Kevorkian JP, Zhang S, Vexiau P, German MS. Vaisse C. PAX4 gene variations predispose to ketosis-prone diabetes. Hum Mol Genet. 2004;13:3151–9. PubMed PMID: 15509590.

McDonald TJ, Colclough K, Brown R, Shields B, Shepherd M, Bingley P, Williams A, Hattersley AT, Ellard S. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet Med. 2011a;28:1028–33. PubMed PMID: 21395678.

McDonald TJ, Shields BM, Lawry J, Owen KR, Gloyn AL, Ellard S, Hattersley AT. High-sensitivity CRP discriminates HNF1A-MODY from other subtypes of diabetes. Diabetes Care. 2011b;34:1860–2. PubMed PMID: 21700917.

Meur G, Simon A, Harun N, Virally M, Dechaume A, Bonnefond A, Fetita S, Tarasov AI, Guillausseau PJ, Boesgaard TW, Pedersen O, Hansen T, Polak M, Gautier JF, Froguel P, Rutter GA, Vaxillaire M. Insulin gene mutations resulting in early-onset diabetes: marked differences in clinical presentation, metabolic status, and pathogenic effect through endoplasmic reticulum retention. Diabetes. 2010;59:653–61. PubMed PMID: 20007936.

Molven A, Ringdal M, Nordbo AM, Raeder H, Stoy J, Lipkind GM, Steiner DF, Philipson LH, Bergmann I, Aarskog D, Undlien DE, Joner G, Sovik O, Bell GI, Njolstad PR, et al. Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes. Diabetes. 2008;57:1131–5. PubMed PMID: 18192540.

Montoli A, Colussi G, Massa O, Caccia R, Rizzoni G, Civati G, Barbetti F. Renal cysts and diabetes syndrome linked to mutations of the hepatocyte nuclear factor-1 beta gene: description of a new family with associated liver involvement. Am J Kidney Dis. 2002;40:397–402. PubMed PMID: 12148114.

Neve B, Fernandez-Zapico ME, Ashkenazi-Katalan V, Dina C, Hamid YH, Joly E, Vaillant E, Benmezroua Y, Durand E, Bakaher N, Delannoy V, Vaxillaire M, Cook T, Dallinga-Thie GM, Jansen H, Charles MA, Clement K, Galan P, Hercberg S, Helbecque N, Charpentier G, Prentki M, Hansen T, Pedersen O, Urrutia R, Melloul D, Froguel P. Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. Proc Natl Acad Sci U S A. 2005;102:4807–12. PubMed PMID: 15774581.

Østoft SH, Bagger JI, Hansen T, Pedersen O, Faber J, Holst JJ, Knop FK, Vilsbøll T. Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. Diabetes Care. 2014;37:1797–805. PubMed PMID: 24929431.

Patel KA, Oram RA, Flanagan SE, De Franco E, Colclough K, Shepherd M, Ellard S, Weedon MN, Hattersley AT. Type 1 Diabetes Genetic Risk Score: A Novel Tool to Discriminate Monogenic and Type 1 Diabetes. Diabetes. 2016;65:2094–9. PubMed PMID: 27207547.

Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, Ellard S, Ferrer J, Hattersley AT. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. PLoS Med. 2007;4:e118. PubMed PMID: 17407387.

Pearson ER, Pruhova S, Tack CJ, Johansen A, Castleden HA, Lumb PJ, Wierzbicki AS, Clark PM, Lebl J, Pedersen O, Ellard S, Hansen T, Hattersley AT. Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. Diabetologia. 2005; 2005;48:878–85. PubMed PMID: 15830177.

Pearson ER, Velho G, Clark P, Stride A, Shepherd M, Frayling TM, Bulman MP, Ellard S, Froguel P, Hattersley AT. beta-cell genes and diabetes: quantitative and qualitative differences in the pathophysiology of hepatic nuclear factor-1alpha and glucokinase mutations. Diabetes. 2001; 2001;50 Suppl 1:S101–7. PubMed PMID: 11272165.

Pihoker C, Gilliam LK, Ellard S, Dabelea D, Davis C, Dolan LM, Greenbaum CJ, Imperatore G, Lawrence JM, Marcovina SM, Mayer-Davis E, Rodriguez BL, Steck AK, Williams DE, Hattersley AT, et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab. 2013;98:4055–62. PubMed PMID: 23771925.

Plengvidhya N, Kooptiwut S, Songtawee N, Doi A, Furuta H, Nishi M, Nanjo K, Tantibhedhyangkul W, Boonyasrisawat W, Yenchitsomanus PT, Doria A, Banchuin N. PAX4 mutations in Thais with maturity onset diabetes of the young. J Clin Endocrinol Metab. 2007;92:2821–6. PubMed PMID: 17426099.

Poolsup N, Suksomboon N, Amin M. Efficacy and safety of oral antidiabetic drugs in comparison to insulin in treating gestational diabetes mellitus: a meta-analysis. PLoS One. 2014;9:e109985. PubMed PMID: 25302493.

Prudente S, Jungtrakoon P, Marucci A, Ludovico O, Buranasupkajorn P, Mazza T, Hastings T, Milano T, Morini E, Mercuri L, Bailetti D, Mendonca C, Alberico F, Basile G, Romani M, Miccinilli E, Pizzuti A, Carella M, Barbetti F, Pascarella S, Marchetti P, Trischitta V, Di Paola R, Doria A. Loss-of-function mutations in APPL1 in familial diabetes mellitus. Am J Hum Genet. 2015;97:177–85. PubMed PMID: 26073777.

Raeder H, Johansson S, Holm PI, Haldorsen IS, Mas E, Sbarra V, Nermoen I, Eide SA, Grevle L, Bjorkhaug L, Sagen JV, Aksnes L, Sovik O, Lombardo D, Molven A, Njolstad PR. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. Nat Genet. 2006;38:54–62. PubMed PMID: 16369531.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Raile K, Klopocki E, Holder M, Wessel T, Galler A, Deiss D, Muller D, Riebel T, Horn D, Maringa M, Weber J, Ullmann R, Gruters A. Expanded clinical spectrum in hepatocyte nuclear factor 1b-maturity-onset diabetes of the young. J Clin Endocrinol Metab. 2009;94:2658–64. PubMed PMID: 19417042.

Rubio-Cabezas O, Hattersley AT, Njolstad PR, Mlynarski W, Ellard S, White N, Chi DV, Craig ME. International Society For P, Adolescent D. ISPAD Clinical Practice Consensus Guidelines 2014. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes. 2014;15 Suppl 20:47–64. PubMed PMID: 25182307.

Schober E, Rami B, Grabert M, Thon A, Kapellen T, Reinehr T, Holl RW, et al. Phenotypical aspects of maturity-onset diabetes of the young (MODY diabetes) in comparison with Type 2 diabetes mellitus (T2DM) in children and adolescents: experience from a large multicentre database. Diabet Med. 2009;26:466–73. PubMed PMID: 19646184.

Shepherd M, Ellis I, Ahmad AM, Todd PJ, Bowen-Jones D, Mannion G, Ellard S, Sparkes AC, Hattersley AT. Predictive genetic testing in maturity-onset diabetes of the young (MODY). Diabet Med. 2001;18:417–21. PubMed PMID: 11472455.

Shepherd M, Pearson ER, Houghton J, Salt G, Ellard S, Hattersley AT. No deterioration in glycemic control in HNF-1alpha maturity-onset diabetes of the young following transfer from long-term insulin to sulphonylureas. Diabetes Care. 2003;26:3191–2. PubMed PMID: 14578267.

Shepherd M, Shields B, Hammersley S, Hudson M, McDonald TJ, Colclough K, Oram RA, Knight B, Hyde C, Cox J, Mallam K, Moudiotis C, Smith R, Fraser B, Robertson S, Greene S, Ellard S, Pearson ER, Hattersley AT, et al. Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the U.K. pediatric diabetes population with monogenic diabetes. Diabetes Care. 2016;39:1879–88. PubMed PMID: 27271189.

Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetologia. 2010;53:2504–8. PubMed PMID: 20499044.

Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. Diabetologia. 2012;55:1265–72. PubMed PMID: 22218698.

Silva JC, Fachin DR, Coral ML, Bertini AM. Perinatal impact of the use of metformin and glyburide for the treatment of gestational diabetes mellitus. J Perinat Med. 2012;40:225–8. PubMed PMID: 22505499.

Spyer G, Hattersley AT, Sykes JE, Sturley RH, Macleod KM. Influence of maternal and fetal glucokinase mutations in gestational diabetes. Am J Obstet Gynecol. 2001;185:240–1. PubMed PMID: 11483936.

Stanik J, Dusatkova P, Cinek O, Valentinova L, Huckova M, Skopkova M, Dusatkova L, Stanikova D, Pura M, Klimes I, Lebl J, Gasperikova D, Pruhova S. De novo mutations of GCK, HNF1A and HNF4A may be more frequent in MODY than previously assumed. Diabetologia. 2014;57:480–4. PubMed PMID: 24323243.

Steele AM, Shields BM, Shepherd M, Ellard S, Hattersley AT, Pearson ER. Increased all-cause and cardiovascular mortality in monogenic diabetes as a result of mutations in the HNF1A gene. Diabet Med. 2010;27:157–61. PubMed PMID: 20546258.

Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. JAMA. 2014;311:279–86. PubMed PMID: 24430320.

Steele AM, Wensley KJ, Ellard S, Murphy R, Shepherd M, Colclough K, Hattersley AT, Shields BM. Use of HbA1c in the identification of patients with hyperglycaemia caused by a glucokinase mutation: observational case control studies. PLoS One. 2013;8:e65326. PubMed PMID: 23799006.

Stoffers DA, Ferrer J, Clarke W. LHabener JF. Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. Nat Genet. 1997;17:138–9. PubMed PMID: 9326926.

Stride A, Ellard S, Clark P, Shakespeare L, Salzmann M, Shepherd M, Hattersley AT. Beta-cell dysfunction, insulin sensitivity, and glycosuria precede diabetes in hepatocyte nuclear factor-1alpha mutation carriers. Diabetes Care. 2005;28:1751–6. PubMed PMID: 15983330.

Stride A, Hattersley AT. Different genes, different diabetes: lessons from maturity-onset diabetes of the young. Ann Med. 2002;34:207–16. PubMed PMID: 12173691.

Stride A, Shields B, Gill-Carey O, Chakera AJ, Colclough K, Ellard S, Hattersley AT. Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia. Diabetologia. 2014;57:54–6. PubMed PMID: 24092492.

Thanabalasingham G, Shah N, Vaxillaire M, Hansen T, Tuomi T, Gasperikova D, Szopa M, Tjora E, James TJ, Kokko P, Loiseleur F, Andersson E, Gaget S, Isomaa B, Nowak N, Raeder H, Stanik J, Njolstad PR, Malecki MT, Klimes I, Groop L, Pedersen O, Froguel P, Mccarthy MI, Gloyn AL, Owen KR. A large multi-centre European study validates high-sensitivity C-reactive protein (hsCRP) as a clinical biomarker for the diagnosis of diabetes subtypes. Diabetologia. 2011;54:2801–10. PubMed PMID: 21814873.

Thomas ER, Brackenridge A, Kidd J, Kariyawasam D, Carroll P, Colclough K, Ellard S. Diagnosis of monogenic diabetes: 10-year experience in a large multi-ethnic diabetes center. J Diabetes Investig. 2016;7:332–7. PubMed PMID: 27330718.

Tuomi T, Honkanen EH, Isomaa B, Sarelin L, Groop LC. Improved prandial glucose control with lower risk of hypoglycemia with nateglinide than with glibenclamide in patients with maturity-onset diabetes of the young type 3. Diabetes Care. 2006;29:189–94. PubMed PMID: 16443858.

Uday S, Campbell FM, Cropper J, Shepherd M. Monogenic diabetes and type 1 diabetes mellitus: a challenging combination. Practical Diabetes. 2014;31:327–30.

Ulinski T, Lescure S, Beaufils S, Guigonis V, Decramer S, Morin D, Clauin S, Deschenes G, Bouissou F, Bensman A, Bellanné-Chantelot C. Renal phenotypes related to hepatocyte nuclear factor-1beta (TCF2) mutations in a pediatric cohort. J Am Soc Nephrol. 2006;17:497–503. PubMed PMID: 16371430.

Wright NM, Metzger DL, Borowitz SM, Clarke WL. Permanent neonatal diabetes mellitus and pancreatic exocrine insufficiency resulting from congenital pancreatic agenesis. Am J Dis Child. 1993;147:607–9. PubMed PMID: 8506821.

Xu JY, Dan QH, Chan V, Wat NM, Tam S, Tiu SC, Lee KF, Siu SC, Tsang MW, Fung LM, Chan KW, Lam KS. Genetic and clinical characteristics of maturity-onset diabetes of the young in Chinese patients. Eur J Hum Genet. 2005;13:422–7. PubMed PMID: 15657605.

Chapter Notes

Revision History

- 24 May 2018 (bp) Review posted live
- 5 September 2017 (ddg) Original submission

License