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# Maturity-Onset Diabetes of the Young Overview

Synonym: MODY Overview

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## 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.

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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<br>• 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<br>• 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<br>• Progressive insulin secretory defect<br>• OGTT frequently needed to make an early diagnosis<br>• Renal glycosuria | Common [12] | Stride et al [2005] / 600496 |
| *HNF1B* (MODY5) | <5% [13] | • IUGR<br>• Renal anomalies<br>• Urogenital tract anomalies<br>• 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<br>• Transient neonatal hyperinsulinemic hypoglycemia common [15]<br>• 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<br>• Apparently asymptomatic & heterozygous due to reduced penetrance or variable expressivity OR<br>• Not heterozygous because either:<br>◦ Pathogenic or likely pathogenic variant was *de novo* in proband [1, 2]<br>◦ Parental germline mosaicism | Molecular genetic testing<br>• If familial pathogenic or likely pathogenic variant is identified, surveillance for early manifestations of MODY (see Management)<br>• 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<br>• 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

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# Chapter Notes

## Revision History

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