The Diagnosis of Maturity Onset Diabetes of the Young (MODY)

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Diabetes mellitus (DM), often simply referred to as diabetes—is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced.
**Diabetes: Classification**

**Type 1** DM is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to **insulin deficiency**. Associated to ketoacidosis.

**Type 2** DM is characterized by **insulin resistance** which may be combined with relatively reduced insulin secretion (deficiency). Associated to metabolic syndrome.
Diabetes: etiology

Childhood

Type 1 (94%)

Type 2 (~1%)  
Other (incl. monogenic) (5%)

Adulthood

Type 1 (1%)

Type 2 (94%)

Other (incl. monogenic) (5%)
Glucose-regulated insulin release in β-cells

Kir6.2/Sur1
Interactions in the etiology of diabetes

- Insulin resistance
- Insulin secretion defects

Diabetes

Apoptosis

- Glucotoxicity
- Lipotoxicity
- Citokines
- ER stress
- Calcium flux
Pancreatic $\beta$-Cell and Monogenic Diabetes

Pancreatic $\beta$-Cell and Monogenic Diabetes

- Neonatal diabetes
- Friedreich's ataxia
- MODY

Genes and Disorders:
- PERK
- Wolframin
- FRK
- Kir6.2/Sur1
- WRN
- HNF-4a
- HNF-1a
- IPF-1
- HNF-1b
- NeuroD1
- Frataxin
- MODY

Proteins and Processes:
- Secretion
- Apoptosis
- Glucose
- Glucokinase
- ATP
- ATP-sensitive K$^+$ channel
- Voltage-dependent Ca$^{2+}$ channel
- Insulin containing granules
- Insulin secretion
- Ca$^{2+}$
- Depolarization
- Glucose-6-phosphate
- Glycolysis
- Kreb's cycle
- Nucleus
- Endoplasmic reticulum

Medical Conditions:
- Wolcott-Rallison syndrome
- Werner syndrome
- Wolfram (DIDMOAD) syndrome
- MODY

References:
Maturity-Onset Diabetes of the Young (MODY):

A clinically heterogeneous group of disorders characterized by

- Nonketotic diabetes mellitus

- An autosomal dominant mode of inheritance

- An onset usually before the age of 25 years (and frequently in childhood or adolescence)

- A primary defect in the function of the beta cells of the pancreas.
### DISTINGUISHING CLINICAL CHARACTERISTICS OF MODY AND TYPE 2 DIABETES

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>MODY</th>
<th>TYPE 2 DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of inheritance</td>
<td>Monogenic, autosomal dominant</td>
<td>Polygenic + environment</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Childhood, adolescence or young adulthood (&lt;25yr)</td>
<td>Adulthood (40-60yr) occasionally adolescence (obese)</td>
</tr>
<tr>
<td>Pedigree</td>
<td>Usually multigenerational</td>
<td>Rarely multigenerational</td>
</tr>
<tr>
<td>Penetrance</td>
<td>80-95%</td>
<td>Variable (~10-40%)</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Nonobese</td>
<td>Usually obese</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Absent</td>
<td>Usually present</td>
</tr>
</tbody>
</table>
Pancreatic β-Cell and the Proteins Implicated in MODY

Glucose sensing

Insulin gene expression

Glucose

Glucose transporter

Glucokinase

Glucose-6-phosphate

Glycolysis

Mitochondrion

Krebs cycle

Intracellular Ca^{2+} stores

Insulin-containing granules

Insulin secretion

Voltage-dependent Ca^{2+} channel

ATP

ATP-sensitive K^{+} channel

Ca^{2+} Depolarization

Transcription factors involved in pancreas development

- **Stem/progenitor**
  - HNF1α,β
  - HNF6
  - HNF4α
  - HNF3

- **MODY 3, MODY 5**
  - Hlx9
  - Isl1

- **MODY 4**
  - Pdx1
  - Ngn3

- **MODY 1**
  - HNF-4α
  - Pdx1
  - Hlx9

- **β-cell** (insulin)
  - Nkx6.1
  - Pax4
  - ARX
  - Brn4

- **δ-cell** (somatostatin)
  - Hes1
  - PTF1/p48
  - mist1

- **α-cell** (glucagon)
  - HNF1β
  - HNF6
  - HNF4α
  - Sox9

- **PP-cell** (pancreatic polypept)
  - Pax6

- **Acinar cell**

- **Ductal cell**
<table>
<thead>
<tr>
<th>MODY TYPE</th>
<th>GENE</th>
<th>CLINIC OF HETEROZYGOUS STATE</th>
<th>MOST COMMON TREATMENT</th>
<th>MOLECULAR BASIS</th>
<th>CLINIC OF HOMOZYGOUS STATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODY 1</td>
<td>HNF-4&lt;sub&gt;α&lt;/sub&gt;</td>
<td>Diabetes, microvascular complications; reduction in serum concentration of TGC, apoplipoproteins AII and CIII, and Lp(a) lipoproteins</td>
<td>Oral hypoglycemic agents, insulin</td>
<td>Abnormal regulation of gene transcription in beta cells, leading to a defect in metabolic signaling of insulin secretion, beta-cell mass or both</td>
<td></td>
</tr>
<tr>
<td>MODY 2</td>
<td>Glucokinase</td>
<td>Impaired fasting glucose impaired glucose tolerance, normal proinsulin/insulin</td>
<td>Diet and exercise</td>
<td>Defect in sensitivity of beta cells to glucose due to reduced glucose phosphorylation; defect in hepatic storage of glucose as glycogen</td>
<td>Permanent neonatal diabetes, requiring insulin</td>
</tr>
<tr>
<td>MODY 3</td>
<td>HNF-1&lt;sub&gt;α&lt;/sub&gt;</td>
<td>Diabetes, microvascular complications, renal glycosuria, increase sensitivity to sulfonylurea, increased proinsulin/insulin in serum</td>
<td>Oral hypoglycemic agents, insulin</td>
<td>Abnormal regulation of gene transcription in beta cells</td>
<td></td>
</tr>
<tr>
<td>MODY 4</td>
<td>IPF-1/PDX1</td>
<td>Diabetes</td>
<td>Oral hypoglycemic agents, insulin</td>
<td>Abnormal transcriptional regulation of beta-cell development &amp; function</td>
<td>Pancreatic agenesis neonatal diabetes requiring insulin</td>
</tr>
<tr>
<td>MODY 5</td>
<td>HNF-1&lt;sub&gt;β&lt;/sub&gt;</td>
<td>Diabetes, renal abnormalities progressive nondiabetic renal dysfunction and eventually chronic renal insufficiency; uterine abnormalities</td>
<td>Insulin</td>
<td>Abnormal regulation of gene transcription in beta cells</td>
<td></td>
</tr>
<tr>
<td>MODY 6</td>
<td>NeuroD1</td>
<td>Diabetes</td>
<td>Insulin</td>
<td>Abnormal transcriptional regulation in beta cells</td>
<td></td>
</tr>
</tbody>
</table>

**Mutation frequency** *(Ellard et al, Diabetologia, 2008: 51:546)*
Values of genetic testing for MODY

1. **Prognostic:**

   **MODY2** (GCK mutations) is stable and benign, usually without complications

   **MODY 1 and 3** (HNF4α and HNF1α mutations) are bound to show the diabetes-related complications and need to be closely monitored

   Defines risk for family members

2. **Therapeutic**

   **MODY 2** can be treated with life-style measures (diet and exercise)

   **MODY 1 and 3** can be treated with oral antidiabetic drugs (e.g. sulfonylureas) and be insulin-free
Patients and Families

Testing and Diagnosis

There is a genetic test for MODY. This test can help diagnose most people who have MODY. Talk to your doctor about whether or not genetic testing is appropriate if you or your child is a diabetic patient that has symptoms that could be caused by MODY.

Athena Diagnostics offers a genetic test for MODY called the MODY Evaluation. For more information on the MODY Evaluation, please call 800-394-4492 or email info@athenadiagnostics.com.

Why a genetic test is important...

MODY is often confused with type 1 diabetes or type 2 diabetes. That means many patients with MODY are accidentally diagnosed with one of these other forms of diabetes. These patients are often not diagnosed correctly until they are adults, and sometimes, they may never be diagnosed with MODY. This is a problem because patients with MODY sometimes need different treatments than what patients with type 1 or type 2 diabetes need.

Why it's important to get the right treatment...

A person's body may not produce enough insulin if they are not properly diagnosed and treated for MODY. Not having enough insulin can cause high blood sugar levels. This could hurt tissues in the body, particularly the eyes, kidneys, nerves, and blood vessels. These serious problems can be prevented if a patient is properly diagnosed with and treated for MODY.

What you can do...

The good news is that there is a genetic test for MODY. Athena Diagnostics offers a genetic test for MODY called the MODY Evaluation. If you or your child has symptoms that could be caused by MODY, talk with a doctor about whether or not genetic testing might be the right choice for you or your family.

Because MODY is usually inherited, there is a chance that several people in one family may have MODY. If you or your child is diagnosed with MODY, it is important to talk to your doctor about whether or not other family members should also be tested for MODY.
Clinical criteria for MODY genetic testing (1)

• Mild fasting hyperglycemia
  >5.5 mmol/l in 3 separate occasions
  stable over months or years

• HbA1c >6 but <7.5%

• OGTT: Glucose 2hrs-Glucose basal <3 mmol

• Family history: Parents
  1. Type 2 diabetes w/o complications
  2. No diabetes
  3. Fasting glucose 5.5-8 mmol

TEST FOR GCK MUTATIONS
Clinical criteria for MODY genetic testing (2)

Gestational diabetes

- **Hyperglycemia**: 5.5-8 mmol/l before, during or after pregnancy

- **OGTT**: Glucose 2hrs-Glucose basal <4.6 mmol during or after pregnancy

- **Family history**: Parents
  1. Type 2 diabetes
  2. No diabetes

TEST FOR GCK MUTATIONS
Clinical criteria for MODY genetic testing (3)

• Mild fasting hyperglycemia

• Strong family history of diabetes
  • Young onset of diabetes in min. 2 family member @ 20-30 years of age for two generations

• Insulin independence for more than 3 years (honeymoon)
  • No ketoacidosis w/o insulin
  • Detectable C-peptide under insulin and glucose >8mM

• OGTT : Glucose 2hrs-Glucose basal >5 mmol

• Anti-islet antibodies: negative

• Glucosuria with blood glucose <10mM (lower renal threshold)

• Marked sensitivity to sulfonylureas (hypoglycemias)

**TEST FOR HNF1α MUTATIONS**
Clinical criteria for MODY genetic testing (4)

- **Mild fasting hyperglycemia** (as in HNF1A mut)
- **Strong family history of diabetes** (as in HNF1A mut)
- **Insulin independence for more than 3 years (honeymoon)** (as in HNF1A mut)
- **OGTT**: Glucose 2hrs-Glucose basal >5 mmol (as in HNF1A mut)
- **Anti-islet antibodies**: negative (as in HNF1A mut)
- **Sensitivity to sulfonylureas** (as in HNF1A mut)
- **No mutations in HNF1α**
- **Neonatal macrosomia (>4.4 kg) or neonatal hyperinsulism (= hypoglycemia) responsive to diazoxide**

**TEST FOR HNF4α MUTATIONS**
Methods

Sequencing: GCK (exons 1A-10 + intron/exon boundaries)
    HNF1A (exons 1-10 + intron/exon boundaries)
    HNF4A (exons 1d-10 + intron/exon boundaries; Promoter 2)

Multiplex Ligation-dependent Probe Amplification: All
<table>
<thead>
<tr>
<th>Reporting scenarios</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affected proband (or relative), mutation identified</strong>&lt;sup&gt;a&lt;/sup&gt; (nonsense, frameshift, conserved splice site or previously reported missense mutation)</td>
<td>This result confirms a diagnosis of MODY, subtype GCK (or HNF1A or HNF4A). State that the mutation has been reported previously if appropriate (include the reference if space permits). Testing for relatives is now possible.</td>
</tr>
<tr>
<td><strong>Affected proband (or relative), novel mutation identified (likely to be pathogenic)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>This result is consistent with a diagnosis of MODY, subtype GCK (or HNF1A or HNF4A). State that the mutation is novel and include evidence for pathogenicity. Suggest testing of other affected relatives to investigate co-segregation with diabetes/hyperglycaemia.</td>
</tr>
<tr>
<td><strong>Affected proband (or relative), novel variant identified (unlikely to be pathogenic)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>State that a novel variant was identified but is thought unlikely to be pathogenic. This result does not confirm a diagnosis of MODY, subtype GCK (or HNF1A or HNF4A). Include suggestions for further testing if appropriate.</td>
</tr>
<tr>
<td><strong>Affected proband, no mutation identified</strong></td>
<td>This result does not confirm a diagnosis of MODY, subtype GCK (or HNF1A or HNF4A). Include suggestions for further testing if appropriate.</td>
</tr>
<tr>
<td><strong>Neonate/infant affected with hypoglycaemia, HNF4A mutation identified</strong></td>
<td>This result confirms/is consistent with a diagnosis of neonatal hypoglycaemia caused by an HNF4A mutation. The child is genetically predisposed to MODY, subtype HNF4A.</td>
</tr>
<tr>
<td><strong>Predictive test&lt;sup&gt;c&lt;/sup&gt;, mutation present</strong></td>
<td>This patient is genetically predisposed to MODY, subtype GCK (or HNF1A or HNF4A).</td>
</tr>
<tr>
<td><strong>Predictive test, mutation absent</strong></td>
<td>The risk of this patient developing diabetes is reduced to that of the population.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Likely to be pathogenic—not found in at least 210 ethnically matched control chromosomes and/or predicted to be pathogenic (e.g. conserved amino acid or data from SIFT/polyPHEN/fruity, etc.). Local practice may vary regarding the reporting of novel variants but guidelines produced by the Clinical Molecular Genetics Society may serve as a useful reference.

<sup>b</sup>Unlikely to be pathogenic—little or no evidence to support pathogenicity.

<sup>c</sup>We recommend that unaffected relatives are offered a biochemical test (fasting blood glucose for GCK mutations or OGTT for HNF1A/HNF4A mutations). If the biochemical test is consistent with a diagnosis of diabetes or hyperglycaemia then the genetic test will be diagnostic, not predictive.

GCK, glucokinase; HNF1A, hepatocyte nuclear factor-1 alpha; HNF4A, hepatocyte nuclear factor-4 alpha.
REPORT OF
MOLECULAR GENETIC
INVESTIGATIONS

Patient (family name, personal name, date of birth, internal sample number):

case 2 (MD-456)

sex: ☐ male ☐ female
origin / ethnic background (if known):

Parent(s) (family name, personal name, date of birth):

Sample material:
☐ genomic DNA ☐ primary skin fibroblasts

Additional sample material:
☐ Mother ☐ Father ☐ Siblings ☐ Others

Date of sample:
Date of sample received: 12.11.2010
Date of analysis: 16.12.2010

Analyses performed:
PCR and sequence analysis of genomic DNA. We tested all coding exons of the HNF1A gene plus flanking intronic regions. Reference sequence for the HNF1A gene is ENSG00000135100.7. Reference sequence for the HNF1A-mRNA is NM_000545.5.

Result:
Exon 1: heterozygous for c.51C>G, p.Leu17Leu (polymorphism, rs1169289)
Exon 1: heterozygous for c.137A>C, p.Lys46Thr

Interpretation:
A heterozygous missense mutation was found in exon 1, p.Lys46Thr. To our knowledge, this alteration has not been reported in any database for HNF1A gene mutations (e.g. http://www.uniprot.org/uniprot/P20823; updated Nov 2010). Nevertheless it is expected that this mutation causes MODY (type 3) which would agree with diagnosis of diabetes.

Because of their complexity and their potential implications for other family member, all genetic tests should be accompanied by genetic counseling; genetic counseling is mandatory in predictive tests including carrier tests.

Signatures:
Checked and Signed by 2 qualified persons

The “Vademecum” of the Division …… is an integral part of this report. It specifies all information regarding the quality management, including possible analytical errors. You are not allowed to copy this report; however use of single results with the reference to original report is permitted. You are not allowed to publish any data from this report in any form without prior approval of the …… Laboratory. This report was generated according to the “Best Practice Guidelines of the …… Society of Medical Genetics” and the “Nomenclature Recommendations in DNA and protein sequences” by Dunnen & Antonarakis, Hum Genet (2001) 109:121-124.
Results

Mutation detection rate for samples received for MODY testing from January 2000 to March 2008

Royal Devon & Exeter Hospital (Wonford), UK
Results (2)

Percent Disease Variant* Detection Rates for Monogenic Diabetes

Percentages are calculated by taking the number of positive reports of each disease variant category and dividing by the total number of reports released during the analysis timeframe. Percentages are presented by gene and by multi-gene profile where appropriate.

*Disease Variants = Disease Variants, Probable Disease Variants and Possible Disease Variants.

http://www.modyawareness.com/healthcare-professionals/testing-diagnosis.php
MODY1 (125850) is determined by heterozygous mutation in the hepatocyte nuclear factor-4-alpha gene (HNF4A; 600281) on chromosome 20.

MODY2 (125851) is caused by heterozygous mutation in the glucokinase gene (GCK; 138079) on chromosome 7.

MODY3 (600496) is caused by heterozygous mutation in the hepatocyte nuclear factor-1alpha gene (HNF1A; 142410) on chromosome 12q24.2.

MODY4 (606392) is caused by heterozygous mutation in the pancreas/duodenum homeobox protein-1 gene (PDX1; 600733) on chromosome 13q12.1.

MODY5 (137920) is caused by heterozygous mutation in the gene encoding hepatic transcription factor-2 (TCF2; 189907) on chromosome 17cen-q21.3.

MODY6 (606394) is caused by heterozygous mutation in the NEUROD1 gene (601724) on chromosome 2q32.

MODY7 (610508) is caused by heterozygous mutation in the KLF11 gene (603301) on chromosome 2p25.

MODY8 (609812), or diabetes-pancreatic exocrine dysfunction syndrome, is caused by heterozygous mutation in the CEL (carboxyl-ester-lipase) gene (114840) on chromosome 9q34.

MODY9 (612225) is caused by heterozygous mutation in the PAX4 (Paired box 4) gene (167413) on chromosome 7q32.

MODY10 (613370) is caused by heterozygous mutation in the insulin gene (INS; 176730) on chromosome 11p15.5.

MODY11 (613375) is caused by heterozygous mutation in the BLK (B-Lymphocyte specific Kinase) gene (191305) on chromosome 8p23.
Schematic representation illustrating the concept of diabetes spectrum with the genes responsible for the variable phenotypes

### Putative biomarkers of MODY subtypes investigated to date

<table>
<thead>
<tr>
<th>Test</th>
<th>Suggested differential diagnosis</th>
<th>Prospect of clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum apolipoprotein M (apoM)</td>
<td>HNF1A-MODY vs. HNF-4A-MODY and type 2 diabetes</td>
<td>Not replicated in subsequent study 1,2</td>
</tr>
<tr>
<td>Serum complement 5 (C5)</td>
<td>HNF1A-MODY and HNF4A-MODY</td>
<td>Insufficient specificity 3</td>
</tr>
<tr>
<td>Serum complement 8 (C8)</td>
<td>HNF1A-MODY and HNF4A-MODY</td>
<td>Insufficient specificity 3</td>
</tr>
<tr>
<td>Serum transthyretin (TTR)</td>
<td>HNF4A-MODY vs. type 2 diabetes</td>
<td>Insufficient specificity 3</td>
</tr>
<tr>
<td>Serum 1,5-anhydroglucitol</td>
<td>HNF1A-MODY vs. type 2 diabetes</td>
<td>Requires confirmation and validation in other types of diabetes 4</td>
</tr>
</tbody>
</table>

MODY diagnostic: conclusions (1)

• Because MODY shares some symptoms with types 1 and 2 diabetes, the majority of patients with MODY are first wrongly diagnosed with one of these other forms of diabetes, or diagnosed very late.

• Correct diagnosis of MODY is essential, as it can predict the clinical course of the patient and guide the most appropriate treatment.
MODY diagnostic: conclusions (2)

- Genetic testing for MODY is available and should be seriously considered for diabetics of any age with non-ketotic insulin-sensitive hyperglycemia or with a family history of diabetes.

- In families of MODY patients, genetic testing can detect mutation carriers before they become hyperglycemic, identifying diabetes risk.
## Human genes responsible for MODY and associated with increased risk of diabetes in adulthood (from case-control studies of common variants)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Monogenic disease</th>
<th>Polygenic type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF4α</td>
<td>MODY1</td>
<td>Variants at the P2 promoter (MAF &gt; 0.15) OR = 1.15 [1.00–1.30] in Europeans</td>
</tr>
<tr>
<td>GCK</td>
<td>MODY2</td>
<td>Variant–30G/A (β-cell promoter) OR = 1.22 [1.13–1.32] in Europeans</td>
</tr>
<tr>
<td>HNF1α</td>
<td>MODY3</td>
<td>G319S, OR = 2.0 in Oji-Cree (carriers) OR = 1.17 [1.06–1.30] in Europeans</td>
</tr>
<tr>
<td>HNF1β</td>
<td>MODY5</td>
<td>Intronic variants (MAF &gt; 0.10) OR = 1.12 [1.07–1.17] in Europeans</td>
</tr>
</tbody>
</table>

Vaxillaire & Froguel, Endocrine Reviews 2008, 29 (3): 254-264