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

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Diabetes: Definition

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.

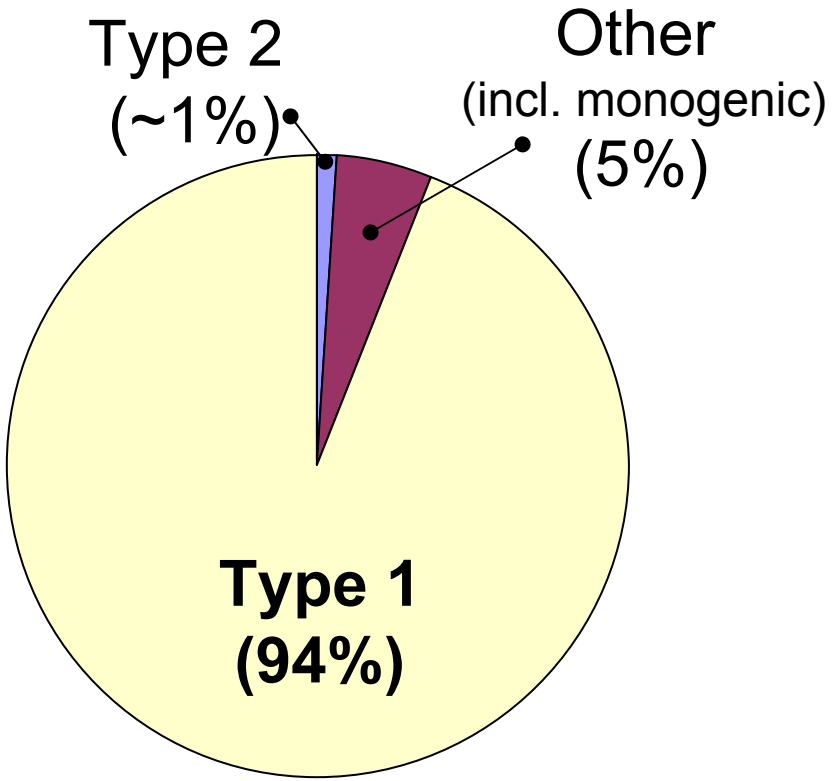
http://en.wikipedia.org/wiki/Diabetes_mellitus

Diabetes: Classification

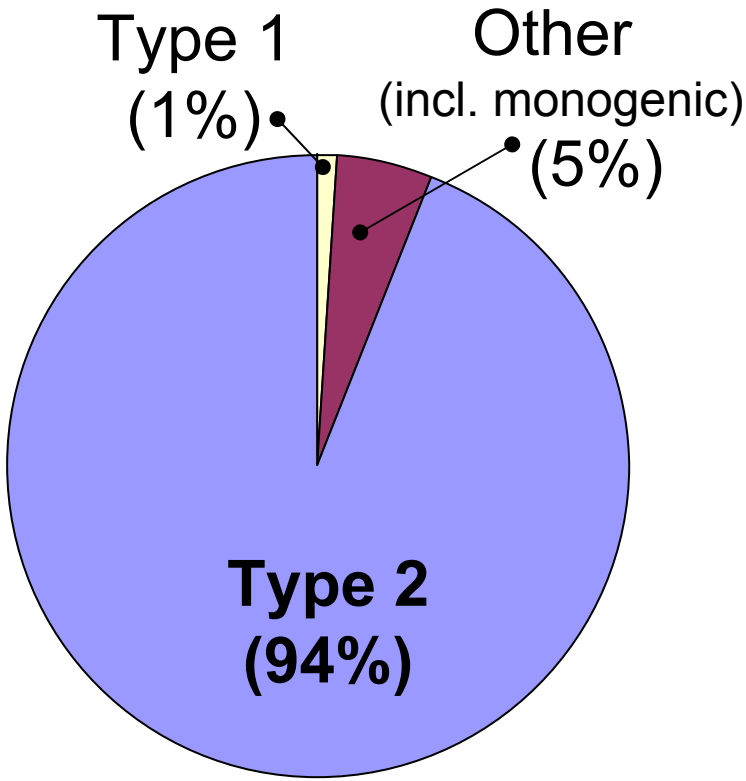
Type 1 DM is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to **insulin deficiency.** Associated to ketoacidosis.

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

Diabetes: etiology

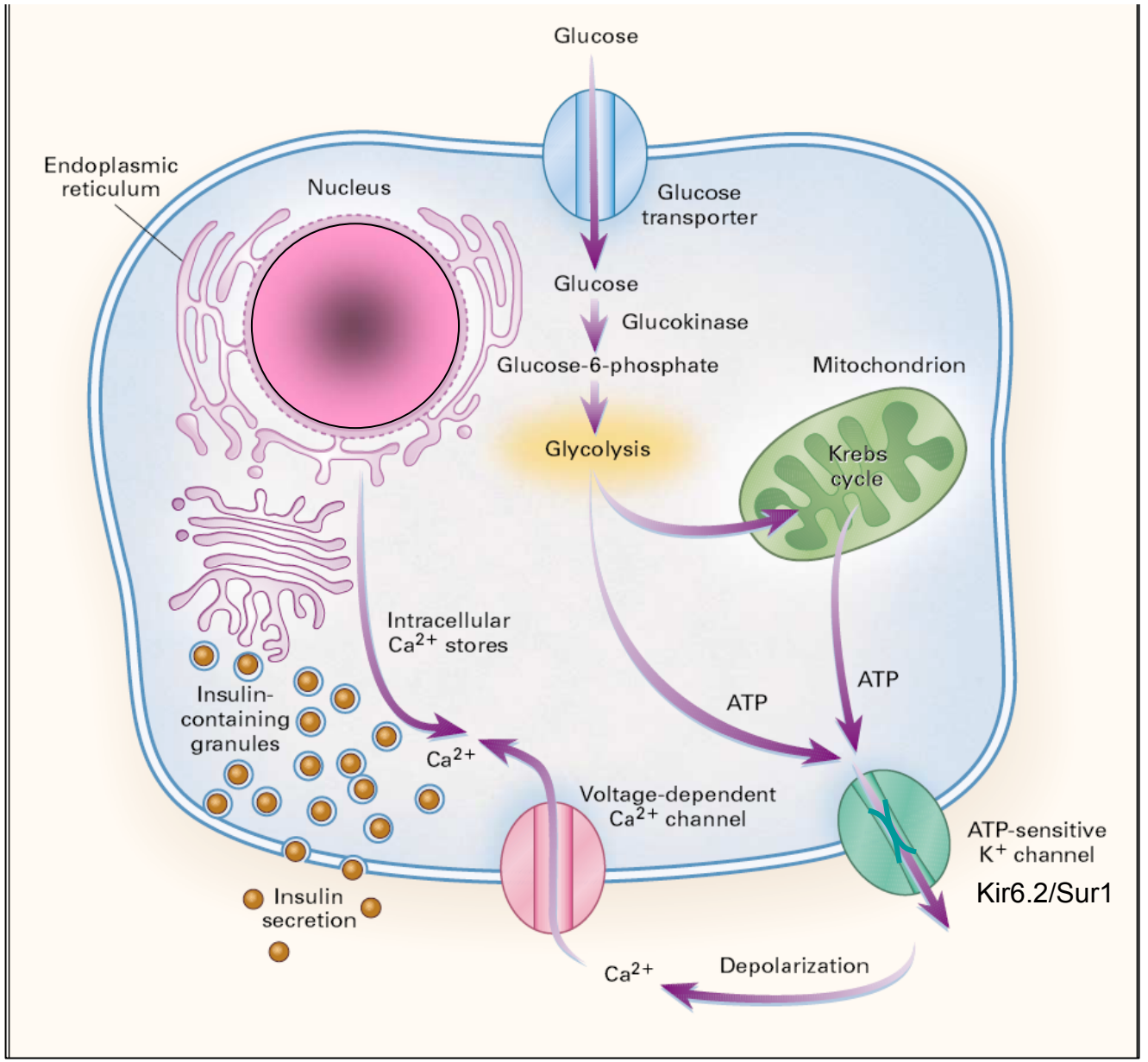


Childhood



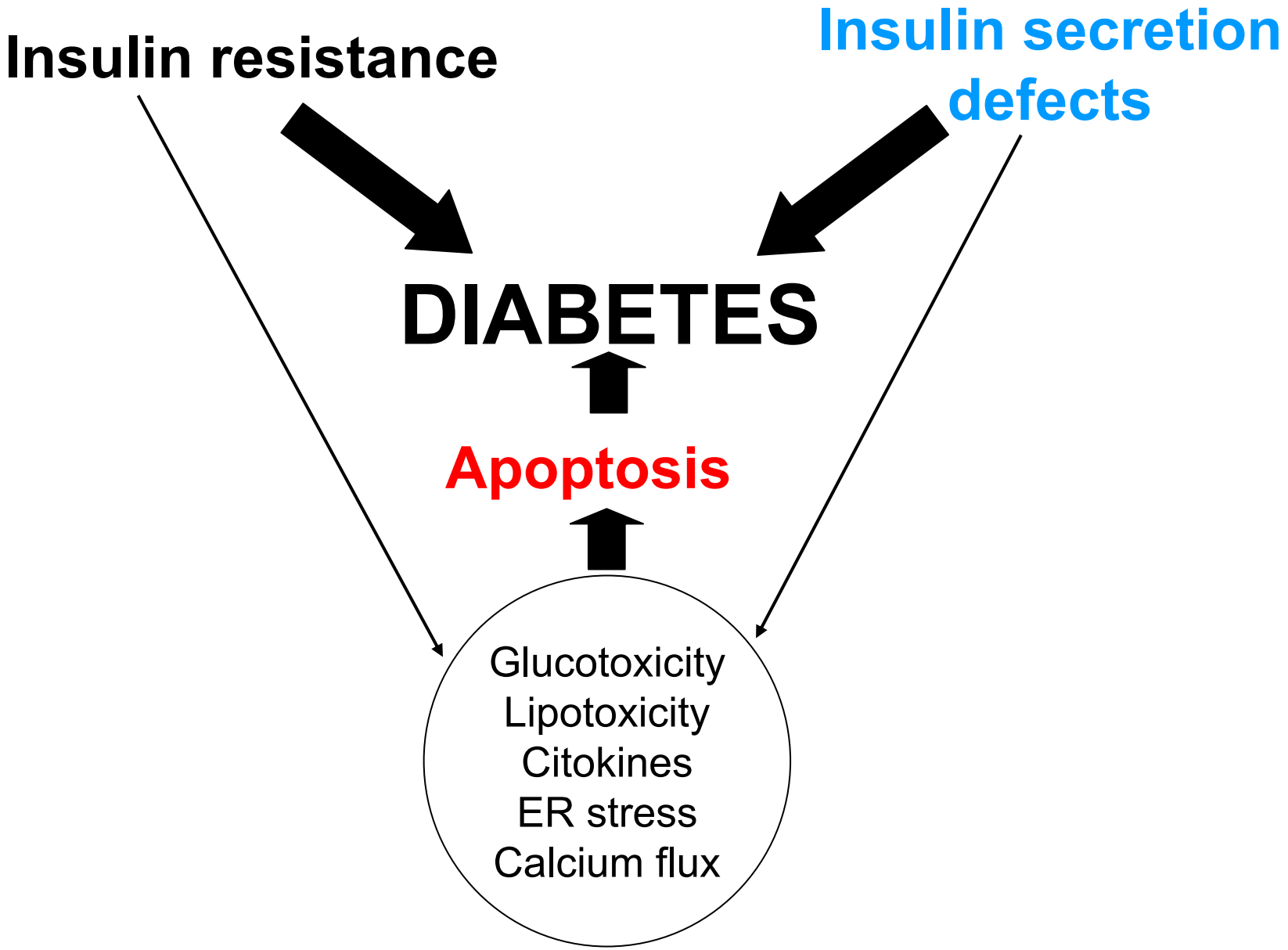
Adulthood

Glucose-regulated insulin release in β-cells

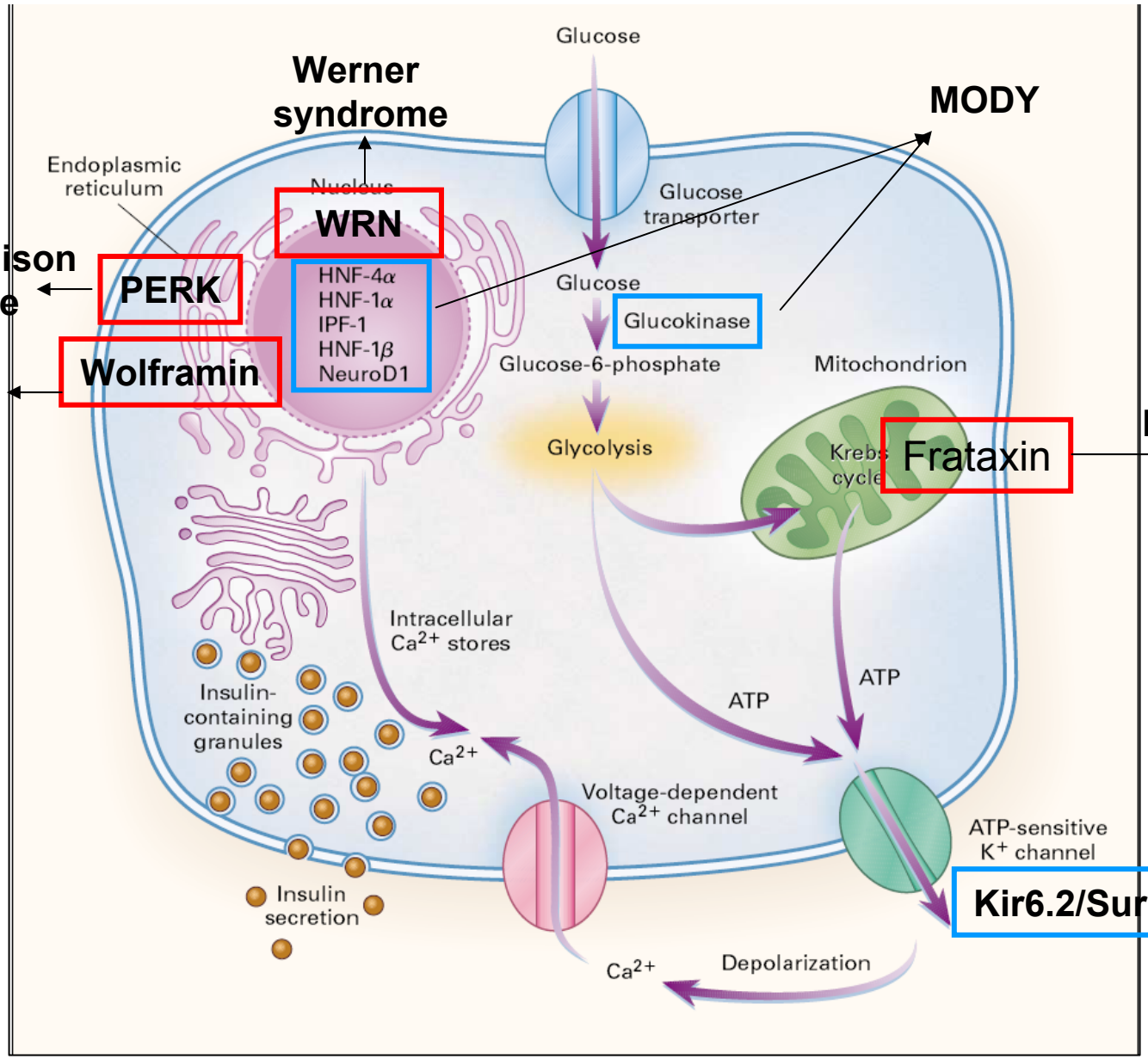


N Engl J Med, Vol. 345, No. 13 · September 27, 2001

Interactions in the etiology of diabetes



Pancreatic β-Cell and Monogenic Diabetes



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Maturity-Onset Diabetes of the Young (MODY) :

A clinically heterogeneous group of disorders characterized by

• Nonketotic **diabetes** mellitus

• An **autosomal dominant** mode of inheritance

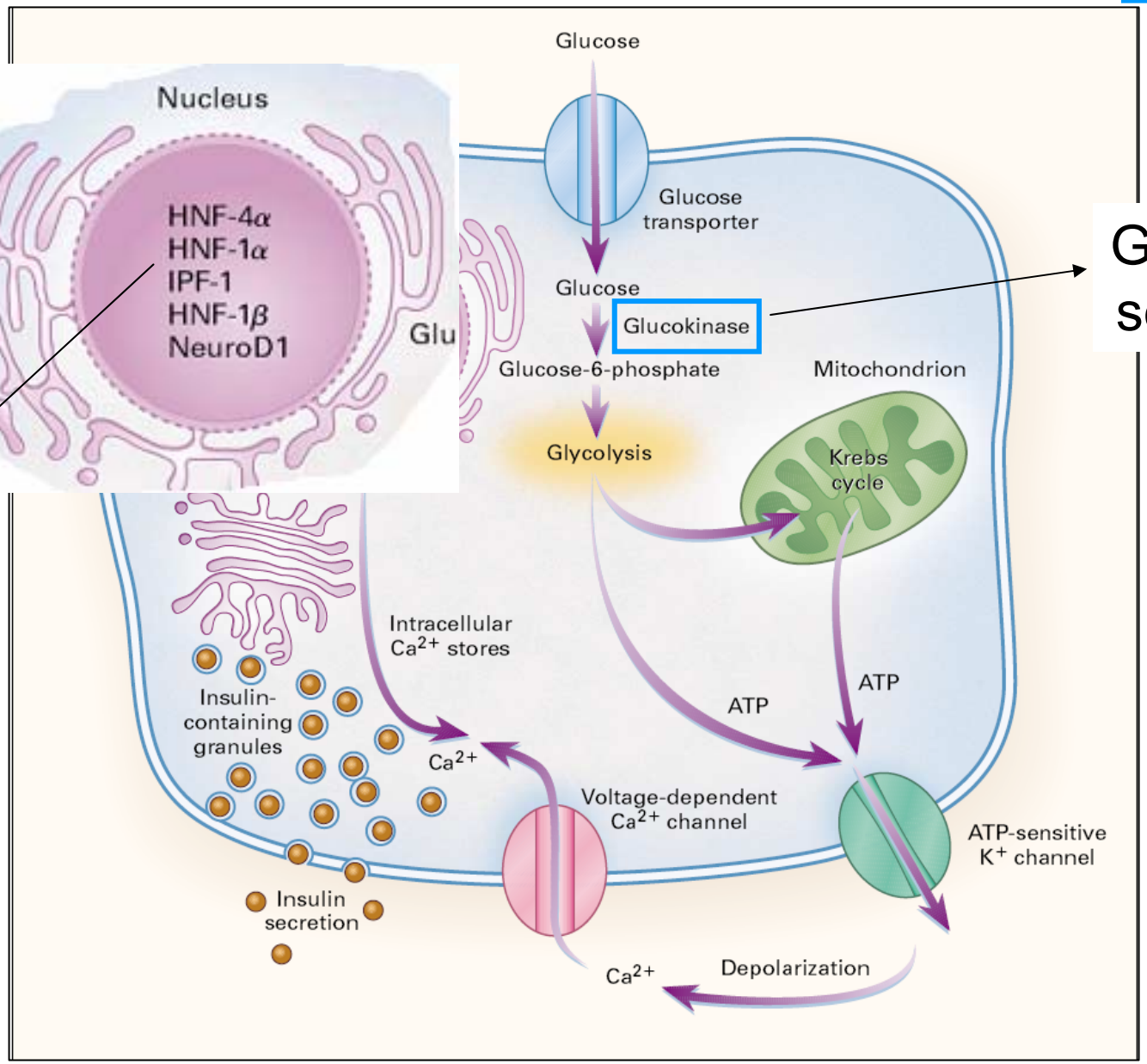
• An onset usually **before** the age of **25 years** (and frequently in childhood or adolescence)

• A primary **defect** in the **function** of the **beta cells** of the pancreas.

DISTINGUISHING CLINICAL CHARACTERISTICS OF MODY AND TYPE 2 DIABETES

CHARACTERISTIC	MODY	TYPE 2 DIABETES
Mode of inheritance	Monogenic, autosomal dominant	Polygenic + environment
Age of onset	Childhood, adolescence or young adulthood (<25yr)	Adulthood (40-60yr) occasionally adolescence (obese)
Pedigree	Usually multigenerational	Rarely multigenerational
Penetrance	80-95%	Variable (~10-40%)
Body habitus	Nonobese	Usually obese
Metabolic syndrome	Absent	Usually present

Pancreatic β-Cell and the Proteins Implicated in MODY



Glucose sensing

Insulin gene expression

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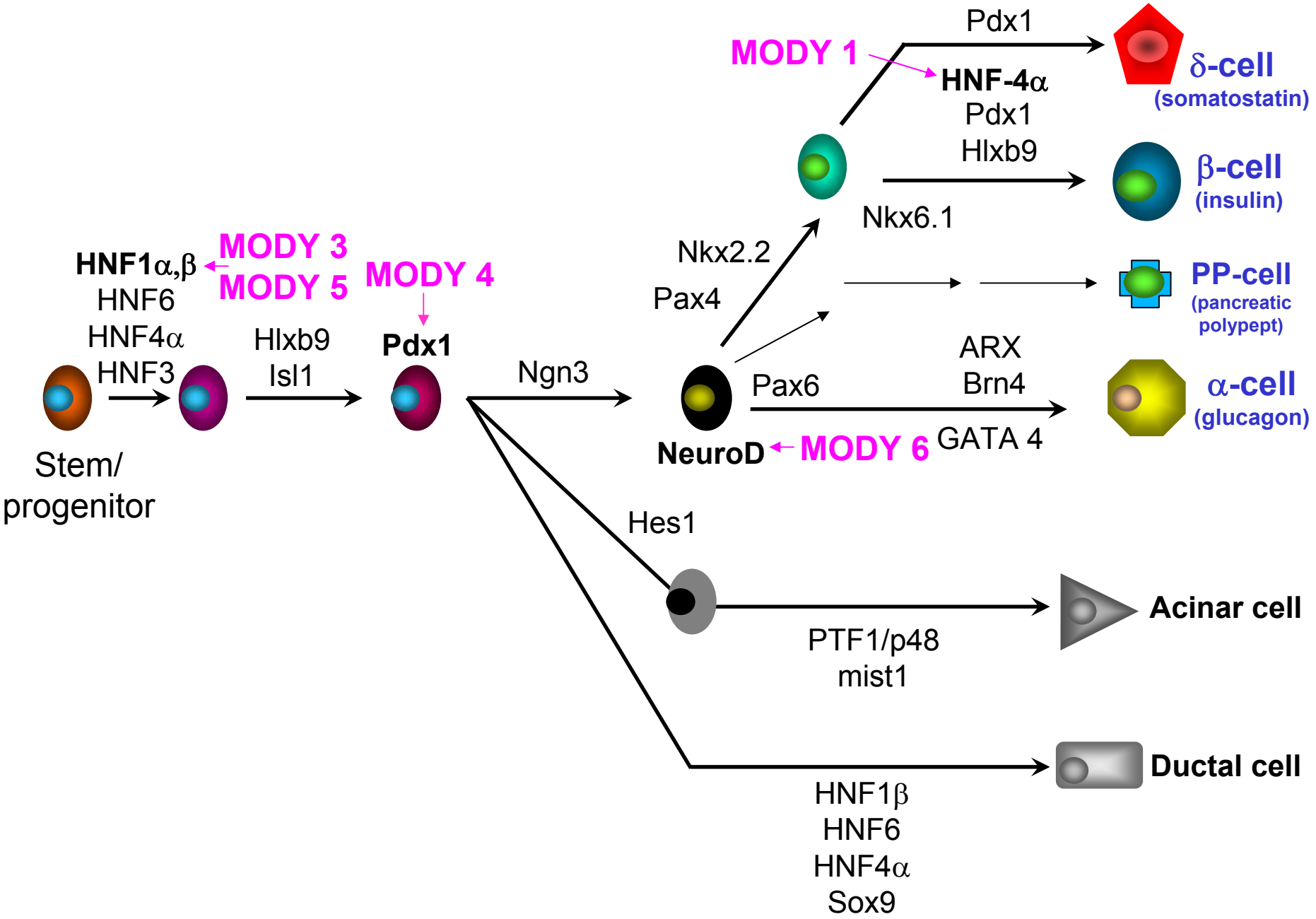
Transcription factors involved in pancreas development



MODY TYPE	GENE	CLINIC OF HETEROZYGOUS STATE	MOST COMMON TREATMENT	MOLECULAR BASIS	CLINIC OF HOMOZYGOUS STATE
MODY 1	HNF-4α **~ 5%**	Diabetes, microvascular complications; reduction in serum concentration of TGC, apoplipoproteins AII and CIII, and Lp(a) lipoprot	Oral hypogly_ cemic agents, insulin	Abnormal regulation of gene transcription in beta cells, leading to a defect in metabolic signaling of insulin secretion, beta-cell mass or both	
MODY 2	Glucokinase **20-50%**	Impaired fasting glucose impaired glucose tolerance, normal proinsulin/insulin	Diet and exercise	Defect in sensitivity of beta cells to glucose due to reduced glucose phosphorylation; defetc in hepatic storage of glucose as glycogen	Permanent neonatal diabetes, requiring insulin
MODY 3	HNF-1α **20-50%**	Diabetes, microvascular complications, renal glycosuria, increase sensitivity to sulfunylurea, increased proinsulin/insulin in serum	Oral hypogly-cemic agents, insulin	Abnormal regulation of gene transcription in beta cells	
MODY 4	IPF-1/PDX1 **<1%**	Diabetes	Oral hypogly-cemic agents, insulin	Abnormal transcriptional regulation of beta-cell development & function	Pancreatic agenesis neonatal diabetes requiring insulin
MODY 5	HNF-1β **~ 5%**	Diabetes, renal abnormalities progressive nondiabetic renal dysfunction and eventually chronic renal insufficiency; uterine abnormalities	Insulin	Abnormal regulation of gene transcription in beta cells	
MODY 6	NeuroD1 **<1%**	Diabetes	Insulin	Abnormal transcriptional regulation in beta cells	

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

Testing and Diagnosis - Patients and Families - MODYawareness.com - Microsoft Internet Explorer

Datei Bearbeiten Ansicht Favoriten Extras ?

Zurück Suchen Favoriten

Adresse http://www.modyawareness.com/patients-families/testing-diagnosis.php Wechseln zu Links

MODY awareness.com

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Patients and Families

What is MODY? | Living with MODY | Testing and Diagnosis | MODY FAQ | Resources

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 800-394-4493 extension 2 or email mody@athenadiagnostics.com.

Why a genetic test is important...

MODY is often confused with type 1 diabetes or type 2 diabetes.[1] 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.[2]

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.

Meet people who have MODY

Watch Now

Meet Marie and Karlee, a mother-daughter duo who both have MODY.

Connect with us

Events, news, and connect with other people with MODY GO

Internet

Start | Posteingang ... | mody | Microsoft Po... | Dokument1 -... | Testing and... | Varia - Nachri... | 10:48

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

Reporting scenarios

Ellard et al, Diabetologia, 2008: 51:546

Scenario	Interpretation
Affected proband (or relative), mutation identified (nonsense, frameshift, conserved splice site or previously reported missense mutation)	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
Affected proband (or relative), novel mutation identified (likely to be pathogenic[a])	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
Affected proband (or relative), novel variant identified (unlikely to be pathogenic[b])	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
Affected proband, no mutation identified	This result does not confirm a diagnosis of MODY, subtype GCK (or HNF1A or HNF4A) Include suggestions for further testing if appropriate
Neonate/infant affected with hypoglycaemia, *HNF4A* mutation identified	This result confirms/is consistent with a diagnosis of neonatal hypoglycaemia caused by an *HNF4A* mutation This child is genetically predisposed to MODY, subtype HNF4A
Predictive test[c], mutation present	This patient is genetically predisposed to MODY, subtype GCK (or HNF1A or HNF4A)
Predictive test, mutation absent	The risk of this patient developing diabetes is reduced to that of the population

[a]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/fruitfly, 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
[b]Unlikely to be pathogenic—little or no evidence to support pathogenicity
[c]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

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Request by:

EMQN MONODIAB 2010

Examination / Indication:

Genetic testing for *HNF1A* mutations

☐ copy of report sent to:

Invoice: ☒ Referring physician
☐ Patient / Parents ☐ scientific*

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
Analysis performed by:

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
Exon 4: heterozygous for c.864G>C, p.Gly288Gly, (polymorphism, rs56348580)

Interpretation:

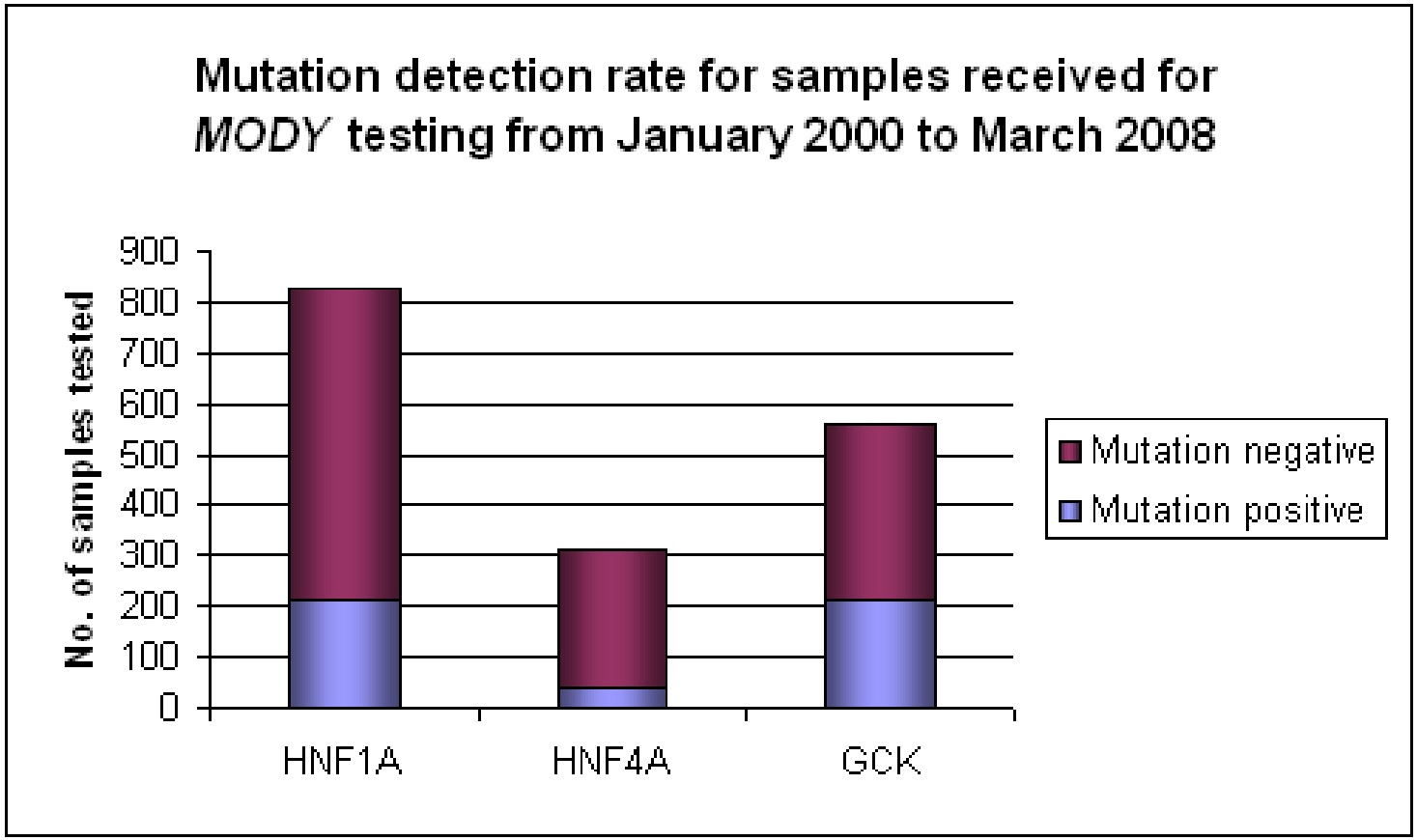
A heterozygous missense mutation was found in exon 1, p.Lys46Thr. To our knowledge, this alteration has not been reported in any database for *HNF1A* gene mutations (e.g. http://www.uniprot.org/uniprot/P20823; updated Nov 2010). Nevertheless it is expected that this mutation causes MODY (type 3) which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

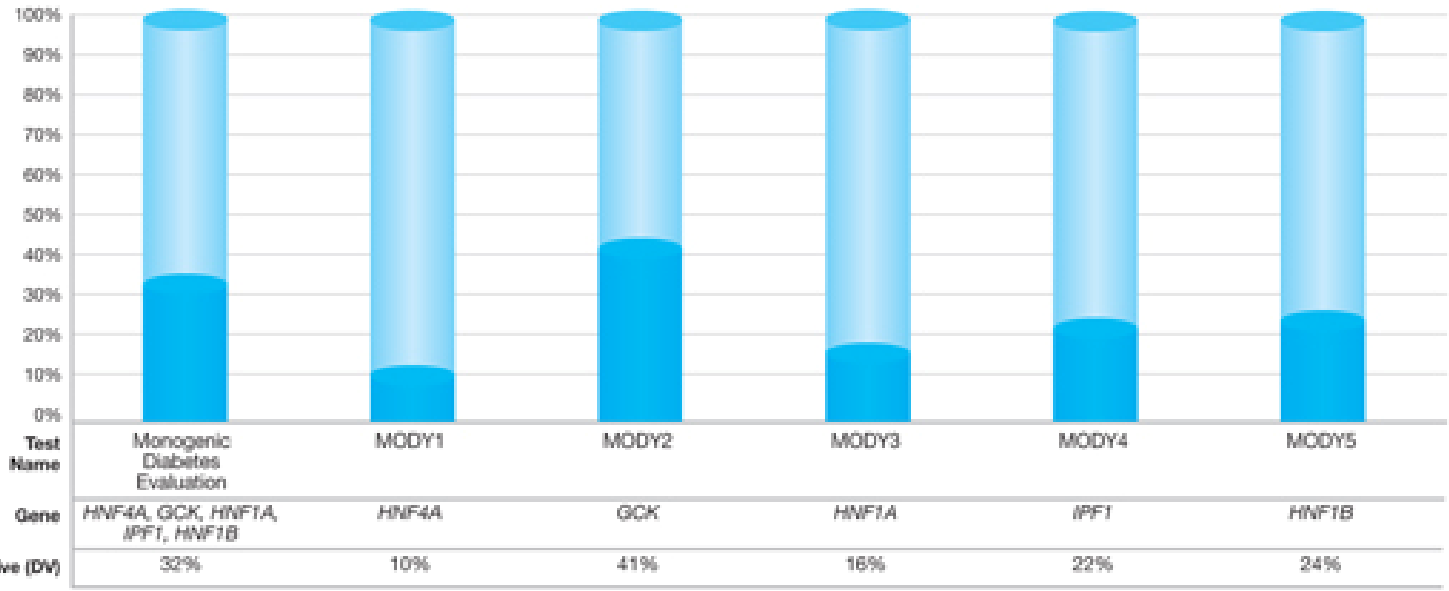
Results



Royal Devon & Exeter Hospital (Wonford), UK

Results (2)

Percent Disease Variant* Detection Rates for Monogenic Diabetes



Test Name	Monogenic Diabetes Evaluation	MODY1	MODY2	MODY3	MODY4	MODY5
Gene	*HNF4A, GCK, HNF1A, IPF1, HNF1B*	*HNF4A*	*GCK*	*HNF1A*	*IPF1*	*HNF1B*
% Positive (DV)	32%	10%	41%	16%	22%	24%

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

OMIM #606391 MATURITY-ONSET DIABETES OF THE YOUNG; MODY

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.

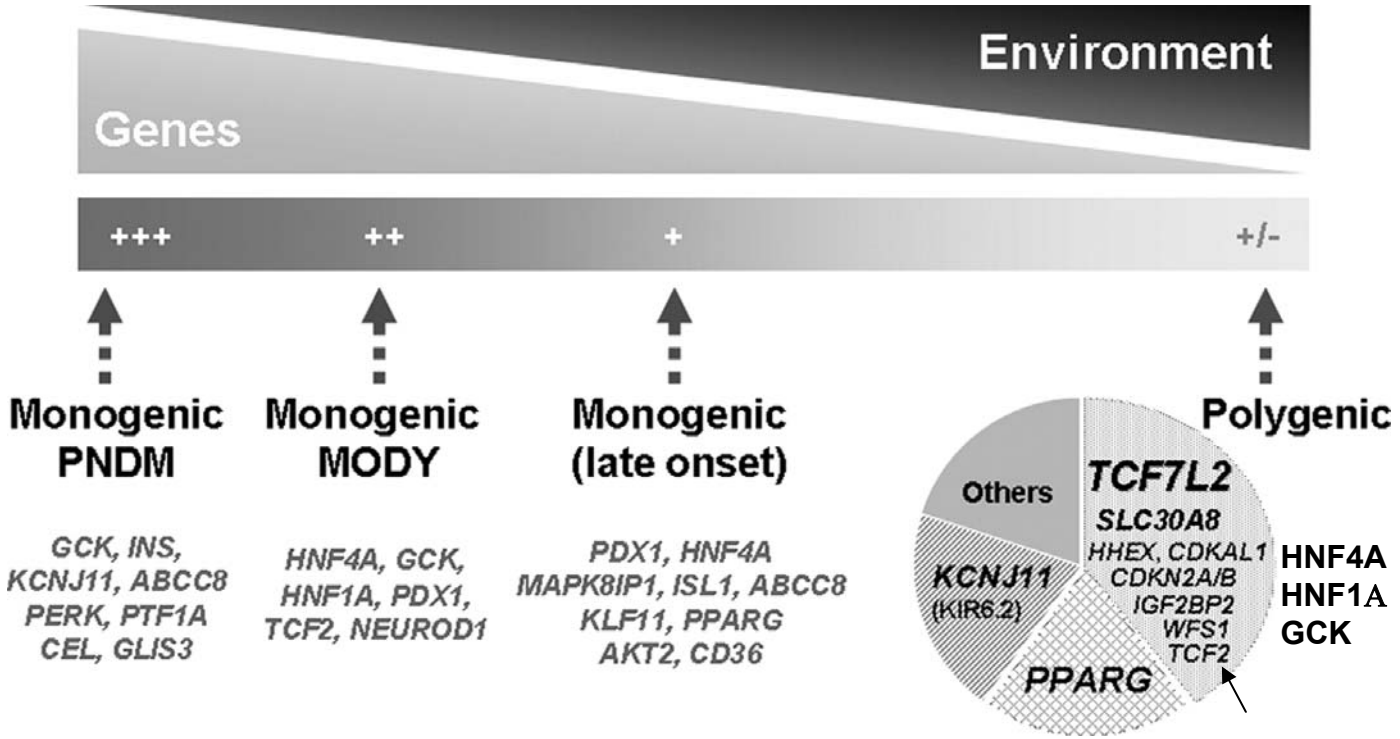
MODY8 (609812), or diabetes-pancreatic exocrine dysfunction syndrome, is caused by heterozygous mutation in the **CEL** (carboxyl-esther-lipase) gene (114840) on chromosome 9q34.

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



Vaxillaire, M. et al. Endocr Rev 2008;29:254-264

ENDOCRINE REVIEWS

Putative biomarkers of MODY subtypes investigated to date

Test	Suggested differential diagnosis	Prospect of clinical use
Serum apolipoprotien M (apoM)	HNF1A-MODY vs. HNF-4A-MODY and type 2 diabetes	Not replicated in subsequent study [1,2]
Serum complement 5 (C5) **Serum complement 8 (C8)**	HNF1A-MODY and HNF4A-MODY vs. type 2 diabetes	Insufficient specificity [3]
Serum transthyretin (TTR)	HNF4A-MODY vs. type 2 diabetes	Insufficient specificity[3]
Serum 1,5-anhydroglucitol	HNF1A-MODY vs. type 2 diabetes	Requires confirmation and validation in other types of diabetes [4]

1. Richter S, et al, Diabetes 2003;52(12):2989–2995; **2.** Skupien J et al. Rev Diabet Stud 2007;4(4):231–235; **3.** Karlsson E et al, Diabet Med2008;25(7):788–791; **4.** Skupien J et al, Diabetes Care 2008;31(8):1496–1501

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)

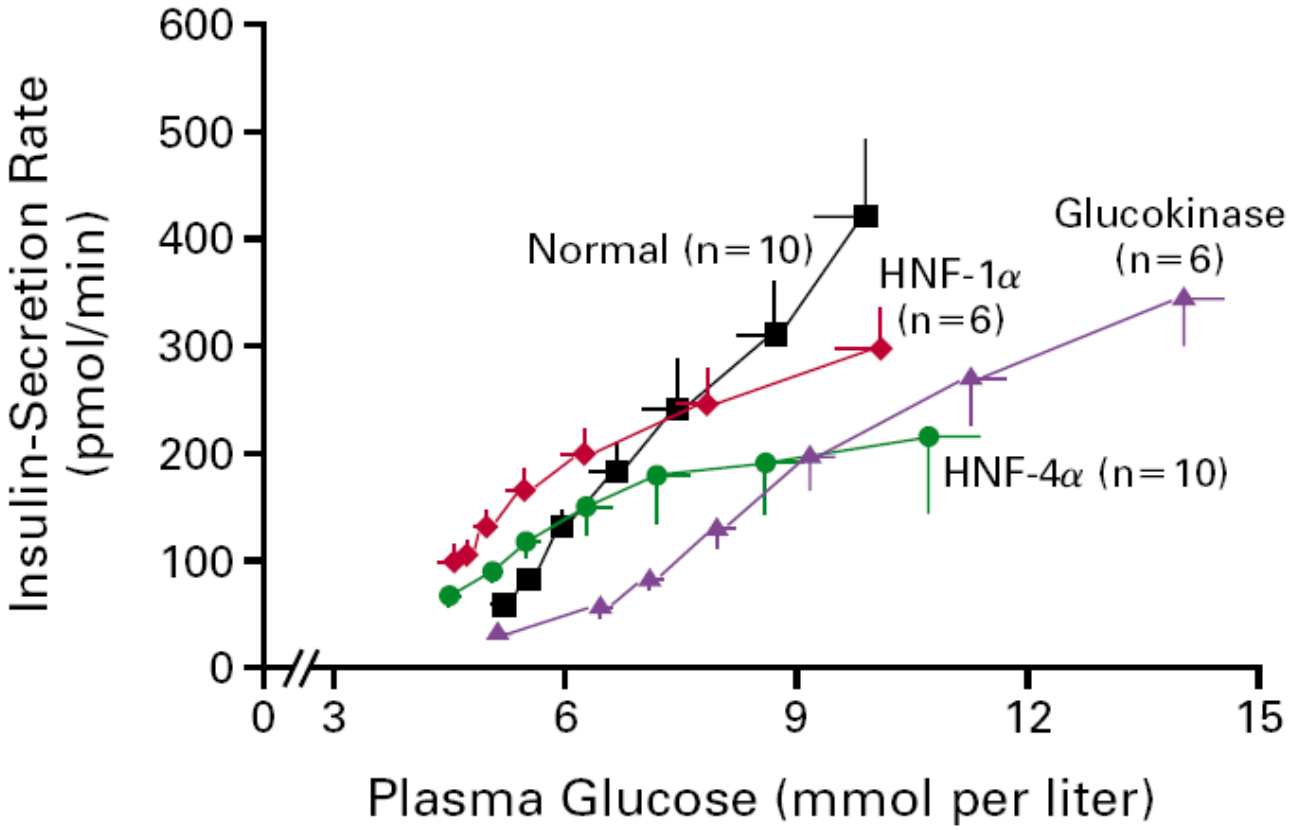
- Genetic testing for MODY is **available** and should be seriously considered for diabetics of any age with non-ketotic insulin-sensitive hyperglycemia or with a family history of diabetes

- 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)

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

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


Insulin-Secretion Rate
(pmol/min)
600
500
400
300
200
100
0
0
3
6
9
12
15
Plasma Glucose (mmol per liter)
Normal (n=10)
HNF-1α
(n=6)
Glucokinase
(n=6)
HNF-4α (n=10)