MGZ

Medical Genetics Center

Clinician Information

HEREDITARY DIABETES

LEADING SYMPTOM: DIABETES WITH INITIAL MANIFESTATION BEFORE AGE 45.

Genetic Differential Diagnosis

A large number of **monogenetically-based syndromes** and **metabolic disorders** can appear together with diabetes. The most common ones are:

- **MODY (Maturity Onset Diabetes Of the Young)** and
- **MIDD (Maternal Inherited Diabetes and Deafness)**

Characteristics of MODY (Maturity Onset Diabetes Of the Young)

MODY is difficult to diagnose because it displays both typical features of type 1 and type 2 Diabetes mellitus, and is therefore often misidentified as one of the two major forms of diabetes.

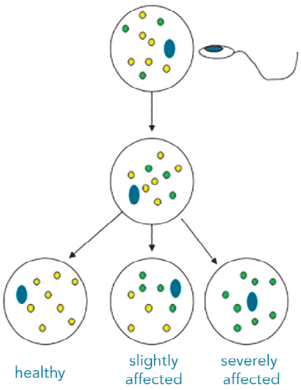
- As opposed to Diabetes mellitus type 2, manifestation generally occurs **before age 45.**
- **Only rarely accompanied by a metabolic syndrome**
- **Autosomal dominant inheritance**, therefore family medical history is usually positive
- As opposed to Diabetes mellitus type 1, there are **usually no autoantibodies**, and for many MODY forms, no insulin therapy is necessary.

Overview: MODY Forms

	MODY	Pathophysiology	Characteristics	Therapy
HNF4A	1	B cell dysfunction	Neonatal hyperinsulinemia, low triglycerides	Sulphonylurea
GCK	2	B cell dysfunction	Hypoglycemia in neonatal age	Diet
HNF1A	3	B cell dysfunction	Glucosuria	Sulphonylurea
PDX1	4	B cell dysfunction	Homozygous: pancreatic agenesis	Diet, OAD or Insulin
HNF1B	5	B cell dysfunction	CAKUT type, pancreatic hypoplasia	Insulin
NEUROD1	6	B cell dysfunction	Diagnosis in adulthood	OAD or Insulin
KLF11	7	B cell dysfunction	Similar presentation to D.m. type 2	OAD or Insulin
CEL	8	Endocrine and exocrine pancreatic dysfunction	Exocrine insufficiency, lipomatosis	OAD or Insulin
PAX4	9	B cell dysfunction	Possible ketoacidosis	Diet, OAD or Insulin
INS	10	Insulin gene mutation	Also PNDM	OAD or Insulin
BLK	11	Insulin secretion defect	Overweight, relative insulin secretion defect	Diet, OAD or Insulin
ABCC8	12	K-channel dysfunction	Homozygous: PNDM Heterozygous: transient neonatal diabetes	OAD (Sulphonylurea)
KCNJ11	13	K-channel dysfunction	Homozygous: PNDM	Diet, OAD or Insulin
APPL1	14	Insulin secretion defect		Diet, OAD or Insulin

Characteristics of MIDD (Maternally Inherited Diabetes and Deafness)

- Manifestation generally **between ages 30 and 40**
- Almost always accompanied by **inner ear deafness**
- **Maternally inherited** through **mitochondrial DNA**



Mitochondrial Inheritance:
Pathogenic changes in the mitochondrial genome are inherited **maternally**, as the mitochondria are transmitted exclusively to the offspring via the mother's ovum. Since the ratio between healthy and pathogenically altered mitochondrial DNA can be different for people who are affected by this (even if they are from the same family), as well as between tissues in the same person (**heteroplasmy, mitotic segregation within the tissues**), both the progression of the disease and the **involvement of the organs** are **variable** and not predictable.

DIAGNOSTIC STRATEGY

Diagnostic Algorithm for MODY

The MODY diagnosis is **primarily accomplished through genetic testing**. NGS panel testing analyzes all 14 previously known causative genes simultaneously, and can thereby confirm or largely exclude a clinical diagnosis.

Possible Indications for Human Genetic Diagnostics with Suspected MODY:

- Pregnancy diabetes
- Diabetes mellitus before age 45 that cannot be clearly classified as type 1 or type 2
- Persistent low insulin demand
- Suspected Diabetes mellitus type 1 without detection of autoantibodies
- Positive family medical history in accordance with autosomal dominant inheritance
- Suspected Diabetes mellitus type 1 with persistent evidence of C-peptide
- Diabetes and positive family medical history for abnormalities of kidneys and/or pancreas or kidney cysts

Diagnostic Algorithm for MIDD

The most common **mutation is m.3243 A>G, which is also associated with MELAS syndrome** and an underlying cause for mitochondrial diabetes. The presence of this variant should be tested as a first step in case of suspected MIDD. However, other mutations in the mitochondrial genome are more rarely described as the cause, so that the complete sequencing of the mitochondrial DNA can take place in the second step. Detection from blood can be difficult because the degree of heteroplasmy of the blood can shift in favor of healthy mitochondrial DNA during the course of life and therefore the diagnosis from the blood becomes more difficult. If necessary, testing a second type of tissue can be useful.

Possible Indications for Human Genetic Diagnostics with Suspected MIDD:

- Diabetes and inner ear deafness
- Pregnancy diabetes
- Positive family medical history in accordance with maternal inheritance

Mutation Detection Rates

- It is assumed that at least **1 - 2 % of all diabetics** have **MODY**, of which most are not correctly diagnosed as such.
- About **1 %** of all diabetes cases are based on a **mitochondrial inherited form** (MIDD).

Clinical Utility / Clinical Value of Human Genetic Diagnostics

The exact molecular genetic testing is important for:

- the prognosis regarding vascular complications,
- the therapy recommendation, and
- the genetic counseling of affected persons and their families regarding the risk of recurrence.

MODY: The correct diagnosis is especially of vital importance for MODY, because the recommendations for therapy, and the risk for the development of macro- and microvascular complications, depend largely on the genotype.

MIDD: Since mitochondrial diseases are associated with a higher risk of lactate acidosis, a metformin therapy is contraindicated. With mitochondrial inherited diabetes, there are high risks of microvascular and macrovascular complications, and appropriate controls are recommended. Often, insulin therapy for controlling blood sugar levels is necessary.

INHERITED DIABETES

Leading Symptom

Diabetes mellitus before age 45.

Genetic Causes

MODY: heterogeneous (14 associated genes known), MIDD: most frequent detection of the mitochondrial mutation m.3243A>G, less frequently, other mutations of mitochondrial DNA

Frequency

At least 1 - 2% of diabetes cases

Inheritance

Autosomal dominant (MODY) or maternal (MIDD)

Manifestation

Possible from childhood until late adulthood. Usually before age 45.

Progression

Dependent on the type of genetic cause. The spectrum ranges from forms that don't require treatment, without significant risk of associated complications (GCK-associated MODY), to prognostically unfavorable forms that are difficult to control.

REFERENCES

Suzuki et al. Diabetes Res Clin Pract., 2003; 59(3):207-17

Wang et al. Biochem Biophys Res Commun, 2006; 340(2): 583-8

Tim J. McDonald and **Sian Ellard**, Annals of Clinical Biochemistry, 2013; 50(5): 403-415

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