Monogenic forms of diabetes mellitus (MODY)

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Definition

- Maturity-onset diabetes of the young (MODY) is a heterogeneous group of autosomal dominant hereditary disorders characterized by mild nonketotic diabetes with onset usually under age 25 in nonobese subjects.
- MODY can be a consequence of mutations of at least 6 different genes and accounts probably for 1 - 5 % of all cases of diabetes
- The same genes are expressed in other tissues and abnormalities of liver and kidney functions may be present is some forms of MODY
- Lessons learned from study of MODY may improve our understanding the pathogenesis of type 2 diabetes

Occurence and manifestation of MODY and other rare diabetes types

• MODY 3	20 – 75 %	SEVERE
• MODY 2	10 – 65 %	MODERATE
• OTHER	RARE	1 – SEVERE 4,5 ?
• MITOCHONDRIAL DM	RARE	
• NEONATAL DM (transient and permanent)	RARE	

Type	Gene	Features of heterozygous state	treatment	Features of homozygous state
1	HNF 4α	Diabetes, microvascular complications, lipoprotein abnormalities	oral agents or insulin	
2	glucokinase	IFG, IGT,mild diabetes, mostly without complications	diet and exercise	permanent neonatal diab.
3	HNF 1α	Diabetes, renal glycosuria, sensitivity to sulfanylureas	SULFANYLUREA	
4	IPF 1	diabetes	oral agents or insulin	pancreatic agenesis with neonatal diabetes
5	HNF 1β	diabetes, renal cysts with kidney dysfunction	insulin	
6	Beta 2	diabetes	insulin	

MODY

1. Hepatocyte nuclear factor 4A
2. Glucokinase
3. Hepatocyte nuclear factor 1A
4. Insulin promotor factor
5. Hepatocyte nuclear factor 1B
6. Neurogene differentiation protein
7. Transcription factor Islet-1

GLUCOKINASE AND MODY 2

- Glucokinase is the glucose sensor of B cells
- Glycolysis, energy formation and also insulin secretion depends on the activity of enzyme
- Glucokinase in liver is reponsible for glycogen synthesis
- 130 mutations in the gene

MODY 2 – HETEROZYGOTES FOR GK GENE MUTATIONS

- Insulin secretion is not disturbed but occurs at higher glucose leves as in healthy subject
- Mild hyperglycaemia in children and in young women („gestational diabetes")
- Autosomal dominant – relatives, children!
- No progression, no complications, treatment by diet and exercise
- Homozygotes – permanent neonatal diabetes

MODY 2 AND GRAVIDITY

- Possibility of diagnosis – screening of gestational diabetes mellitus
- Hyperglycaemia of mother = big baby (fetal insulin hypersecretion)
- Intrauterine malnutrition = small baby (later risk of T2DM)

MODY 2 AND GRAVIDITY

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- Intrauterine malnutrition = small baby
  - (later risk of T2DM)

MOTHER MODY 2, FOETUS NO ?
MOTHER MODY 2, FOETUS MODY 2 ?
MOTHER HEALTHY, FOETUS MODY 2 ?

MODY 2 AND GRAVIDITY

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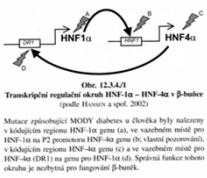
  (fetal insulin hypersecretion)
- Intrauterine malnutrition = small baby
  - (later risk of T2DM)

MOTHER MODY 2, FOETUS NO	MACROSOMIA
MOTHER MODY 2, FOETUS MODY 2	NORMA
MOTHER HEALTHY, FOETUS MODY 2	HYPOTROFIA

MODY 1,3,5

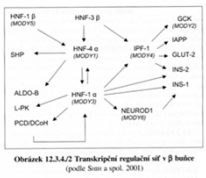
- Genes for transcription factors important for embryonal development
- MODY 3 is the most common form (120 mutations in the gene) MODY 1 and 5 are very rare
- Progressive condition, SA treatment but some of them require insulin treatment
- Complications possible
- MODY 5 also renal cysts and female genital abnormalities

HNF and the transcriptional regulatory network in B cells



Obr. 12.3.4/1
Transkripční regulační okruh HNF-1α – HNF-4α v β-buňce
(podle Hansen a spol. 2002)

Mutace způsobující MODY diabetes u člověka byly nalezeny v kódujícím regionu HNF-1α genu (a), ve vazebném místě pro HNF-1α na P2 promotoru HNF-4α genu (b; vlastní pozorování), v kódujícím regionu HNF-4α genu (c) a ve vazebném místě pro HNF-4α (DR1) na genu pro HNF-1α (d). Správná funkce tohoto okruhu je nezbytná pro fungování β-buněk.



Obrázek 12.3.4/2 Transkripční regulační síť v β buňce
(podle Sinn a spol. 2001)

MODY 4

- Rare, gene for IPF-1, transcription factor for islet development, insulin and somatostatin gene expression
- Discovered after a case of pancreatic agenesis (homozygote)

MODY 6, 7, 8

- 6 – Transcription factor Beta 2, mutation found in 2 families
  - K.O. mouse: Reduction of B cell number and perinatal diabetes
- 7 – In one family, SNP
- 8 – disturbance of both exo- and endocrine function, SNP in a noncoding region

Mitochondrial diabetes

- DIDMOAD or Wolfram sy (diabetes insipidus, diabetes mellitus, optic atrophy, sensorineural defects)
  - Various deletions in mtDNA or mutations in nuclear genes WFS1 or 2 (chr. 4) Diabetes and other spt. from childhood
- MIDD (Maternally inherited diabetes and deafness)
  - Manifestation in age 35 – 40 years
  - Up to 1 – 2 % cases of diabetes mellitus (?!)
  - Point mutation or deletion of mtDNA gene for tRNA Leu.
  - The same mutation can cause MELAS.
  - Symptomatology depends on the percentage of mutated tRNA in different tissues
- 20 different mutations (mostly in tRNA genes) associated with diabetes mellitus

MODY is dead – Murphy, 2008
4 subtypes of monogenic beta-cell diabetes

- Diabetes diagnosed before 6 months of age
  - TNDM (mostly 6q24, imprinting)
  - PNDM (KCNJ11 or ABCC8 – sulfonylurea treatment)
- Familial, mild fasting hyperglycemia (MODY 2)
  - heterozygotes, GCK mutations, homozygotes PNDM
- Familial, young-onset diabetes (MODY 3,1 and other)
  - Sulfonylurea treatment
- Diabetes with extrapancreatic features (MODY 5, mitochondrial diabetes – MIDD, DIDMOAD)

Murphy et al, 2008
MODY is dead

- Not a T1DM
  - 2 – 3 generation family history
  - No markers of autoimmunity
  - Measurable C-peptide for a long time
- Not a T2DM
  - No obesity, no insulin resistance
  - Normal lipids