Monogenic diabetes mellitus due to defects in insulin secretion

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Summary

Monogenic forms of diabetes mellitus cover a heterogeneous group of diabetes which are uniformly caused by a single gene mutation and are characterised by impaired insulin secretion of the pancreatic beta cell. It is estimated that they account for up to 5% of all cases of diabetes mellitus, which are often not diagnosed or are misclassified as type 1 or 2 diabetes. However, accurate diagnosis is important because of the special implications for treatment, prognosis and family risk. The knowledge of typical clinical features such as mode of inheritance, age at diagnosis and impaired insulin secretion, as well as genetic testing establishes the diagnosis of MODY, mitochondrial diabetes and neonatal diabetes.

Key words: *monogenic diabetes; MODY; mitochondrial diabetes; neonatal diabetes*

Introduction

It is estimated that monogenic forms of diabetes mellitus, i.e. caused by a single gene mutation, account for some 2–5% of all cases of diabetes mellitus [1–3]. Monogenic diabetes mellitus due to defects in insulin secretion comprises a genetically heterogeneous group of diabetes mellitus including MODY (maturity-onset diabetes of the young), mitochondrial diabetes and neonatal diabetes. However, the common pathophysiological pathway in monogenic disorders is impaired insulin secretion of the pancreatic beta cell [1]. The proper diagnosis of monogenic diabetes mellitus and differentiation from type 1 and type 2 diabetes is important in view of the implications for treatment and prognosis as well as for identification of family members at risk of diabetes [4–6]. Although monogenic diabetes mellitus is characterised by typical features such as young age at diagnosis (<25 years), a pronounced family history and non-obesity, low HbA_{1c} and negative pancreatic auto-antibodies, definite diagnosis is possible only by genetic testing, which is expensive and not readily available [7, 8]. Therefore, knowledge of the clinical presentation of monogenic diabetes mellitus is essential to establish high pretest probability and the diagnosis, which on average is delayed by more than 10 years [9]. At present it is estimated that more than 80% of patients with monogenic diabetes are not diagnosed or are misclassified as type 1 or type 2 diabetes [3].

Insulin secretion in monogenic diabetes mellitus

Blood glucose concentration is the main determinant of beta cell insulin secretion: glucose is transported into the
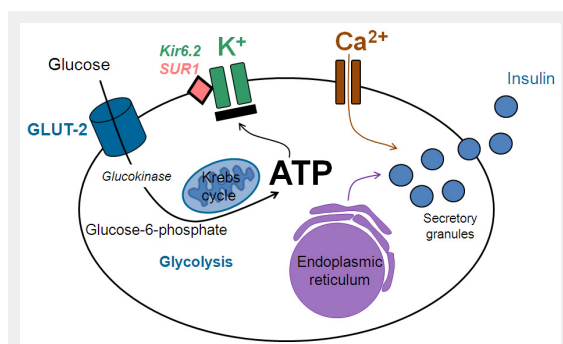

Figure 1

Pancreatic beta cell: the coupling of glucose sensing via GLUT-2 transporters, generation of ATP, membrane depolarization by closing potassium channels, entering of calcium ions, and exocytosis of insulin.
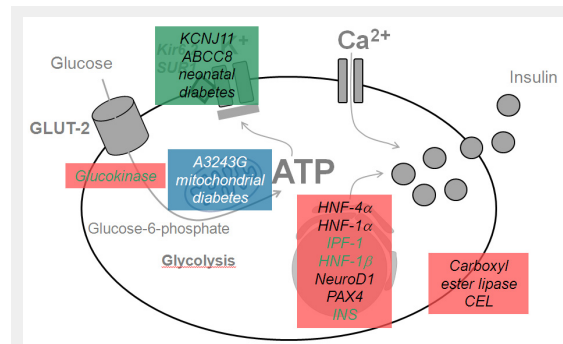

Figure 2

Location of the gene mutations and affected proteins in the pancreatic beta cell in monogenic diabetes mellitus.
MODY (red), mitochondrial diabetes (blue) and neonatal diabetes (green).

beta cell by the GLUT-2 transporter. After glucose phosphorylation by glucokinase, ATP is generated via glycolysis and the Krebs cycle in the mitochondria. ATP then closes sensitive potassium channels leading to membrane depolarisation and opening of calcium channels, which initiates exocytosis of insulin; this is biosynthesised in the endoplasmic reticulum and stored in secretory granules (fig. 1) [10, 11]. A large number of gene mutations have been described to date (e.g. over 800 mutations for the MODY genes) uniformly causing monogenic diabetes mellitus by disturbing the coupling of blood glucose concentration and insulin secretion [1, 12, 13]. Depending on the specific gene mutation, the biosynthesis and secretion of beta cell insulin is altered at various stages (fig. 2): the genes affected in MODY encode the enzyme glucokinase (GCK [MODY 2]), the transcription factors (HNF4A [MODY 1], HNF1A [MODY 3], PDX1 [MODY 4], HNF1B [MODY 5], NeuroD1 [MODY 6]), the tumour suppressor protein KLF-11 (MODY 7), the carboxyl ester lipase CEL (MODY 8), the transcription factor PAX-4 (MODY 9), and the insulin gene (MODY 10) [13–22]. Still more novel gene variants have been described very recently and their possible role in diabetes is under investigation [23]. The mitochondrial DNA mutation A3243G causes mitochondrial dysfunction in mitochondrial diabetes (also designated by the acronym MIDDM = maternally inherited deafness and diabetes mellitus) [24]. Neonatal diabetes mellitus may result from different mutations involving the Kir6.2 genes (KCNJ11 and ABCC8) [25], the transcription factor genes (HNFB1B and IPF-1 gen) [26, 27], or the glucokinase gene [28, 29].

Maturity-onset diabetes of the young (MODY)

The prevalence of the different gene mutations varies widely in patients with MODY: whereas the mutation of HNF1A (encoding hepatic nuclear factor-1α, MODY 3) accounts for 50–70%, the mutation of the GCK (encoding glucokinase, MODY 2) for 20–30%, and the mutation of HNF4A and HNF1B (encoding hepatic nuclear factor-4α and hepatic nuclear factor-1β, MODY 1 and MODY 5 respectively) account for 5% each, the remaining gene mutations are very rare and described only in a few families representing fewer than 1% of all MODY cases [2, 9, 10].

The clinical pattern of MODY is characterised by (1.) young age at diagnosis, i.e. usually between age 10 to 45, (2.) a marked family history with diabetes in every generation due to autosomal dominant inheritance, (3.) absence of obesity and insulin resistance, (4.) commonly mild hyperglycaemia without the need for insulin therapy, and (5.) negative testing for auto-antibodies against pancreatic beta cell antigens (GAD 65 and IA2) [1, 2, 4, 9, 30]. A recently published clinical predictive score to calculate the individual risk of contracting MODY [8] considered lower HbA$_{1c}$, parent with diabetes, female sex and older age to distinguish MODY from type 1 diabetes, and lower BMI, younger age, female sex, lower HbA$_{1c}$ and no treatment with oral antidiabetic drugs or insulin to distinguish from type 2 diabetes. The sensitivity and specificity of the models now available online at www.diabetesgenes.org attained over 90% by using optimal cut-offs, and are thus a valuable means of identifying patients with probable MODY and optimising genetic testing. Table 1 summarises the manner of distinguishing clinical features of MODY from type 1 and type 2 diabetes.

MODY 3, the most prevalent MODY form, is denoted by high penetrance and a typical age of manifestation of under 30 years [31]. It presents early glucosuria and accentuated postprandial hyperglycaemia which increases over time due to a decline in beta cell insulin secretion by 1–4% per year [32]. Treatment with antidiabetic drugs is therefore needed, preferably with sulfonylurea and insulin during pregnancy [33]. Strict glycaemic control during pregnancy is mandatory because maternal hyperglycaemia lowers the age of MODY manifestation in the offspring by more than 10 years [34]. The occurrence of microvascular (particularly retinal and renal) and macrovascular complications is comparable to type 1 and type 2 diabetes, likewise depending on the duration and control of diabetes [35, 36].
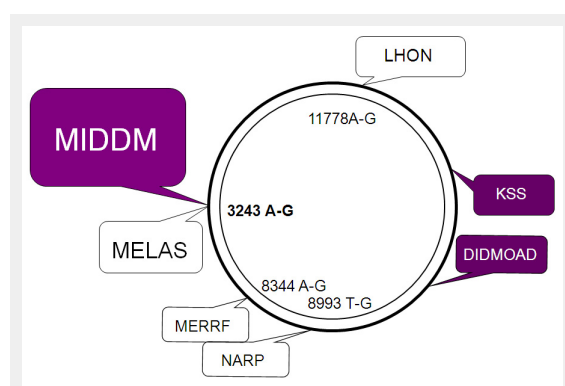

Figure 3

Mitochondrial DNA schematically depicted as circular double-strand DNA with some mutation syndromes.
MIDDM = maternally inherited deafness and diabetes mellitus; MELAS = mitochondrial encephalomyopathy, lactic azidosis and stroke-like episodes; DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, and deafness; KSS = Kearns-Sayre syndrome; LHON = Leber's hereditary optic neuropathy; MERRF = myoclonic epilepsy, ragged-red fibers; NARP = neuropathy, ataxia, and retinitis pigmentosa.
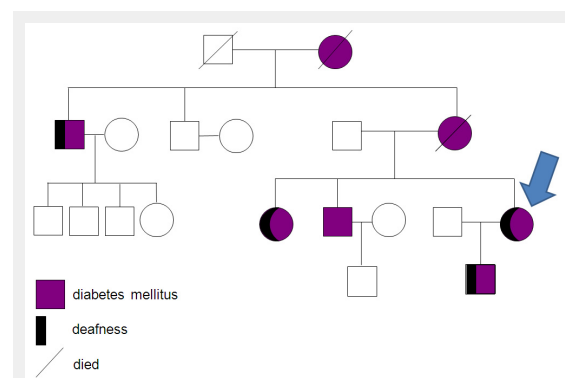

Figure 4

Pedigree of a 52-year-old woman with MIDDM (arrow), in whom diabetes was diagnosed at the age of 31 years during her first pregnancy with characteristic matrilinear transmission and hearing loss. In her son mitochondrial diabetes mellitus was diagnosed at the age of 16.

MODY 2, the other common MODY form, typically causes hyperglycaemia starting at birth [13, 37]. As a consequence of the impaired conversion of glucose to glucose-6-phosphate and hence reduced glucose sensing, insulin secretion starts at a higher threshold (at blood glucose of 6–7 mmol/l instead of 5 mmol/l) resulting in mild and not worsening hyperglycaemia without the need for treatment and without secondary complications [38].

MODY 1 presents in a similar manner to MODY 3 (given the mechanism whereby HNF-4α regulates the expression of HNF-1α) but is relatively uncommon [1, 2].

MODY 5 is a distinct MODY form with additional renal cysts and genitourinary malformation (aplasia of the vasa deferentia and of the vagina) [39]. The spectrum of clinical features varies, in that at one time diabetes dominates and at another time the urinary tract malformations [40–42]. Contrary to the other MODY forms there is a high rate of spontaneous mutations, making family history unreliable and often rendering insulin treatment necessary [43].

The remaining rare MODY forms are accompanied by disturbances of endocrine *(MODY 4, MODY 6)* [19, 44] and exocrine *(MODY 7, MODY 8, MODY 9)* pancreatic development [21, 45], or the mutation in the insulin gene and neonatal diabetes *(MODY 10)* [46]. Table 2 summarises the features of the various MODY types.

At present sequencing of the most frequent MODY genes is routinely performed, i.e. HNF4A (MODY 1), GCK (MODY 2), HNF1A (or transcription factor-1 TCF-1) (MODY 3), and HNF1B (or transcription factor-2 TCF-2) (MODY 5), confirming the diagnosis of MODY in the majority of cases. However, new gene mutations are regularly detected [23, 47], also expanding the clinical spectrum of the MODY subtypes with sometimes considerable overlap with type 1 and type 2 diabetes. Therefore, other characteristics distinguishing MODY from both common types of diabetes have been investigated, such as serum high-sensitive C-reactive protein (CRP), which has proved to be lower in MODY 3 patients than in healthy individuals (because HNF-1α promotes the expression of CRP [48]). The role of MRI/CT imaging in identifying pancreatic alterations (i.e., pancreatic size, lipomatosis, fibrosis and calcification) in MODY has also been evaluated. Recent studies described a slightly reduced pancreatic volume in MODY 3, pancreatic hypoplasia with agenesis of the dorsal and caudal part in MODY 5, as well as pancreatic atrophy and an increased fat content in MODY 8 [49, 50].

Accurate diagnosis of MODY has important prognostic and therapeutic implications for the individual and the family. Best practice guidelines have been established for mo-

lecular genetic testing in patients with suspected MODY [2, 5, 7, 9]. They advocate testing in individuals with a strong family history, presentation at younger age (<25 years) and features atypical for type 1 diabetes (negative antibodies, insulin independence) or type 2 diabetes (absent components of the metabolic syndrome). However, taking further specific clinical features into consideration increases the likelihood of detecting the different MODY subtypes: if the above-mentioned features are present in young-onset diabetes, which remains insulin-independent for more than 3 years and there is marked sensitivity to sulfonylureas, MODY 3 and 1 are likely; additional renal and genital abnormalities indicate MODY 5; if there is persistent mild hyperglycaemia >5.5 mmol/l with only a small increase in <3 mmol/l in the oGTT, typically diagnosed in pregnancy, MODY 2 is suspected and testing for GCK mutations recommended. These MODY subtypes 1, 2, 3 and 5 make up over 95% of all MODY gene mutations. Laboratories performing certified sequencing of the suspected gene(s) are listed on the following website http://www.ncbi.nlm.nih.gov/sites/GeneTests/. The actual cost of one gene sequencing is about CHF 1,200.–, and reimbursement by the insurance companies must be applied for.

Mitochondrial diabetes mellitus

Mitochondrial DNA (mtDNA), which is almost exclusively of maternal origin (fig. 3), harbours 37 genes many of which encode enzymes involved in oxidative phosphorylation [51]. Hence mutations in the mtDNA predominantly affect organs with a high energy demand such as skeletal muscle, brain, sensory organs and pancreatic beta cells causing a wide spectrum of syndromes (fig. 4): the point mutation A→G at position 3243 generates mitochondrial diabetes with deafness (MIDDM) at an estimated prevalence of 0.4 to 1.5% [52], and the MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes). The clinical manifestations of MIDDM, including age of onset and requirement of insulin treatment depend on the heteroplasmy, i.e. the level of mutated mtDNA in the individual patient [53, 54]. Thus the age when diabetes is diagnosed ranges from 8–70 years with a mean of 35 years, and ketoacidosis occurs in almost one third of patients. Hearing loss affects 90% and myopathy 30% of patients with MIDDM. Because diabetes develops due to failure of insulin secretion, most patients will eventually need insulin treatment, whereas metformin should be not be given because of possible myopathy [55]. Diabetes

Table 1: Clinical characteristics of MODY vs diabetes type 1 and type 2 (adapted from [1, 2, 9]).

Characteristic	MODY	Type 1 diabetes	Type 2 diabetes
Age at diagnosis	<25 y	5–20 y	>25 y
Parental history	60–95%	<10%	10–40%
Inheritance	Autosomal dominant autoimmune disease		polygenic
Obesity Insulin resistance Metabolic syndrome	} Uncommon	Uncommon	Common
Beta cell antibodies	Absent	Present	Absent
C-peptide	Normal	Undetectable	High – low
Optimal treatment	Sulfonylurea (MODY 1,3,4)	Insulin	Metformin

is also associated with other mtDNA mutation syndromes such as the Wolfram syndrome (the acronym DIDMOAD stands for diabetes insipidus, diabetes mellitus, optic atrophy and deafness) [57] or Kearns-Sayre syndrome (KSS, external ophthalmoplegia, cardiac conduction block, retinal degeneration, deafness, and ragged red muscle fibers) [57].

Neonatal diabetes mellitus

Neonatal diabetes mellitus describes a heterogeneous group of diabetes forms occurring until the age of six months in about 1:200,000 live births [58], caused by mutations of different genes involved in pancreatic organogenesis, formation of beta cells and insulin synthesis. Depending on the underlying gene mutations, neonatal diabetes is classified into transient or permanent. Due to the intrauterine insulin deficiency children are small for gestational age, with diminished subcutaneous fat.

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Table 2: Different MODY subtypes: gene mutations, pathophysiology and clinical manifestations (with prevalence amongst MODY patients).

MODY	Pathophysiological mechanism	Clinical characteristics
1	Abnormal beta cell gene transcription leading to deficient insulin secretion	Rare (5%); neonatal hyperinsulism, low triglycerides, diabetes prone to microvascular complications, sensitive to sulfonylurea
2	Reduced glucose sensitivity due to deficient phosphorylation, impaired glycogen storage	Common (30-50%); impaired fasting glucose, increment <3 mmol/l in oGTT (<4.6 mmol/l in pregnancy); mild diabetes, usually no antidiabetic treatment needed
3	Abnormal gene transcription causing deficient insulin secretion, progressive beta cell failure	Common (30-50%) and high penetrance; glucosuria, microvascular complications, treatment with sulfonylurea (and insulin)
4	Impaired pancreatic development, pancreatic agenesis in homozygous state	Rare (1%); average onset at age 35 years, oral antidiabetic drugs (and insulin)
5	Abnormal gene transcription causing deficient insulin secretion	Rare (5%); diabetes with extrapancreatic manifestations (renal cysts or dysplasia, genital abnormalities in female, azoospermia in male), large variability in phenotype, insulin treatment needed
6	Abnormal development of beta cell function	Very rare (<1%); adult onset of diabetes
7	Reduced glucose sensitivity of the beta cell, tumour suppressor gene in pancreas (KLF-11)	Very rare (<1%); phenotype similar to type 2 diabetes
8	Impaired control of endocrine and exocrine pancreatic function (pathophysiology?)	Very rare (<1%); diabetes with typical autosomal dominant heredity
9	Impaired gene transcription in pancreatic beta cells on apoptosis and proliferation	Very rare (<1%); ketoacidosis possible
10	Heterozygous mutation of the insulin gen	Very rare (<1%); diabetes diagnosed <20 years, sulfonylurea and insulin late in follow-up
11	Heterozygous mutation of the BLK gene (tyrosin kinase expressed in pancreatic islets) affecting insulin secretion	Very rare (<1%); higher penetrance with increasing body mass index

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Figures (large format)

Figure 1

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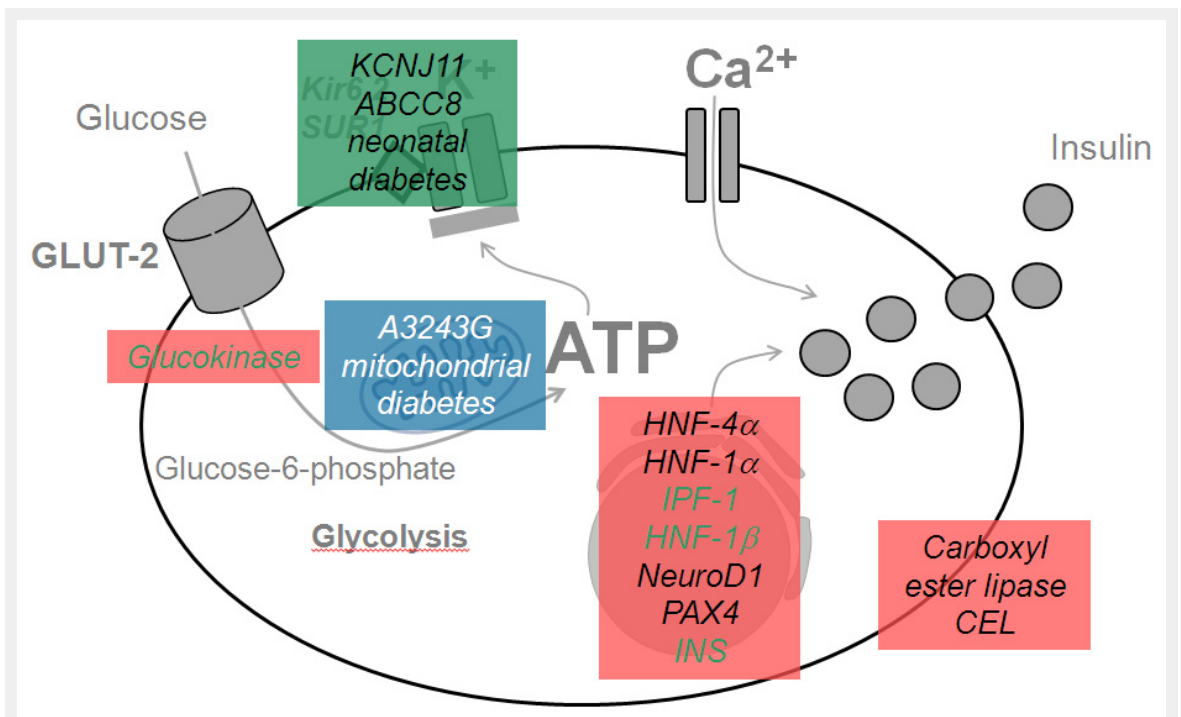

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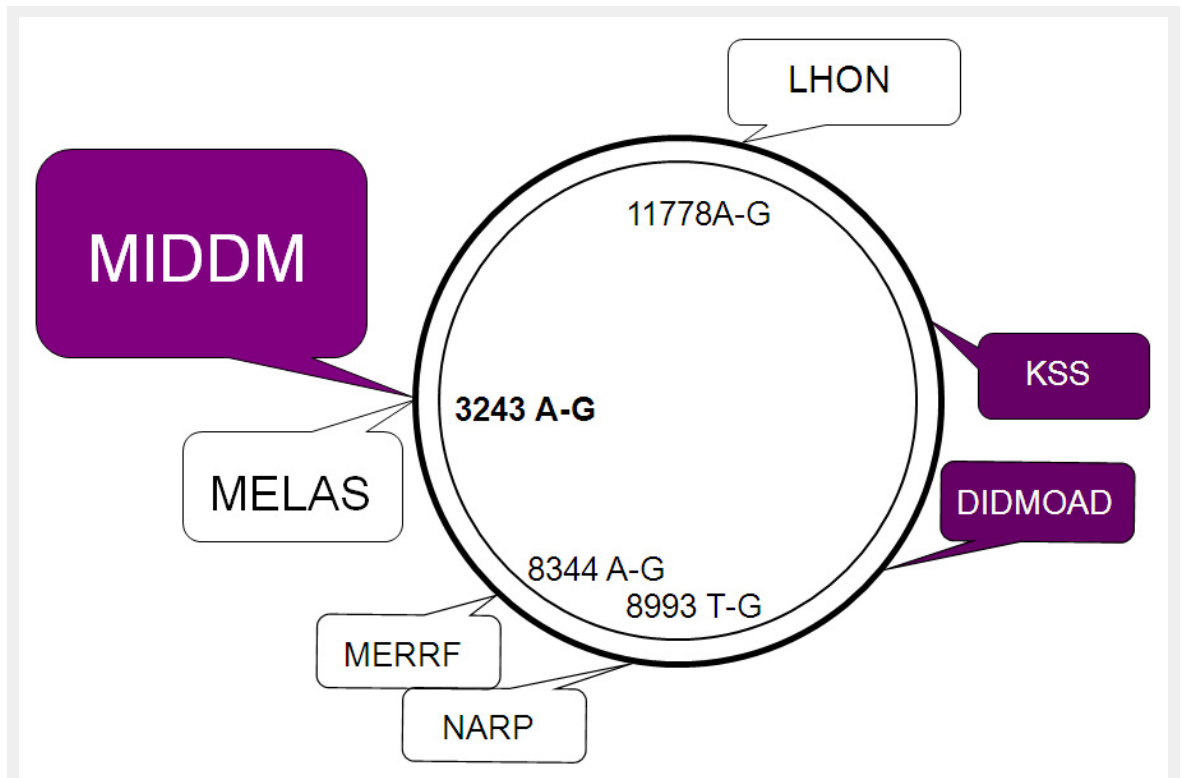MODY (red), mitochondrial diabetes (blue) and neonatal diabetes (green).

Figure 3

Mitochondrial DNA schematically depicted as circular double-strand DNA with some mutation syndromes.

MIDDM = maternally inherited deafness and diabetes mellitus; MELAS = mitochondrial encephalomyopathy, lactic azidosis and stroke-like episodes; DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, and deafness; KSS = Kearns-Sayre syndrome; LHON = Leber's hereditary optic neuropathy; MERRF = myoclonic epilepsy, ragged-red fibers; NARP = neuropathy, ataxia, and retinitis pigmentosa.
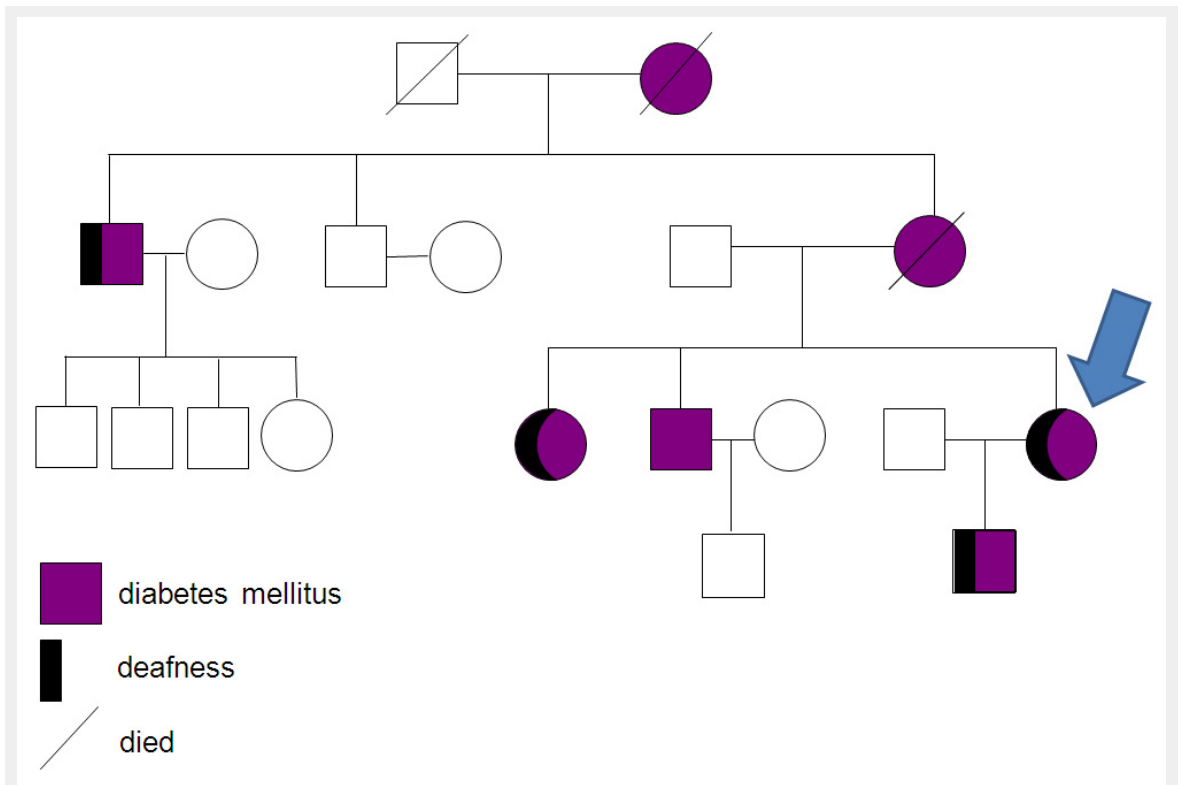
Figure 4

Pedigree of a 52-year-old woman with MIDDM (arrow), in whom diabetes was diagnosed at the age of 31 years during her first pregnancy with characteristic matrilinear transmission and hearing loss. In her son mitochondrial diabetes mellitus was diagnosed at the age of 16.