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Atypical phenotypic features among carriers of a novel Q248X nonsense mutation in the *HNF1B* gene

Atypowe cechy fenotypowe u nosicieli nowej mutacji nonsens Q248X w genie *HNF1B*

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Abstract

Introduction: Hepatocyte transforming factor 1B-maturity onset diabetes mellitus of the young (*HNF1B*-MODY) is an autosomal dominant type of monogenic diabetes caused by a mutation in the gene encoding hepatocyte nuclear factor 1beta (HNF-1beta).
The aim of this study was to determine if a *HNF1B* gene mutation was responsible for a dominantly inherited form of diabetes mellitus among the members of a three-generation Polish family.
Material and methods: The index subject was a 13-year-old boy with metabolic syndrome, spina bifida occulta, posterior urethral valves, congenital ureteropelvic junction obstruction, and a family history of diabetes of autosomal dominant trait of inheritance. We performed clinical and laboratory examinations of his family and sequenced the *HNF1B* gene.
Results: A novel Q248X mutation (nucleotide C to T transition at position 742 of the exon 3 of *HNF1B* gene, resulting in stop codon formation) was identified. Phenotypes of family members sharing this mutation are highly variable, and include previously known abnormalities of the urinary system and pancreas, diabetes mellitus of variable onset and severity, hyperinsulinaemia, insulin resistance, metabolic syndrome, elevated aminotransferases, hyperbilirubinemia, hyperamylasemia, short stature and cataracts. To the best of our knowledge, spina bifida occulta, pectus carinatum, and splenomegaly have not been previously reported.
Conclusions: Our results broaden the spectrum of *HNF1B* gene mutations and *HNF1B*-MODY-related phenotypes.
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Key words: *hepatocyte nuclear factor 1-beta; HNF1B-MODY; pectus carinatum; phenotype; spina bifida occulta; splenomegaly; Q248X mutation*

Streszczenie

Wstęp: Cukrzyca HNF1B-MODY dziedziczona w sposób autosomalnie dominujący jest rodzajem cukrzycy monogenowej, którą powoduje mutacja w genie *HNF1B* (hepatocyte transforming factor 1B). Celem pracy było zbadanie czy mutacja w *HNF1B* jest przyczyną występowania cukrzycy w trzech pokoleniach polskiej rodziny.
Materiał i metody: Przeprowadzono ocenę kliniczną i laboratoryjną oraz sekwencjonowanie genu *HNF1B* trzynastoletniego chłopca z zespołem metabolicznym, rozszczepem kręgosłupa, zastawkami cewki tylnej i wrodzonym zwężeniem moczowodu oraz obciążonym wywiadem rodzinnym w kierunku cukrzycy. Ze względu na wywiad rodzinny o autosomalnie dominującym sposobie dziedziczenia cukrzycy zbadano również członków jego rodziny.
Wyniki: Stwierdzono obecność nowej mutacji Q248X będącej skutkiem przeniesienia nukleotydu C na miejsce T w pozycji 742 eksonu 3 genu *HNF1B* i powstaniem kodonu stop. Cechy fenotypowe członków rodziny będących nosicielami tej mutacji okazały być się bardzo zróżnicowane, a niektóre z nich takie jak *spina bifida occulta, pectus carinatum* i splenomegalia nie były dotychczas opisywane.
Wnioski: Wyniki poszerzają spectrum mutacji genu *HNF1B* oraz związanych z nimi cech fenotypowych cukrzycy *HNF1B*-MODY .
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Słowa kluczowe: *hepatocytowy czynnik jądrowy 1-beta; HNF1B-MODY; pectus carinatum; fenotyp; spina bifida occulta; splenomegalia; Q248X mutacja*

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Introduction

HNF1B-MODY is one of the most rarely diagnosed types of diabetes, affecting 0.6% of children and adolescents with all forms of diabetes mellitus. It accounts for 4.7% in subjects with auto-antibody-negative diabetes and 11% in a subgroup of those with genetic testing for a monogenic form of diabetes called MODY (maturity onset diabetes in the young) [1]. It was first described in 1997 in a Japanese family as the association of early-onset diabetes and non-diabetic nephropathy [2]. Due to its rarity, detailed scientific information about genotype/phenotype correlation is still very limited.

HNF1B-MODY results from a mutation in the gene encoding HNF1-beta (hepatocyte nuclear factor 1-beta, also known as vHNF1 or TCF2), a widely distributed transcription factor which forms an integrated regulatory network with other transcription factors [3]. HNF1-beta is expressed in many organs including the pancreas, liver, lung and thymus, as well as the gastrointestinal and genitourinary tracts, and plays a critical role in early development and embryonic survival [4, 5]. Therefore, *HNF1B*-MODY has a wide clinical spectrum including the most common features such as diabetes, nondiabetic renal disease, congenital malformations and dysfunction of the above mentioned organs [1].

Here we present a three-generation family diagnosed with *HNF1B*-MODY caused by a novel nonsense mutation in the *HNF1B* gene.

Material and methods

Subjects

The index subject (III-1) was a 13-year-old boy referred to hospital due to fasting hyperglycaemia (7.2–7.8 mmol/L), increased blood pressure, and tachycardia. He was born on the due date with a birth weight of 2,900 g and with asymptomatic spina bifida occulta of the lumbo-sacral region. In the first month of his life, he was diagnosed with posterior urethral valves and underwent surgical treatment. At nine months of age, he was operated on again due to congenital ureteropelvic junction obstruction. The family history revealed that his father, father's brother and grandmother (the father's and uncle's mother) also suffered from diabetes.

Autoantibodies detection

The conventional autoantibodies were measured on serum samples: ICA with immunofluorescence, antibodies against GAD and IA2 by ELISA (RSR, USA), and insulin antibodies with RIA (CisBiointernational, France). The cut-off values for ICA, GADA and IA2A positivity were 10 Juvenile Diabetes Foundation units, 10 U/mL, and 20 U/mL respectively. According to the Diabetes Autoantibody Standardisation Programme (DASP) 2010, the disease sensitivity of the ICA, GADA, and IA2A was 69.4%, 88% and 70% respectively, while the corresponding specificities were 93.3%, 94.4% and 83.3%.

Mutation detection

Genomic DNA was isolated from peripheral blood leukocytes using QiaAmp DNA mini kits from Qiagen (Qiagen, Hilden, Germany) in accordance with the manufacturer's instructions. DNA sequences of the *HNF1B* region were amplified by means of PCR reaction [2]. Products were evaluated by means of 2% agarose gel electrophoresis with ethidium bromide. Results were analysed and stored as digital UV photographs. DNA purification was performed using Qiaquick columns (Qiagen, Hilden, Germany) according to the manufacturer's instructions. DNA sequencing was performed using BigDye Seq kit v3.1 (Applied Biosystems, Foster City, CA, USA). Sequencing reaction was conducted by using 200 ng of PCR product as a matrix in a labelling reaction, 50pM of one oligonucleotide (forward and reverse, separately) and 2.5x sequencing buffer. Sequencing reactions were conducted under the following protocol: 15 sec. at 95°C, 36 replications of: 95°C 20 sec., 60°C 5 sec. and 61°C 4 min. After the sequencing reaction, the products were precipitated with 125 mM EDTA, 3M sodium acetate and 96% ethanol. The vials were centrifuged for 45 min. at 8,000 rpm, kept dry at room temperature afterwards, and resolved in HiDi Formamide (Applied Biosystems).

The identification of mutations was performed by direct sequencing using the ABI 3130 genetic analyser (Applied Biosystems). Analysis of chromatograms was performed using DNA Sequencing Analysis Software (Applied Biosystems). For comparative analysis of evaluated sequences with the human genome reference (RefSeq NM_000162.3), the Sequencher software v4.1.4 (GeneCodes, Ann Arbor, MI, USA) was used.

This study was approved by the Bioethics Committee of the Medical University of Lodz, Poland. Informed consent was obtained from all patients / parents.

Results

Phenotypic variability among family members

Proband

On admission, the boy's height was 174 cm (97th centile) and weight 72 kg. The BMI (body mass index) of 23.8 kg/m^2 indicated overweight (BMI-for-age at the 92nd percentile for boys aged 13 years 1 month, Z-Score 1.41). His blood pressure was increased (average 150/110 mmHg). Laboratory analyses showed fasting hypergly-

Table I. *Summary of clinical features of the affected family members*
Tabela I. *Cechy fenotypowe I profil biochemiczny pacjentów z mutacją Q248X w genie* **HNF1B**

Patient No	III-1	III-3	III-4	II-1	II-3	I-2
Genetic status	N/M	N/M	N/M	N/M	?	?
Present age	13	10	8	37	36	57
Age at diagnosis	13	10	8	36	34	33
BMI at diagnosis (kg/m^2)	24.5	19.6	16.9	25.9	23.5	33.5
BMI at diagnosis (Z-score)	1.41	0.93	0.17			
Pancreas structure (CT)	partial agenesis	partial agenesis	?		?	?
Liver structure (USG)	normal	normal	normal	normal	normal	–
Diabetes	+	–	–	+	+	+
Hypertension	+	non–dipper	–	+	–	+
Kidney structure cysts	bilateral cortical cysts hydronephrosis	single hypoplastic ectopic cortical cysts	kidney cortical cysts	bilateral cortical cortical cysts	bilateral cortical cyst	single left kidney renal stone
Genitourinary tract	PUV abnormalities UJO	UJO	–	–	–	–
Spleen size (USG/CT)	normal	splenomegaly*	splenomegaly*	normal	normal	normal
Skeletal abnormalities	spina bifida occulta*	pectus carinatum*	–	–	–	–
Eye defects	–	–	–	–	early cataracts	early cataracts
Other features						short stature

PUV — posterior urethral valves; UJO — uretheropelvic junction obstruction; * new phenotypic feature

caemia 6.11 mmol/L (normal 3.3–5.9 mmol/L). The glucose level of 12 mmol/L in 120′ during oral glucose tolerance test (OGTT) confirmed the diagnosis of diabetes. The level of HbA_{1c} at the time of admission was 5.91% (normal range 4.8–6.0). Fasting hyperinsulinaemia and insulin level at 120 minutes of OGTT was 101.7 uU/mL, indicating insulin resistance (insulin level at 120 minutes > 75 uU/mL) [6, 7]. This, however, was not confirmed by the HOMA-IR (Homeostasis model assessment insulin resistance) of 2.88, which was calculated by dividing the basal insulin (microunits per millilitre) and basal glucose (millimoles per litre) by 22.5 [8, 9]. The patient's C-peptide production was normal. Islet-cell antibodies (ICA), GAD (glutamic acid carboxylase) antibodies, and protein tyrosine phosphatase antibodies (IA2) were negative. Other laboratory tests revealed the presence of proteinuria, hyperuricemia, hypomagnesemia and dyslipidemia (hypercholesterolemia, high level of LDL cholesterol) (Table I). Ultrasound examination of the abdomen revealed the presence of multiple cortical cysts in both of his kidneys. His glomerular filtration rate (GFR) was normal. He had no signs of retinopathy or other vision distortion. The co-existence of diabetes, hypertension, overweight, hyperuricemia and hypertriglyceridemia was consistent with the diagnosis of metabolic syndrome. The child was initiated on treatment with metformin and ramipril. However, taking into account the co-existence of diabetes and congenital anomalies of the urinary tract, as well as the autosomal dominant history of diabetes in the family, the suspicion of *HNF1B*-MODY was worth considering.

Genetic findings

The promoters and 9 exons of *HNF1B* gene were sequenced and revealed that the patient was heterozygous for a novel Q248X mutation (nucleotide C to T transition at position 742 of the exon 3 of *HNF1B* gene) according to reference sequence NM_000458). Due to the positive family history, a genetic evaluation was also performed in five family members of the proband — the proband's sister, father and two male cousins. All of them, except the proband's sister, were shown to be heterozygous for the same mutation of the *HNF1B* gene.

Family members

The patient's father (II-1), aged 37, had been diagnosed with Latent Autoimmune Diabetes of Adulthood (LADA) at the age of 36 (i.e. a year before his son's diagnosis) and was treated with insulin. He was admitted to hospital with hyperosmolar non-ketosis diabetes syndrome (HNKDS), blood glucose 1,065 mg/dL (59.1 mmol/L), and neurologic symptoms. His C-peptide plasma

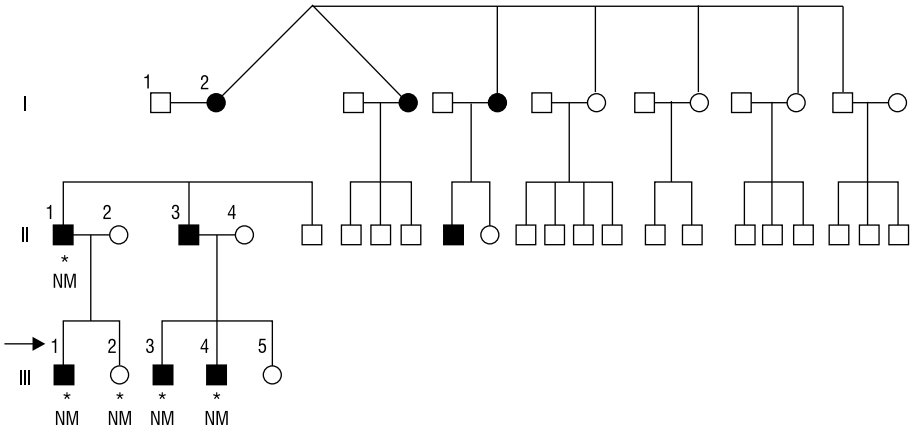

Figure 1. *Pedigree of a Polish family with Q248X mutation. The index subject (III-1) is indicated with an arrow. Black squares represent symptomatic family members. Asterisks denote individuals from whom DNA was obtained. N/M — heterozygous mutation carrier, N/N — both normal alleles*

Rycina 1. *Drzewo genealogiczne polskiej rodziny z mutacją Q248X. Strzałka wskazuje pacjenta III-1. Czarne kwadraty oznaczają pacjentów z objawami choroby. Gwiazdki wskazują członków rodziny, od których uzyskano DNA. N/M — heterozygotyczny nosiciel mutacji, N/N — obydwa allele prawidłowe*

concentration was within normal values. He was ICA and anti-GAD negative, but he was positive for IA2/ICA512 antibodies 45.04 U/mL (N < 20 U/mL). He was overweight and suffered from hypertension. He also had hypercholesterolaemia, hypertriglyceridemia, hyperuricemia and elevated concentrations of alanine aminotransferase (ALT) and proteinuria. At the time of his hospitalisation, ultrasonography revealed several cortical cysts in his kidneys — the largest of 4.7 cm diameter. GFR of 51 mL/1.73 m^2 indicating stage 3 chronic kidney disease was also revealed.

The proband's uncle (father's brother — II-3) aged 36, had initially been diagnosed with mild diabetes at the age of 34. Unlike his brother, he was lean and, until *HNF1B*-MODY diagnosis, treated with sulphonylurea. He had suffered from vision impairment since early childhood caused by bilateral cataracts. He had elevated aminotransferases without any other signs of liver dysfunction and slightly increased serum amylase. At the time of diagnosis, abdominal ultrasonography did not confirm any anomalies. However, five years later, he presented with multiple small cortical cysts in both kidneys. He was negative for ICA, anti-GAD, IA2/ICA512 antibodies and had a normal value of C-peptide plasma concentration. Due to the suspicion of *HNF1B*-MODY in this family, both his sons aged 11 and eight years (i.e. the index subject's two cousins) were invited for clinical evaluation. Until the day of examination, they had been both thought to be healthy, except for a history of atopic diseases in the elder and episodes of enuresis in the younger one. Interestingly, in both of them splenomegaly was detected.

The proband's cousin (III-3), aged 11, had pectus carinatum. Ultrasound examination revealed the presence of a single (right) kidney with hydronephrosis resulting from ureteropelvic junction obstruction. His left kidney was detected renoscintigraphically as a small hypoplastic formation of almost no function. He had proteinuria, but glomerular filtration rate (GFR) remained normal. He also exhibited hyperbilirubinemia, and elevated aminotransferases.

The proband's younger cousin (III-4), aged eight, was also diagnosed with multiple cysts of maximal diameter 4.3 mm in the right kidney. The left kidney was found to be ectopic and hypodysplastic (small with multiple cysts). He had hypercholesterolaemia with a high LDL cholesterol level and elevated serum amylase and aminotransferases. OGTT performed in both brothers showed increased blood glucose concentrations of over 11.1 mmol/L (200 mg/dL) at 30 and 60 minutes of the test, but the results did not meet the criteria for diabetes at 0 and 120 minutes. **The proband's paternal grandmother (I-2)**, aged 57, was obese, short-statured (147 cm), and had suffered from a brittle diabetes since she was 33, treated with insulin. She died suddenly from cardiac infarction at the age of 57. The woman was reported to have had bilateral cataracts since childhood, cardiac arrhythmia, dyslipidemia, hypertension, one renal cyst of 23 mm diameter and one non-obstructing renal stone in her left kidney. She had seven siblings. Two of her sisters (one of whom was her monozygotic twin sister) were also reported to be diabetic. Diabetes was also present in the offspring (son) of the other sister.

The second proband's uncle (father's brother, II-5), aged 28, was born prematurely in the sixth

Table II. *Synopsis of biochemical profile of patients with a Q248X mutation in the* **HNF1B** *gene*
Tabela II. *Cechy fenotypowe I profil biochemiczny pacjentów z mutacją Q248X w genie* **HNF1B**

Patient No	III-1	III-3	III-4	II-1	II-3	I-2	Ref. values
Genetic status	N/M	N/M	N/M	N/M	?	?	
HbA_{1c} at diagnosis (%)	5.91	4.95	5.12	**12.1**	**11.3**	7.2	4.8–6.0
C–peptide fasting [ng/mL]	1.41	2.05	1.86	1.43	2.2	1.92	1.1–4.4
C–peptide in 6' [ng/mL]*	3.31	4.27	3.13	–	4.16	–	
AST [U/L]	33	**77**	**87**	**24**	**53**	15	10–37
ALT [U/L]	**41**	**61**	**80**	**76**	**91**	19	10–31
Total bilirubin [mg/dL]	0.37	**1.48**	0.4	0.8	0.65	0.2	<1.2
Total cholesterol [mg/dL]	194	153	**209**	**204**	176	**226**	130–200
HDL cholesterol [mg/dL]	55	60	81	46	–	67	35–80
LDL cholesterol [mg/dL]	**133**	87	120	130	–	**150**	50–130
VLDL cholesterol [mg/dL]	6	6	8	28	–	9	0–45
Triglycerides [mg/dL]	137	95	56	**183**	61	29	65–150
Serum amylase [U/L]	87	55	**119**	57	**102**	–	28–100
Urine amylase [U/L]	132	67	151	35	257	–	1–460
Blood urea nitrogen [mg/dL]	9	14	22	**34**	14	**43**	9–22
Serum creatinine [mg/dL]	0.51	0.53	0.72	**1.7**	1	**1.27**	0.4–1.2
GFR [ml/1,73 m^2]	187	157	98	**51**	187	**46.1**	
Proteinuria [mg/24h]	**554**	**457**	51	**269**	–	**121**	[1]**###**
Uric acid [mg/dL]	9.7	5.6	6.1	8.7	5.2	7.2	2.1–7.0
Magnesium [mEq/L]	**0.96**	1.24	1.3	–	–	–	1.3–2.1

*after intravenous glucagon
[1] ### 4–10y: 26–94 mg/24h; 10–16y: 29–238 mg/24h; adults: 45.0–75 mg/24h

month of pregnancy, with a birth weight of 1,080 g. He is physically and mentally disabled, very obese, and suffers from glaucoma. He has no diabetes so far. **The proband's younger sister (III-2)** aged six, and his mother (II-2) are healthy. Interestingly, the younger sister was found to be positive for ICA (20 JDF). The clinical characteristics of the affected family members are summarised in Table I.

Further evaluation of paediatric mutation carriers

Contrast-enhanced computed tomography (CT) of the abdomen was performed in the proband (III-1) (Fig. 2) and the proband's cousin (III-3). It revealed splenomegaly and complete absence of neck, body and tail of the pancreas with a normal-appearing head, indicating partial agenesis of the pancreas in both of the patients.

The proband's faecal elastase concentration was diminished (169 μg/g, normal range > 200 μg/g), while that of subject III-3 was normal (405 μg/g).

Due to the rapidly deteriorating renal function of patient III-4 (presently stage 3 of chronic kidney failure), a contrast-enhanced CT was not carried out. Nevertheless, partial pancreatic agenesis is also probable in this case as only the presence of the head and body of pancreas was confirmed on ultrasonography.

Discussion

To date, there have been more than 100 different mutations in *HNF1B* reported to cause *HNF1B*-MODY. They are either novel monoallelic mutations within or allelic deletions of chromosome 17q12 including the *HNF1B* locus (17cen-q21.3) [1,10]. The associated phenotypes result from altered expression pattern of the transcription factor HNF1beta during organogenesis *in utero* [11].

We here report on a novel nonsense Q248X mutation of the *HNF1B* gene found in four members of one family. This novel mutation, resulting in stop codon formation in exon 3, is associated with severe phenotypic features such as partial pancreatic agenesis, severe renal and urinary tract malformations, diabetes, liver disease, short stature, and cataracts. All of these have been previously reported in the literature in association with other mutations [5, 12–20].

However, in some members of the family, we also found new and interesting features such as spina bifida

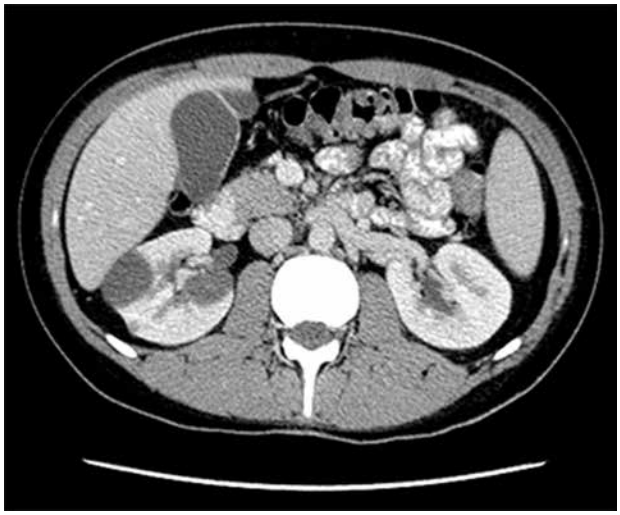

Figure 2. *Axial CT image of the index subject shows multiple cortical cysts in both kidneys, the pancreatic head but the absence of the corpus and tail of the pancreas*

Rycina 2. *Badanie tomograficzne jamy brzusznej (przekrój osiowy) jamy brzusznej pacjenta (III-1) ukazujący wielotorbielowatość nerek oraz obecność jedynie głowy trzustki*

occulta, pectus carinatum, and enlarged spleen, which to the best of our knowledge have not been previously reported in patients with *HNF1B*-MODY. One could argue that spina bifida occulta is not that uncommon in the general population, so it cannot be excluded that this finding is a coincidence.

However, the fact that another Q248X mutation carrier has pectus carinatum strengthens the chance that these changes could also be attributable to a mutation in the *HNF-1B* gene. Recently, Dubois-Laforgue et al. found the presence of another chest abnormality — pectus excavatum — in 6/59 patients with MODY5 (due to both an *HNF1B* point mutation and an *HNF1B* deletion), giving a higher prevalence of pectus excavatum among patients with MODY5 than in the general population [21]. Intriguingly, searching in the literature we encountered a report from 1979 describing an adult with a similar to our proband's phenotype — a patient with diabetes, agenesis of the dorsal pancreas, and spina bifida [22].

Theoretically, together with spina bifida, chest abnormalities could result from altered *HNF1B* expression during embryonic development and growth of the skeleton and neural tube. *HNF1B* is expressed during morphogenesis of several tissues and organs including human trabecular bones of iliac crest and lumbar spinal laminae [23]. Moreover, *HNF1B* is required, directly or indirectly, for the activation of other transcription factors and their target genes [24]. Nevertheless, the precise role of *HNF1B* at different timings and in different compartments of skeleton has not been yet elucidated.

Splenomegaly as a symptom related to *HNF1B* defect is also probable, as *HNF1B* is expressed in the spleen and lymphoid tissue [23]. Hypothetically, it could also be associated with abnormal liver development as it is seen in ciliopathy-associated liver diseases without signs of hypersplenism until adulthood [25].

Short stature and eye defects (such as coloboma, glaucoma or bilateral cataracts at onset of diabetes) have been previously described, but referred to *HNF1B*-deletion syndrome due to heterozygous interstitial microdeletion on chromosome 17q12, leading to monoallelic loss of *HNF1B* [1]. In the family investigated by us, two members reported having had cataracts since childhood, years before their diabetes had been diagnosed.

Phenotypes of family members sharing this mutation are highly variable, which is especially seen in cases of kidney and urinary tract defects, ranging from the presence of only a single cortical cyst in patient I, posterior urethral valves, congenital ureteropelvic junction obstruction and bilateral cortical cysts in the proband, to hypodysplastic, ectopic solitary kidney and rapidly deteriorating chronic kidney disease seen in the youngest patients. Such interfamilial variability of the phenotype in patients who harboured the same mutation in *HNF1B* has also been reported by other authors [12]. The diabetic phenotypes of affected family members are also variable, which suggests incomplete genetic penetrance. The proband was diagnosed with diabetes in his puberty and his overweight, hypertension, hyperinsulinemia, dyslipidemia and hyperuricemia were at first ascribed to metabolic syndrome. After three years of follow-up, his blood sugar is well controlled with metformin and diet (HbA_{1c} 5.7%), although a gradual decrease in C-peptide concentration after stimulation with glucagon indicates that future insulin therapy might be necessary. CT scan of abdomen revealed partial pancreatic agenesis.

In his adult relatives, diabetes was discovered in their thirties, with high HbA1c and normal C-peptide levels. Subject II-1 was positive for IA2 antibodies, which suggests that he might also have mild autoimmune diabetes in addition to *HNF1B*-MODY.

Growing evidence suggests that autoantibodies are present in monogenic forms of diabetes. For example, a quarter of the patients with MODY examined by Urbanová et al. were positive for GAD or IA-2 autoantibodies [26]. The severe onset of his diabetes as hyperosmolar non-ketotic diabetes syndrome (HNKDS) indicates that the amounts of insulin present in some patients with this type of diabetes are sufficient to suppress ketogenesis. The concurrence of two different types of diabetes may also explain the deteriorated

metabolic control in this patient (HbA_{1c} value 12.1%). The mechanisms by which mutations in the *HNF1B* gene cause diabetes mellitus are still not well understood, and might include partial agenesis of the pancreas, abnormal pancreatic islet development during faetal life thereby limiting their later function, as well as impaired transcriptional regulation of genes that play a key role in normal pancreatic beta cell function [27, 28]. Interestingly, insulin resistance is common even among not overweight *HNF1B*-MODY patients [1]. Likewise, the mechanisms underlying the phenotypic variability among diabetic HNF1β-mutant carriers, within and between families, are presently unknown.

Conclusion

HNF1B-MODY is not just a renal cyst and diabetes syndrome (RCAD) [20], but a multi-organ disorder with different symptoms and disease profile. We found a novel Q248X mutation in the *HNF1B* gene responsible for severe phenotypes and probably some new clinical features such as spina bifida occulta, pectus carinatum, and splenomegaly.

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