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Case Report

A case of familial recurrent 17q12 microdeletion syndrome presenting with severe diabetic ketoacidosis

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ABSTRACT

Background. Heterozygous intragenic mutations of the hepatocyte nuclear factor 1 homeobox b gene (*HNF1B*) located on chromosome 17 and microdeletion of 17q12 region (17q12MD) leads to the complete loss of this gene, which causes renal cystic disease, diabetes mellitus (MODY5), hypomagnesemia, hyperuricemia, liver enzyme abnormalities, genital tract abnormalities and exocrine pancreatic insufficiency. In addition, patients with 17q12MD also have facial dysmorphism, neuro-developmental and neuropsychiatric disorders.

Case. A 16-year-old girl with obesity and mild facial dysmorphism was admitted to the hospital with symptoms of diabetes that started two days prior to her admission. She was diagnosed with severe diabetic ketoacidosis and treated accordingly. She had been followed up with the diagnoses of multicystic renal disease, hydronephrosis, hepatosteatosis, hypomagnesemia and hyperuricemia since the age of six. She had mild intellectual disability. Her menarche started two months ago. Cranial magnetic resonance imaging revealed mild diffuse cerebral and cerebellar atrophy and a partial empty sella. Her mother had diabetes, hypomagnesemia and mild intellectual disability and her maternal grandfather and uncle had diabetes. Her grandfather also had renal cystic disease. All of them are on oral antidiabetic medication. The genetic analysis of the patient and her mother revealed a loss of 1.6 megabases in chromosome 17q12.

Conclusions. MODY5 should be kept in mind in patients with diabetes who present with extra pancreatic findings, especially with renal cystic disease, more over, a genetic analysis including the study of 17q12MD should be carried out in patients who present with additional neuropsychiatric findings. Ketoacidosis can be seen in patients with MODY5. Ketoacidosis and renal anomalies and dysfunction are factors that increase and affect the severity of each other in these patients.

Key words: MODY5, renal cyst, 17q12 microdeletion, ketoacidosis, intellecual disability.

The hepatocyte nuclear factor 1 homeobox gene (*HNF1B*) located on chromosome 17 encodes a transcription factor that plays a role in the development of the kidneys, pancreas, liver, thymus, lungs, intestine and gonads.[1,2] The clinical presentation of *HNF1B* related disease emerges as a result of heterozygous *HNF1B* intragenic mutations and deletions. Most of these patients have structural and functional kidney abnormalities characterized by renal cystic disease. In addition, these patients also present with varying frequencies of diabetes [maturity-onset diabetes of the young (MODY5)], hyperuricemia and early onset gout, hypomagnesemia, liver enzyme abnormalities, genital tract abnormalities (Mayer-Rokitansky-Küster-Hauser syndrome, bicornuate uterus, hemiuterus, cryptorchidism, absence of vas deferens and epididymal cysts) and exocrine pancreatic insufficiency.[1-4] The phenotypic findings of *HNF1B* related disease are also observed in the recurrent 17q12 microdeletion syndrome (17q12MD), which includes the whole-gene loss of *HNF1B* gene. In addition,

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the main findings of 17q12MD which are not observed in *HNF1B* molecular defects are facial dysmorphism, neuro-developmental and neuropsychiatric disorders.[5-7] These two genetic abnormalities are inherited autosomal dominantly. However, there are cases that include no family history and de novo mutations are detected in the majority of these cases.[3-5,8-10] Phenotypic heterogeneity has also been reported in patients with these genetic abnormalities. Thus, diagnostic scoring systems consisting of the phenotypic findings have been developed in order to select patients who need *HNF1B* gene analysis.[2,3]

We present a case of a patient who was admitted with severe diabetic ketoacidosis (DKA) while being followed up with multicystic renal disease, hypomagnesemia and was later found to have 17q12MD herself and in her mother.

Case Report

A 16-year-old girl was admitted with complaints of polydipsia, polyuria, difficulty in breathing and impaired speech that started two days prior to admission. She was admitted to the intensive care unit with the diagnosis of severe DKA. She was being followed up by the pediatric nephrology department since the age of six with the diagnosis of multicystic renal disease, hydronephrosis and was also being followed up because of hypomagnesemia which was detected seven years ago and she was on oral magnesium treatment. Hyperuricemia was detected during her follow-ups. She had mild intellectual disability and learning difficulty and was on a special education programme. There was no consanguinity between her parents. Her menarche started two months ago. Her 42 year old mother had diabetes for five years and mild intellectual disability. Her 47 year old maternal uncle had diabetes for seven years and her maternal grandfather had cystic renal disease and diabetes for ten years. All of them were on oral antidiabetic medication.

During her physical examination; she was confused, lethargic and disorientated. The score of Glascow coma scale (GCS) was: 9, body weight was: 79 kg (>97 p), height was: 162 cm (25-50 p), body mass index was: 30.1 kg/m². She had kussmaul breathing, coarse face, sunken eyeballs, high arched eyebrows, tubular nose, long philtrum, dark circles under the eyes, mild prognatism and decreased skin turgor. Acanthosis nigricans was not seen.

In her laboratory work up analysis, urine analysis showed glucose: +4, protein: +3, ketone: +3 and serum biochemistry showed glucose: 1463 mg/dL and concurrent C-peptide and insulin were; 1.63 ng/mL, 4.4 uU/mL, respectively, sodium: 129 mEq/L, potassium: 3.5 mEq/L, chloride: 84 mEq/L, calcium: 9.79 mg/dL, phosphorus: 6.5 mg/dL, alkaline phosphatase: 224 U/L, magnesium: 0.51 mmol/L, BUN: 73.5 mg/dL, creatinine: 2.58 mg/dL, uric acid: 24.2 mg/dL, AST: <5 U/L, ALT: 9 U/L, HbA1c: 13.5%, fT4: 1.07 ng/dL, TSH: 4.19 uIU, cortisol: 25ug/dL, CRP: 127.5 mg/L, myoglobin: 281 ng/mL and CK-MB: 2.23 ng/mL, blood ketone was: +3. Blood gas analysis showed pH: 6.94, HCO3: 6.3 mmol/L, pCO2: 22 mmHg, BE: -27.3, lactate: 2.8 mmol/L. Fractional magnesium excretion was: 3.39%, spot urine calcium/creatinine was: 0.02 and exrection of protein in her 24-hour urine was calculated as: 18 mg/m²/hour. COVID PCR were: negative. Her urine culture showed a growth of *Klebsiella pneumoniae*. No steatorrhea was detected.

Abdominal ultrasonography (USG) revealed grade 1 hepatosteatosis, grade 1 renal echogenicity on the left side and grade 2 hydronephrosis and 4-5 cystic structures in the right kidney, the largest of which was 10 cm. Ecocardiography and pelvic USG were normal.

The findings of our patient are shown in Table I.

During her clinical follow-up; intravenous fluid-electrolyte replacement, NaHCO3, antibiotic and insulin infusion (0.1 unit/kg/hr) were initiated in the intensive care unit. Oral thiamine treatment was started due to persistence of hyperglycemia, acidosis and high lactic acid level at the 20th hour her admission. The insulin infusion dose was gradually increased to 0.3

Table I. Clinical features of our patient.

Gender	Female
Age (year)	16
Family history	No consanguinity Mother had diabetes mellitus, hypomagnesemia, hepatosteatosis, and mild intellecual disability Maternal grandfather had diabetes mellitus and renal cyst Maternal uncle had diabetes
Clinical Findings	Facial dysmorphism Obesity Steatohepatitis Diabetes mellitus İntellectual disability Cerebral and cerebellar atrophy Partial empty sella Hyperuricemia Multicystic dysplastic kidney Hydronephrosis Renal failure
Genetic analysis	A loss of 1.6 megabases was detected in the 17q12 region in the patient and her mother

units/kg/hour at the 28th hour. During the 32nd hour continuous renal replacement therapy (CRRT) was applied for 10 hours because of persistence of acidosis, presence of oliguria, the unconsciousness and the possibility of uremic encephalopathy (urea level above 171 mg/dL). Acidosis resolved at the 4th hour of the CRRT treatment. Serum glucose began to be regulated during the 48th hour of her hospitalization. Although the fundus examination and cranial computed tomography (CT) were normal, cerebral edema was considered clinically, since she had a Glaskow coma scale score of 9, did not respond to painful stimuli and was unconscious during the recovery phase of acidosis, thus treatment was given for cerebral edema. Subcutaneous intensive insulin regimen was started during the 66th hour of hospitalization, upon the recovery of ketosis, acidosis and hyperglycemia. Before discharge, serum urea and creatinine levels returned to normal. However, glomerular filtration rate (GFR) was 37 mL/min/1.73m^2. The patient had poor mild eye contact and communication. Mild intellectual disability was diagnosed with the Porteus Labyrinths Performance test. Cranial magnetic resonance imaging (MRI) revealed mild diffuse cerebral and cerebellar atrophy and findings of partial empty sella were seen which was previously unreported (Fig. 1). Her mother had hepatosteatosis and didn't have renal dysfunction and any anomaly on her renal USG. The patients mothers laboratory work up

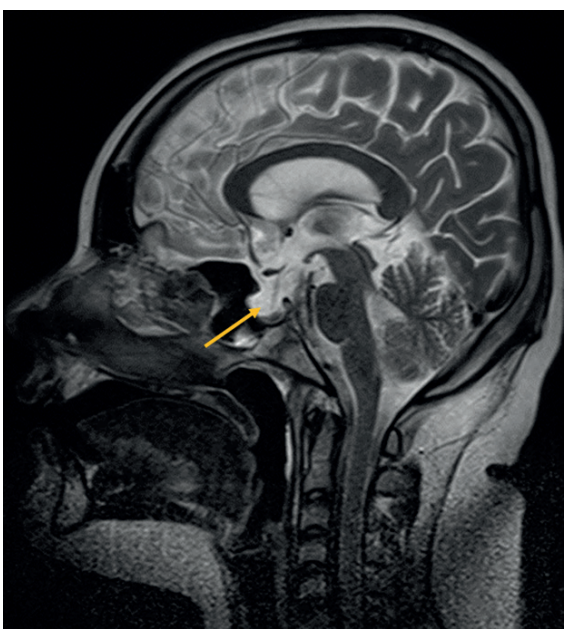

Fig. 1. Cranial MRI findings of our patient; partial empty sella and cerebral atrophy.

showed serum magnesium level of 0.4 mmol/dL, fractionated magnesium excretion of 6%, spot urine calcium/creatinine was 0.08, serum glucose was 172 mg/dL, insulin level was 4.35 uU/mL, C-peptide was 1.68 ng/mL and HbA1C was 8.7%.

Diabetes and extrapancreatic findings in patients were compatible with *HNF1B*-related renal cyst and diabetes syndrome (OMIM# 137920). But since facial dysmorphism, cranial MRI findings and intellectual disability were additionally found, chromosome 17q12MD syndrome (OMIM# 614527) was thought as more accurate for diagnosis. Than microarray analysis was planned instead of *HNF1B* gene sequencing. Array-CGH +SNP analysis (SurePrint G3 Human Genome CGH+SNP Microarray Kit, 4×180K, Agilent Inc, USA) revealed 1,637.567 kb deletion in 17q12 band including *HNF1B* locus (Fig.2) and was reported as arr[GRCh37] 17q12 (34611352-36248918X1). 2019 ACMG criteria was implemented for clinical classification of the deletion.[11] Hence patient's aberration was compatible with recurrent 17q12MD syndrome's critical region and included all morbid genes (*HNF1B, LHX1, ACACA*) associated with recurrent 17q12MD syndrome, the aberration was classified as "pathogenic". Genetic counselling was given to patient's family and segregation analyses were planned. Segregation analyses showed her mother had also the same abberation.

Written informed consent was obtained from the parents to publish this case report.

Discussion

Our patient was being followed up with a diagnosis of cystic renal disease and hydronephrosis since the age of six years and was found to have hypomagnesemia and hyperuricemia during her follow ups. The sudden onset of diabetes and presentation of severe ketoacidosis suggested type 1 diabetes, while the presence of obesity, hepatosteatosis, endogenous insulin release and family history of diabetes made us consider type 2 diabetes in the patient. However, a diagnosis of MODY5 was made due to the presence of extrapancreatic findings in the patient and her family. A genetic analysis was carrried out, and recurrent 17q12MD was detected in the patient. The presence of similar phenotypic findings in other family members indicated that this disease was inherited autosomal dominantly.

MODY5 occurs as a result of heterozygous *HNF1B* mutations and deletions.[1-3,5] *HNF1B* molecular defects are investigated especially in cases that present with renal cysts and diabetes.[2-4,8,12,13] Dotto et al.[13] detected heterozygous *HNF1B* whole-gene deletion in one of 28 patients with renal cysts and prediabetes/diabetes, body and tail pancreatic agenesis and *HNF1B* mutation

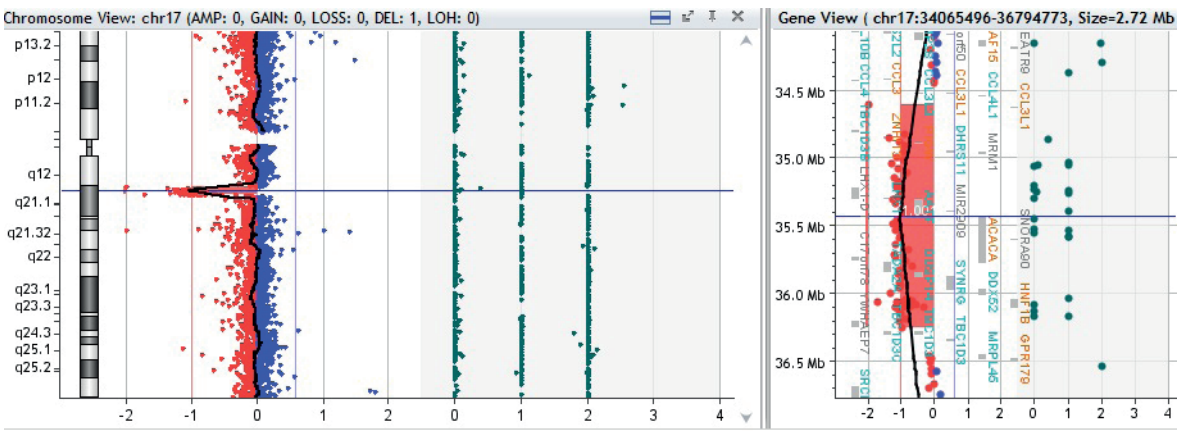

Fig. 2. SNP-Microarray analysis shows the 1.6 megabase deletion in 17q12 locus includes the *HNF1B* gene which is the responsible for MODY5 phenotype.

and hypomagnesemia in the other. Edghill et al.[8] reported that 11 of 23 patients with renal cystic disease and *HNF1B* mutations had diabetes and 7 of them had de novo mutations. Roehlen et al.[5] first found heterozygous *HNF1B* deletion in a patient with MODY5. Later, they noticed that the patient had liver enzyme elevation, pancreatic atrophy, renal cystic disease, facial dysmorphism and mild intellectual disability and detected 1.58 Mb 17q12 MD by microarray tests in repeated genetic analysis.

Inadequate insulin secretion of pancreatic beta cells is responsible for the diabetes in these patients. But, in some patients pancreatic atrophy, hypoplasia of pancreatic trunk, tail and neck were observed.[1-5,13,14] Hepatic insulin resistance was also shown in these patients.[15] Pancreatic imaging was not performed in our patient, whose diabetes etiology was considered to be MODY. On the other hand, insulin resistance develops in patients with renal failure.[16] It is thought that insulin resistance also contributed to the etiopathogenesis of diabetes in our patient, who was obese and had renal dysfunction.

It has been reported that the age of diagnosis of diabetes in *HNF1B* molecular defects is >25 years.[4] Bingham et al.[1] reported that 58% diabetes, 4% impaired glucose tolerance test in *HNF1B* mutation carriers and diabetes were diagnosed at the mean age of 26 years (10-61 years). However, the age of diabetes in a patient with *HNF1B*-related disease was 6 years.[17] In 17q12MD, it was found that 63% of patients had diabetes and the age of diagnosis was <40 years in the review of literature by Roehlen et al.[5] However, the study reported a patient with 17q12MD, in which diabetes was diagnosed at the age of 14. Warncke et al.[18] reported that the average age of diabetes was 13.5 years in 35 MODY5 patients, most of whom had 17q12 MD. The age of diabetic diagnosis of our patient was 16 years of age.

Diabetes is not observed in every patient with *HNF1B* mutations or 17q12MD.[2,3,5,6,9-11] Ulinski et al.[9] reported that none of 25 patients with renal developmental anomalies and *HNF1B* mutations had diabetes.

In terms of the treatment of diabetes in this disease, not all diabetic patients are insulin dependent. There are phenotypic differences between families with *HNF1B* mutations or within the same family; some patients use insulin, and some use oral antidiabetics.[4,5,7,10-13,18-20] Warncke et al.[18] reported that 65.7% of 35 MODY5 cases used insulin, 8.6% used oral antidiabetic drugs and 40% of them were accompanied by extrapancreatic findings. Dubois-Laforgue et al.[4] reported that 159 of 201 adult patients with *HNF1B* molecular defects had diabetes and 122 had renal cysts. 29 patients were using oral antidiabetic drugs, 111 were using insulin. They found that 79% of these patients were insulin dependent during a ten-year follow-up and the frequency of insulin use was higher in those with deletions compared to *HNF1B* mutations. They found diabetic retinopathy and nephropathy in 46 out of 114 patients. It has been reported that the patients with 17q12MD initially used oral antidiabetic drugs and then they eventually became insulin dependent.[5] This heterogeneity observed in the treatment of diabetes in these patients was explained by the expressivity variability of the genetic defects.[1,5,10,12,19]

Diabetic ketoacidosis has been rarely reported in MODY5 cases.[19] Despite having the same genetic defect as her mother, our patient presented with severe ketoacidosis and then an intensive insulin regimen was started. Diabetes developed in other family members at an older age and they were treated by oral antidiabetic drugs.

Developmental and functional abnormalities of the kidneys are common findings of *HNF1B*-related disease and 17q12MD syndrome, and are observed in most patients. Renal multicystic dysplasia is the main finding and the other abnormalities detected are isolated renal cortical cysts, renal hyperechogenicity, renal

hypoplasia, single kidney, ureteral dilatation, horseshoe and duplex kidneys, urinary tract abnormalities, oligomeganephronia, and bilateral hydronephrosis.[1-3,5,10,12] It is possible to diagnose patients by showing bilateral hyperechogenic kidneys in the prenatal period.[2,3,5,10] It has been found that these patients develop severe renal failure, which can lead to dialysis/transplantation at a very high rate.[1-3,5,9,10] It was found that the prognosis of renal disease was worse in those with *HNF1B* mutations than those with deletions.[4] Our patient was being followed up with a diagnosis of multicystic kidney and hydronephrosis since the age of six. We thought that in our case, the coexistence of diabetes and congenital renal anomalies might cause more severe DKA. Cystic kidney disease was also detected in the grandfather. Her mother had no renal abnormalities and dysfunction.

In this group of patients, hypomagnesemia is detected with a varying frequency.[2,3,5,20,21] The *HNF1B gene* plays a role in the genetic regulation of sodium-potassium ATPase, which is critical for magnesium reabsorption in the distal convulated tubule of the kidney.[20,21] Van der Made et al.[21] reported that hypomagnesemia was the first presentation in a patient with heterozygous *HNF1B* deletion and in a patient with 17q12MD. Hypomagnesemia and increased fractional magnesium excretion were detected in both our patient and her mother.

Neurodevelopmental and neuropsychiatric diseases such as autism spectrum disease, agression, anxiety, hyperactivity, developmental delay, cognitive impairment, learning impairment, and seizures are the characteristic symptoms of 17q12MD syndrome. It has also been reported that these patients have facial dysmorphism, growth retardation and skeletal problems.[5,7,17,22-25] These neuropsychiatric abnormalities are not observed in intragenic *HNF1B* pathogenic variants.[3,5] Dixit et al.[7] reported that two of three patients aged <12 years with a history of neonatal transient hypercalcemia, renal cystic disease, no diabetes and 17q12MD between 1.6-2.07 Mb had speech difficulties, autism and mild learning difficulties, one had severe facial dysmorphism and one had hypospadias. An adult woman with 17q12MD without diabetes and cognitive impairment, had right kidney aplasia, left kidney dysplasia, renal failure from infancy, Mayer-Rokitansky-Kuester-Hauser syndrome, congenital joint laxity, kyphoscoliosis and bilateral hip dysplasia.[22] Loirat et al.[25] reported three patients aged 3-9 years, who had no diabetes, had cystic or hyperechogenic kidneys and were diagnosed with 17q12MD (1.49-1.85 Mb). These patients had autism spectrum disease, intellectual disability, social interaction impairments, verbal and non-verbal communication deficits and stereotyped behaviors. Roberts et al.[6] detected de novo 17q12MD including 28 genes in a 17-year-old boy with tall stature, facial dysmorphism, joint laxity, small pancreas, splenomegaly, mild pectus deformity, behavioral changes and cognitive impairment (schizophrenia, autism spectrum disease, developmental delay, intellectual disability, anxiety, and hyperactivity). This patient did not have diabetes, renal or liver pathology. Bernardini et al.[26] reported that two patients with Mayer-Rokitansky-Kuster-Hauser syndrome and one patient with renal cystic disease and mild facial dysmorphism which were all psychomotorly normal.

As seen, although the critical deletion region (1.4 Mb) is the same in all cases of microdeletions, phenotypic heterogeneity from case to case is detected in 17q12MD. It has been suggested this may be related to the extent of the deletion emcompassing the *HNF1B* gene and the other neighbooring genes located in this region, and the number and haploinsufficiencies of the other genes may be responsible for the phenotypic differences. It has been suggested that the loss of *ACACA* and *LHX1* genes may be related to neurodevelopmental and neropsychiatric problems observed in these patients.[5,19,23,24] In our

patient and mother who both had intellectual disability, a 1.6 Mb deletion was detected in the 17q12 region, including morbid genes such as *HNF1B*, *LHX1*, and *ACACA*.

Our patient and some of her family members had phenotypic findings of recurrent 17q12MD. MODY5 should be kept in mind in cases with extrapancreatic multisystem findings especially renal cystic disease; however, genetic analysis should be performed in patients with neuropsychiatric findings with a method that will detect 17q12MD. Genetic counseling should be given to cases related to autosomal dominant inheritance.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: CA, BK; data collection: CA, BK; analysis and interpretation of results: CA, BK, EK, ES, AKT, NÇ, CY, SK; draft manuscript preparation: BK. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Bingham C, Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1beta. Nephrol Dial Transplant 2004; 19: 2703-2708. https://doi.org/10.1093/ndt/gfh348
2. Faguer S, Chassaing N, Bandin F, et al. The HNF1B score is a simple tool to select patients for HNF1B gene analysis. Kidney Int 2014; 86: 1007-1015. https://doi.org/10.1038/ki.2014.202
3. Clissold RL, Ashfield B, Burrage J, et al. Genome-wide methylomic analysis in individuals with HNF1B intragenic mutation and 17q12 microdeletion. Clin Epigenetics 2018; 10: 97. https://doi.org/10.1186/s13148-018-0530-z
4. Dubois-Laforgue D, Cornu E, Saint-Martin C, Coste J, Bellanné-Chantelot C, Timsit J. Diabetes, associated clinical spectrum, long-term prognosis, and genotype/phenotype correlations in 201 adult patients with hepatocyte nuclear factor 1B (HNF1B) Molecular Defects. Diabetes Care 2017; 40: 1436-1443. https://doi.org/10.2337/dc16-2462
5. Roehlen N, Hilger H, Stock F, et al. 17q12 Deletion syndrome as a rare cause for diabetes mellitus type MODY5. J Clin Endocrinol Metab 2018; 103: 3601-3610. https://doi.org/10.1210/jc.2018-00955
6. Roberts JL, Gandomi SK, Parra M, et al. Clinical report of a 17q12 microdeletion with additionally unreported clinical features. Case Rep Genet 2014; 2014: 264947. https://doi.org/10.1155/2014/264947
7. Dixit A, Patel C, Harrison R, et al. 17q12 microdeletion syndrome: three patients illustrating the phenotypic spectrum. Am J Med Genet 2012; 158A: 2317-2321. https://doi.org/10.1002/ajmg.a.35520
8. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. J Med Genet 2006; 43: 84-90. https://doi.org/10.1136/jmg.2005.032854
9. Ulinski T, Lescure S, Beaufils S, et al. Renal phenotypes related to hepatocyte nuclear factor-1beta (TCF2) mutations in a pediatric cohort. J Am Soc Nephrol 2006; 17: 497-503. https://doi.org/10.1681/ASN.2005101040
10. Lim SH, Kim JH, Han KH, et al. Genotype and phenotype analyses in pediatric patients with HNF1B mutations. J Clin Med 2020; 9: 2320. https://doi.org/10.3390/jcm9072320
11. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med 2020; 22: 245-257. https://doi.org/10.1038/s41436-019-0686-8
12. Bingham C, Bulman MP, Ellard S, et al. Mutations in the hepatocyte nuclear factor-1beta gene are associated with familial hypoplastic glomerulocystic kidney disease. Am J Hum Genet 2001; 68: 219-224. https://doi.org/10.1086/316945
13. Dotto RP, Santana LS, Lindsey SC, et al. Searching for mutations in the HNF1B gene in a Brazilian cohort with renal cysts and hyperglycemia. Arch Endocrinol Metab 2019; 63: 250-257. https://doi.org/10.20945/2359-3997000000138

14. Horikawa Y, Enya M, Fushimi N, Fushimi Y, Takeda J. Screening of diabetes of youth for hepatocyte nuclear factor 1 mutations: clinical phenotype of HNF1β-related maturity-onset diabetes of the young and HNF1α-related maturity-onset diabetes of the young in Japanese. Diabet Med 2014; 31: 721-727. https://doi.org/10.1111/dme.12416

15. Brackenridge A, Pearson ER, Shojaee-Moradie F, Hattersley AT, Russell-Jones D, Umpleby AM. Contrasting insulin sensitivity of endogenous glucose production rate in subjects with hepatocyte nuclear factor-1beta and -1alpha mutations. Diabetes 2006; 55: 405-411. https://doi.org/10.2337/diabetes.55.02.06.db05-1019

16. Dave N, Wu J, Thomas S. Chronic kidney disease-induced insulin resistance: Current state of the field. Curr Diab Rep 2018; 18: 44. https://doi.org/10.1007/s11892-018-1010-8

17. Gonc EN, Ozturk BB, Haldorsen IS, et al. HNF1B mutation in a Turkish child with renal and exocrine pancreas insufficiency, diabetes and liver disease. Pediatr Diabetes 2012; 13: e1-5. https://doi.org/10.1111/j.1399-5448.2011.00773.x

18. Warncke K, Kummer S, Raile K, et al. Frequency and characteristics of MODY 1 (HNF4A mutation) and MODY 5 (HNF1B mutation): Analysis from the DPV database. J Clin Endocrinol Metab 2019; 104: 845-855. https://doi.org/10.1210/jc.2018-01696

19. Harries LW, Ellard S, Jones RW, Hattersley AT, Bingham C. Abnormal splicing of hepatocyte nuclear factor-1 beta in the renal cysts and diabetes syndrome. Diabetologia 2004; 47: 937-942. https://doi.org/10.1007/s00125-004-1383-x

20. Kołbuc M, Leßmeier L, Salamon-Słowińska D, et al. Hypomagnesemia is underestimated in children with HNF1B mutations. Pediatr Nephrol 2020; 35: 1877-1886. https://doi.org/10.1007/s00467-020-04576-6

21. Van der Made CI, Hoorn EJ, de la Faille R, et al. Hypomagnesemia as first clinical manifestation of ADTKD-HNF1B: A case series and literature review. Am J Nephrol 2015; 42: 85-90. https://doi.org/10.1159/000439286

22. Hinkes B, Hilgers KF, Bolz HJ, et al. A complex microdeletion 17q12 phenotype in a patient with recurrent de novo membranous nephropathy. BMC Nephrol 2012; 13: 27. https://doi.org/10.1186/1471-2369-13-27

23. Moreno-De-Luca D, Mulle JG, Kaminsky EB, et al. Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. Am J Hum Genet 2010; 87: 618-630. https://doi.org/10.1016/j.ajhg.2010.10.004

24. Nagamani SC, Erez A, Shen J, et al. Clinical spectrum associated with recurrent genomic rearrangements in chromosome 17q12. Eur J Hum Genet 2010; 18: 278-284. https://doi.org/10.1038/ejhg.2009.174

25. Loirat C, Bellanné-Chantelot C, Husson I, Deschênes G, Guigonis V, Chabane N. Autism in three patients with cystic or hyperechogenic kidneys and chromosome 17q12 deletion. Nephrol Dial Transplant 2010; 25: 3430-3433. https://doi.org/10.1093/ndt/gfq380

26. Bernardini L, Gimelli S, Gervasini C, et al. Recurrent microdeletion at 17q12 as a cause of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome: two case reports. Orphanet J Rare Dis 2009; 4: 25. https://doi.org/10.1186/1750-1172-4-25