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Case of *HNF1B* MODY

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Background

MODY *HNF1B* variants are most frequently associated with extra-pancreatic manifestations like renal cysts [leading to renal cysts and diabetes (RCAD) syndrome], abnormalities of the uro-genital tract and hypomagnesemia, but may also cause MODY or renal structural disease in isolation, therefore cases of *HNF1B* MODY still remained largely undiagnosed. In Ukraine, there are currently three patients with MODY *HNF1B de novo* whole gene deletion*

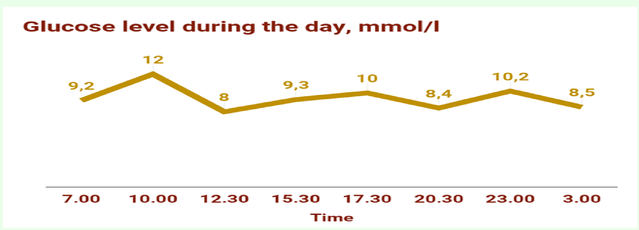
Materials and methods

Targeted next generation sequencing (tNGS) of the known pediatric monogenic diabetes genes *ABCC8*, *GATA6*, *GCK*, *HNF1A*, *HNF1B*, *HNF4A*, *INS*, *KCNJ11*, *NEUROD1*, *PAX6*, *PDX1*, *LMNA*, *PPARG*, *INSR* and the mitochondrial mutation m.3243A>G causing maternally inherited diabetes and deafness (MIDD) was performed. This technique also tests for partial and whole gene deletions and duplications by comparing normalized read depths. Parents and siblings of proband with a variant were tested by direct sequencing for the respective variant. The proband met the current diagnostic criteria for MODY with the exception of a positive family history of hyperglycemia or diabetes inherited in an autosomal dominant pattern

Results

A 17 year old male, was admitted to the nephrology department for a routine examination.
According to the anamnesis, he has been observed by a nephrologist since the age of 7 with chronic pyelonephritis and congenital anomaly in the development of the kidneys (doubling of the right kidney).
The routine examination revealed hyperglycemia (10.5 mmol/l), there were no ketones in the urine. Due to hyperglycemia, the patient was transferred to the endocrinology department.
The results of a general examination are shown in Table 1. He had normal male external genitalia, Tanner 4.
There are no cases of diabetes in the family; however, the father suffers from chronic pyelonephritis.
The results of an additional examination revealed high HbA1c (13.5%), low C-peptide 0.25 ng/ml (N 0.7-1.9). Insulin was administered at a dose 0.6 U/ kg (Fig.1). The results of the additional examination are shown in Table 2.
To continue the diagnostic search, the patient was tested for specific antibodies (GAD, IA2, ZnT8), the results of which were negative. Hereafter genetic testing using tNGS MODY panel was done, where it was found heterozygous pathogenic *HNF1B* whole gene deletion variant (NM_000458.4: c. (?_1)_(*4_?)del, p.(0?). The *HNF1B* whole gene deletion variant was also not detected in parents, and this result suggests that the variant has arisen *de novo* (Fig.2).

Fig.1. Glucose level of the patient during the day



Height	176 cm (+0.1SD)
Weight	58 kg
Body mass index	18.7 kg/m^2 (15 p.c.)
Heart rate	80/min
Tanner	4
Blood pressure	125 / 80 mm (75/90 p.c.)
Glucose level	15.7 mmol/l
Glucosuria	+
Ketonuria	-
Acidosis	-

Table 1. Results of a general examination

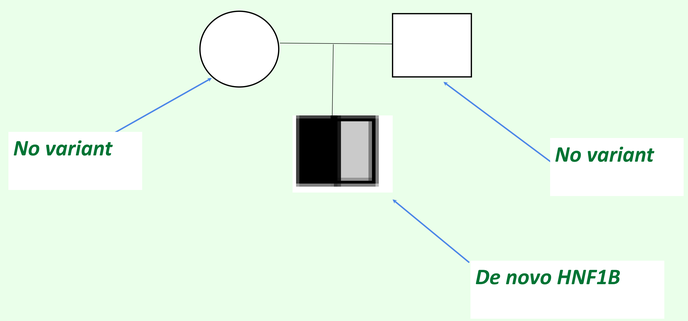


Fig.2. Genetic testing of the patient

Abdominal ultrasound	. Doubling right kidney, Chronic pyelonephritis (2007) . Neoplasm in the liver (hemangioma?) (07.2019) . Cysts in the left kidney
CT scan	Normal liver structure
Family history	Patient`s father: Chronic pyelonephritis

Table 2. Results of the additional examination

Conclusions

Correct (molecular genetic) diagnosis of MODY is necessary to predict the further course of disease, explain the associated clinical manifestations and is necessary to develop a treatment plan. Follow up management is needed to control BP and lab tests (liver function tests, magnesium, uric acid, renal function (eGFR, urea and creatinine), fecal elastase, PTH, urinary albumin), ultrasound of abdomen, CT of abdomen. Early treatment with ACE inhibitors should be also considered.

* *Globa E et al. MODY in Ukraine: genes, clinical phenotypes and treatment. J Pediatr Endocrinol Metab. 2017, Oct 26; 30(10): 1095-1103*