Clinical characteristics of patients referred for *HNF1B* testing - Polish population study

Paweł Sztromwasser [1], Arkadiusz Michalak [1,2], Beata Małachowska [1], Paulina Młudzik [3], Karolina Antosik [3], Anna Hogendorf [2], Agnieszka Zmysłowska [2], Maciej Borowiec [3], Wojciech Młynarski [4], Wojciech Fendler [1,5]

1 - Medical University of Lodz, Department of Biostatistics and Translational Medicine, Łódź, Poland; 2 - Medical University of Lodz, Department of Pediatric Endocrinology, Diabetology and Nephrology, Łódź, Poland;
3 - Medical University of Lodz, Department of Clinical Genetics, Łódź, Poland; 4 - Medical University of Lodz, Department of Pediatric, Oncology and Hematology, Łódź, Poland; 5 - Dana-Farber Cancer Institute, Department of Radiation Oncology, Boston, United States

INTRODUCTION

Maturity-onset diabetes of the young caused by genetic defects of *HNF1B* transcriptional factor (*HNF1B*-MODY) is a rare type of monogenic diabetes. Patients usually present with cystic kidneys and diabetes, but additional symptoms often complicate the clinical picture. Due to up to 50% of mutations being whole-gene deletions, targeted or even panel genetic testing must be accompanied by additional techniques, which necessitates careful preselection of patients for *HNF1B* testing.

AIMS

- Estimate prevalence of *HNF1B*-MODY in Polish children and young adults'
- Compare *HNF1B*-positive and negative cases
- Optimize selection for *HNF1B* genetic testing and testing procedures

METHODS

We searched the Polish Monogenic Diabetes Registry for patients tested for mutations in *HNF1B* in years 2005-2018 and contacted those who gave consent when entering the registry. All underwent a structured medical interview, focused on diabetes, renal disorders, additional symptoms and family history. Each patient was also scored with *HNF1B* score (Faguer et al., Kidney Int, 2014). All genetic findings in the group were reassessed according to the American College of Medical Genetics (AMCG) criteria. (Richards et al., Genet Med., 2015).

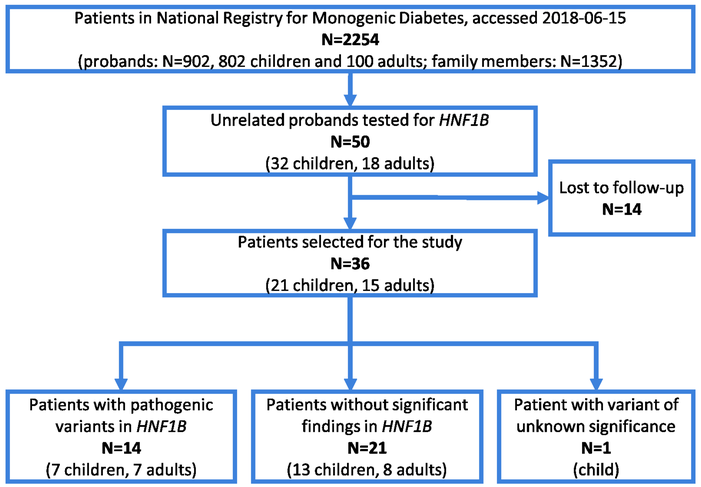


Figure 1. Flowchart of patient selection. Children – patients <18 y.o. at referral.

RESULTS

Out of 50 probands , we managed to contact and interview 36 (28% drop-out, Fig. 1). Among those, 14 harboured pathogenic mutations in *HNF1B,* yielding approximate prevalence of *HNF1B*-MODY of 0.74/1 000 000 people <20 y.o. (95%CI: 0.30 – 1.66). The clinical presentation of *HNF1B*-positive patients was highly diverse (Fig. 2). In a few of remaining 21 patients, we registered mutations in other genes, partly explaining presented phenotypes (Table 1). Clinically, cystic kidneys, significant family history, pancreatic abnormalities and elevated liver enzymes were the best discriminants between *HNF1B*-positive and negative cases (Fig. 3). Coupled with *HNF1B* score, these features identified the carriers of pathogenic variants in a sensitive and specific manner. (Fig. 4).

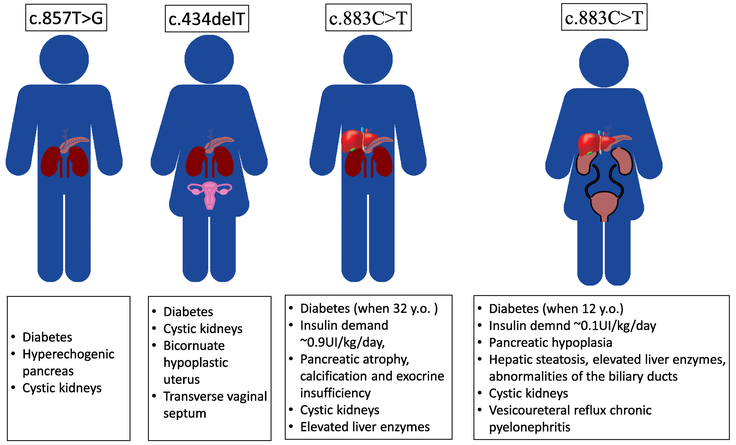
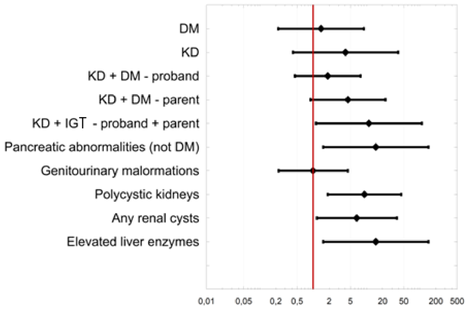


Figure 2. Graphical presetation of *HNF1B*-MODY-associated phenotypes. First two cases harbour novel mutations, the other two present different clinical profiles despite posessing the same mutation.

Gene	N	Genetic coordinates	Protein change	Clinical classification
HNF1B	8	Whole-gene deletion	Loss of protein	Pathogenic
HNF1B	2	c.883C>T	p.Arg295Cys	Pathogenic
HNF1B	1	c.434delT	p.Leu145fs	Pathogenic
HNF1B	1	c.443C>T	p.Ser148Leu	Pathogenic
HNF1B	1	c.742C>T	p.Gln248X	Pathogenic
HNF1B	1	c.857T>G	p.Leu286Arg	Pathogenic
HNF1B	1	c.755G>A	p.Arg252Gln	VUS
PKD1	1	c.7760G>A	p.Trp2587Ter	Pathogenic
PKD1	1	c.8203C>T	p.Gln2735Ter	Pathogenic
PKD1	1	c.1613T>G	p.Val538Gly	VUS
HNF4A	1	c.401G>A	p.Arg134Gln	Likely pathogenic
GCK	1	c.268A>T	p.Lys90Ter	Pathogenic
KCNJ11	1	c.991T>C	p.Ser331Pro	VUS

Table 1. Genetic findings in the studied cohort. All patients were tested for *HNF1B*. Among 21 *HNF1B*-negative probands, 5 were found to harbour significant mutations in other phenotype-relevant genes (mainly *PKD1* – causes autosomal dominant polycystic kidney disease, ADPKD – and other MODY-related genes). 15 patients (41.7%) revealed no significant mutations or awaits further genetic testing. All variants were assessed for pathogenicity using AMCG criteria.

N– number of probands with given variant
VUS – variant of unknown significance



	OR	95%CI	N (%) - not carriers vs carriers
DM	1.41	(0.22 - 8.99)	1 (4.8%) vs 6 (42.9%)
KD	4.06	(0.42 - 39.26)	10 (47.6%) vs 4 (28.6%)
KD + DM - proband	1.88	(0.45 - 7.76)	6 (28.6%) vs 12 (85.7%)
KD + DM - parent	4.50	(0.89 - 22.67)	6 (28.6%) vs 11 (78.6%)
KD + IGT - proband + parent	11.11	(1.13 - 109.36)	1 (4.8%) vs 6 (42.9%)
Pancreatic abnormalities (not DM)	15.00	(1.55 - 145.23)	1 (4.8%) vs 5 (35.7%)
Genitourinary malormations	1.00	(0.22 - 4.47)	3 (14.3%) vs 6 (42.9%)
Polycystic kidneys	9.17	(1.87 - 44.92)	6 (28.6%) vs 6 (42.9%)
Any renal cysts	6.60	(1.18 - 37.03)	9 (42.9%) vs 7 (50.0%)
Elevated liver enzymes	15.00	(1.55 - 145.23)	17 (81.0%) vs 12 (85.7%)

Figure 3. Phenotype-based univariate discrimination between HNF1B-positive and negative cases. IGT – impaired glucose tolerance, DM – diabetes, KD – kidney disease

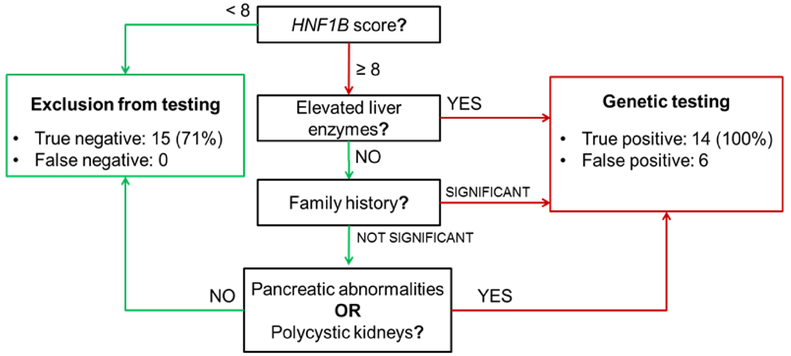


Figure 5. Classification and regression tree analysis in qualification for genetic testing. Excluding patients not presenting typical *HNF1B*-MODY symptoms from the group with HNF1B score ≥8 increased selection specificity to 71% while retaining 100% sensitivity

CONCLUSIONS

- Careful clinical preselection for *HNF1B*-testing can be improved by detailed medical interviews.
- Gene panels performed in patients suspected of *HNF1B*-MODY should also include genes responsible for other types of monogenic diabetes or polycystic kidney disease.
- Over half of patients with clinical suspicion of HNF1B-MODY do not harbour*HNF1B* mutations and are candidates for more detailed genetic testing.

Project funded by National Science Center in Poland (2016/23/P/NZ2/04251, 2016/21/N/NZ5/01448, 2015/19/B/NZ5/02243). This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 665778.