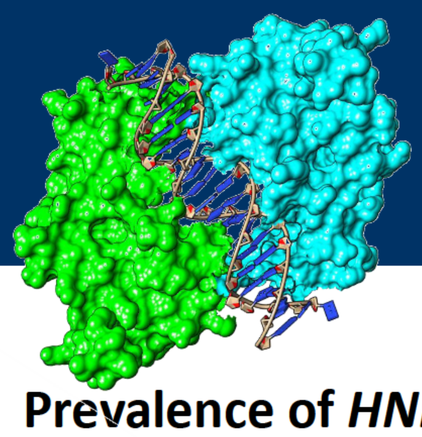

Prevalence of *HNF1B* gene mutations in children with clinical phenotype of polycystic kidney diseases

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Introduction

Hepatocyte nuclear factor 1 beta (gene *HNF1B*) is an essential transcription factor for kidney, liver and pancreas development.

Mutations in *HNF1B* are known to cause broad spectrum of kidney pathology including cystic kidney diseases.

Combination with other PKD genes mutations in individual patients worsening the phenotype.

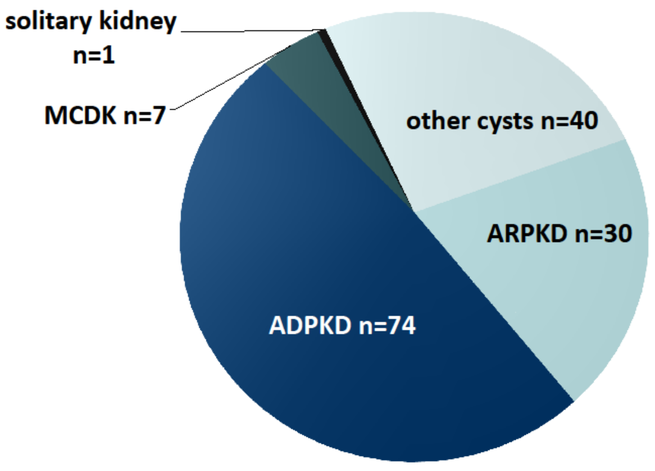
The aim of our study: to analyze the prevalence of *HNF1B* gene anomalies in a large cohort of children with clinical phenotype of autosomal dominant a recessive polycystic kidney diseases (ADPKD and ARPKD; *PKD1*, *PKD2* and *PKHD1* genes) to identify patients with more than one mutated gene and to analyse the specific phenotypes.

Methods

- Direct sequencing of *HNF1B* gene with exon/intron boundaries.
- MLPA of *HNF1B* gene.

Patients

- 152 Czech patients were investigated .
- (110 children from a Czech registry of kidney polycystosis).



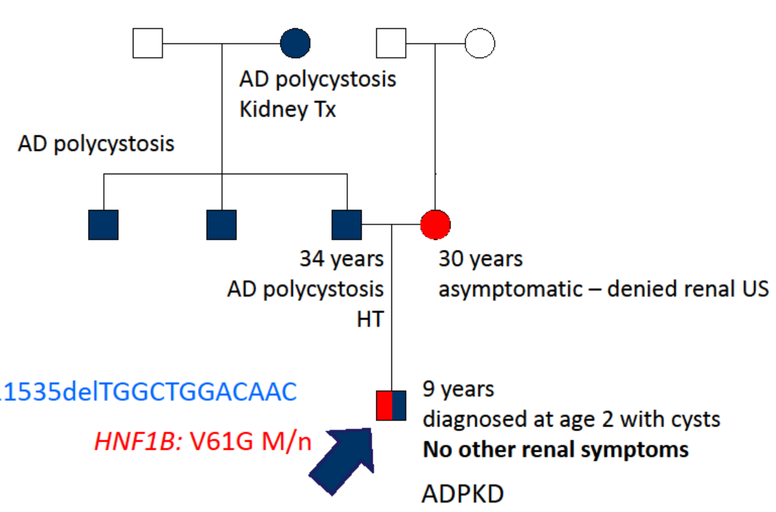
Clinical diagnosis based on phenotype only

Diabetes

Diabetes as initial symptom
1 child (boy with solitary kidney, 17 years)
Diabetes after renal anomaly detection
1 child (14 years)
Hyperglycemia in follow-up
1 child impaired glucose tolerance (10 years)
1 child steroid induced diabetes at time of renal Tx
1 child high glucose levels in GH therapy
Normal glucose metabolism – 4 patients

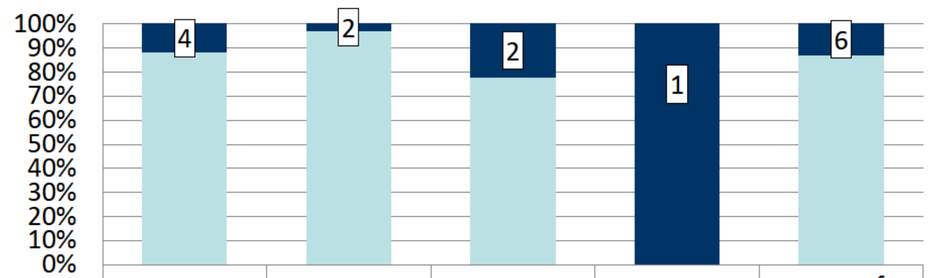
Combined mutation *PKD1+HNF1B*

Low prevalence of combined gene mutations in children with polycystic kidney diseases (prevalence 1,5% in the ADPKD cohort)
Surprisingly mild phenotype in the patient with combined defect in *PKD1* and *HNF1B* gene.



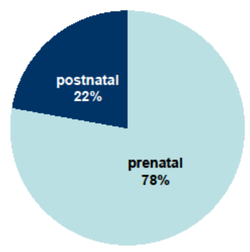
Results

Mutations in clinical phenotype cohorts

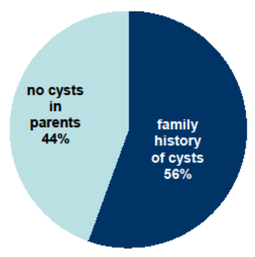


	ARPKD	ADPKD	MCDK	solitary kidney	cysts of unknown etiology
mutation in HNF1B	4	2	2	1	6
number of patients	30	74	7	1	40

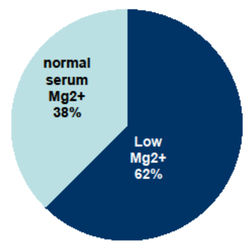
Renal phenotype in patients with mutation



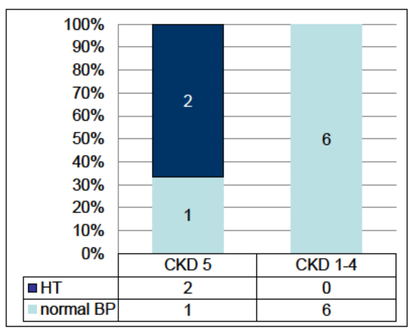
Age at identification of cysts



Family history of cysts

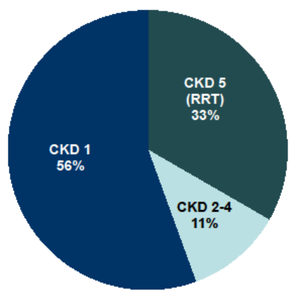


Serum magnesium



	CKD 5	CKD 1-4
HT	2	0
normal BP	1	6

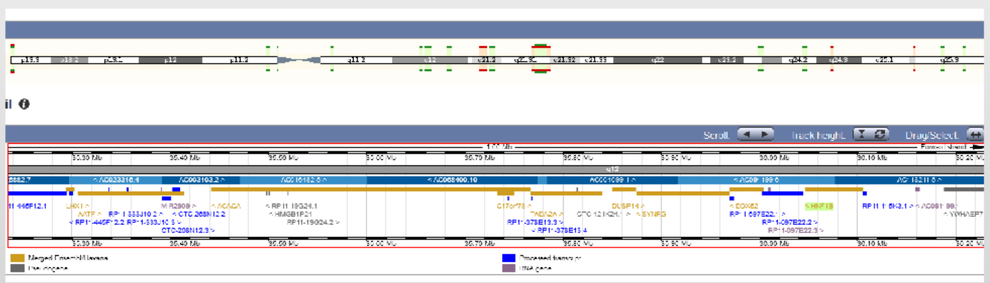
Hypertension
With RRT 2/3
Without RRT 0/6



Renal function

ESRD
-5,5 years (n=2)
-16,5 years (n=1)
-2 children after renal Tx

HNF1B deletions



- **Twelve patients** carried *HNF1B* heterozygous deletion found by MLPA
- In these patients aCGH on CytoChip Oligo 8x60K was performed
- The average length of heterozygous deletion was 1.69 Mb.
- The longest deletion reached **2.5 Mb** affecting 47 genes
- The shortest deletion found in three patients was **1.4 Mb** long and deleted 16 genes.
- All patients lost also *LHX1* gene encoding transcription factor important for the development of the renal and urogenital system.

Regardless to the length of the deletion in the region 17q, the prevailing clinical phenotype of the patients was similar to the patients having point mutation in the *HNF1B* gene. The length of the deletion can probably contribute to the individual variability in the age of manifestation and spectrum of clinical signs.

Conclusion

We have identified mutations in 10% of the screened children with different types of cystic kidney diseases. Majority of the patients has a heterozygous deletion of the gene. In interestingly substantial number of the cases was the deletion not limited to *HNF1B*, but was part of a larger deletion in region 17q12.

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