THE ROLE OF DNA ANALYSIS IN DIAGNOSIS OF AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Lena Obeidova[1], Veronika Elisakova[1], Tomas Seeman[2], Jana Reiterova[3], Jitka Stekrova[1]

[1] Institute of Biology and Medical Genetics, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague
[2] Department of Paediatrics, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital
[3] Department of Nephrology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague

1. INTRODUCTION

Autosomal recessive polycystic kidney disease (ARPKD) is a severe form of chronic kidney disease, frequently diagnosed prenatally with enlarged echogenic kidneys and oligohydramnios. ARPKD is primaly caused by mutations in the *PKHD1* gene, nevertheless, phenotype of polycystic kidneys is present as a part of several syndromes caused by mutations in number of other genes, such as *HNF1β*, *PKD1*, *PKD2*, *NPHP* etc. Thus, the molecular genetic analysis can be very useful in differential diagnosis of ARPKD in patient.

Herein, we present the results of molecular genetic analysis in 52 families with clinically suspected ARPKD, consisting of analysis of *PKHD1*, as well as analysis of the *HNF1β* gene in families without 2 causal mutations found in *PKHD1*.

2. METHODS

The molecular analysis of the *PKHD1* gene was carried out using next-generation sequencing (NGS) method on GS Junior (Roche). In patients without 2 causal mutations, the subsequent MLPA (multiplex ligation-dependent probe amplification) analysis of *PKHD1* was performed, as well as MLPA and Sanger sequencing of *HNF1β*. In addition, amplicon-based NGS of *PKD1* on MiSeq (Illumina) was carried out in one family. The cohort of probands was divided into two groups (Group **A** and **B**) on the basis of their fulfillment of established clinical criteria of ARPKD including: 1) typical kidney involvement; 2) typical liver involvement; and 3) normal renal US of both parents. Patients fulfilling all three criteria were placed in Group A, which consisted of 24 patients. Group B consisted of 30 patients coming from 28 families.

3. RESULTS

In **Group A**, two underlying mutations in *PKHD1* were detected in 17 out of 24 families (71%), one mutation in 5 families (21%), and 2 families had no mutation found (8%) (Fig. 1). Thus, the overall detection rate amounts to 81% in Group A. In **Group B**, two underlying mutations were detected in 6 out of 28 families (21%), one mutation in 3 families (11%), and no mutations could be detected in 19 families (68%) (Fig. 2). Thus, the overall detection rate is 27% in Group B. Nevertheless, 6 families within Group B without mutation in *PKHD1* harbored mutations in other genes: 3 families had mutations in *HNF1β*, 2 families in the *PKD1* gene and 1 family in the *PKD2* gene.

Fig. 1: Number of mutations in patients within **Group A**

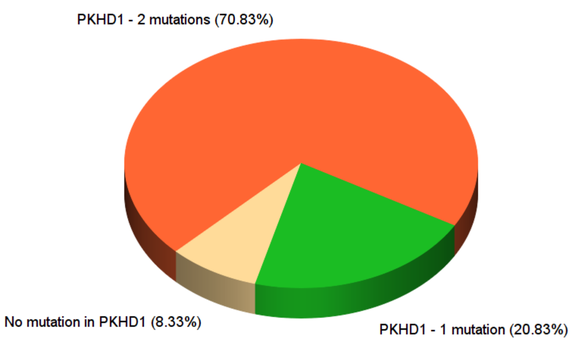


Fig. 2: Number of mutations in patients within **Group B**

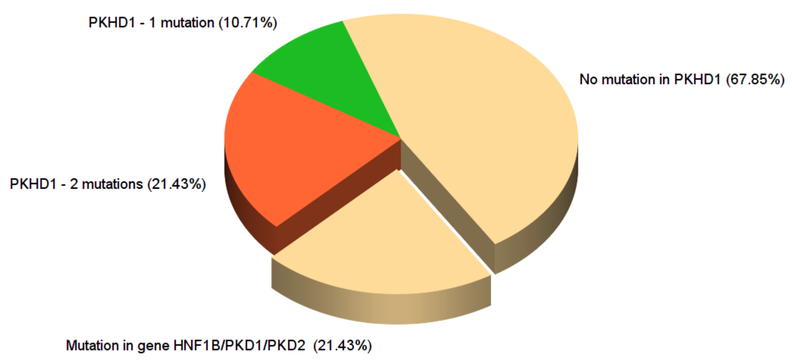
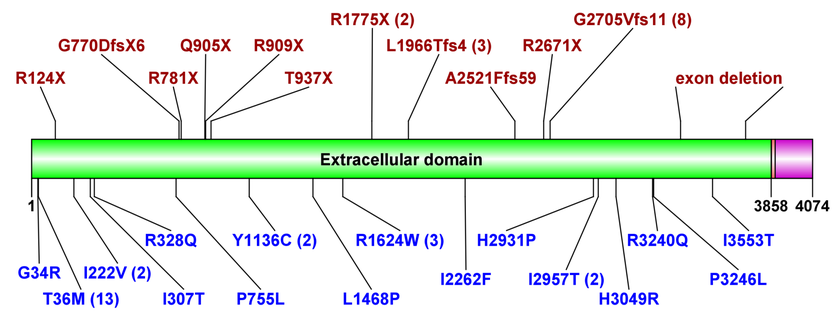


Fig. 3: Mutations and their location on protein Fibrocystin



4. CONCLUSIONS

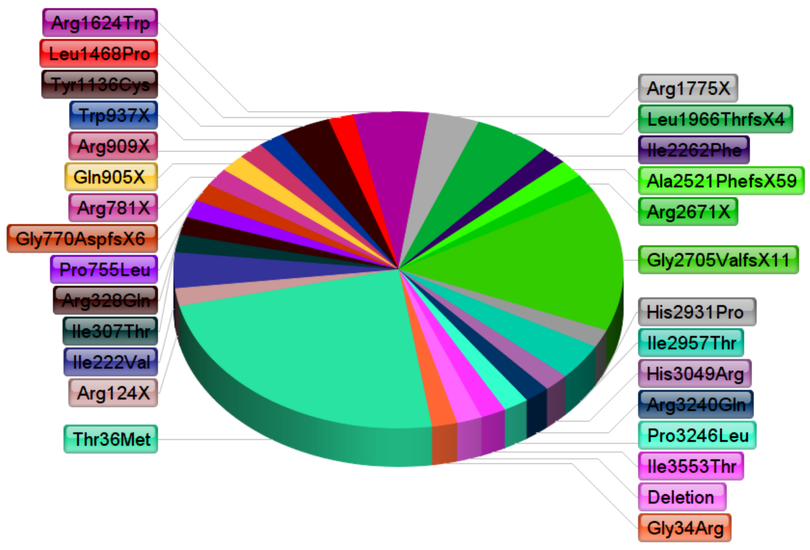
The detection rate of *PKHD1* mutations in children who fulfilled all three of the clinically diagnostic criteria of ARPKD is high, reaching 81%. However, mutations of *PKHD1* were also detected in some of the patients without having met all three clinical criteria, especially in patients who died perinatally with findings such as oligo/anhydramnios, pulmonary hypoplasia, and enlarged kidneys with small cysts.

The important sign of ARPKD in children outside the peri- and neonatal period proved to be congenital hepatic fibrosis, as 11 of 13 children within our study without mutation in *PKHD1* had no liver pathology.

The most frequent mutation was T36M (Fig. 3, 4), accounting for almost 24% of all identified mutations, and most often causing a rather severe form of ARPKD.

Because of the etiologic heterogeneity of polycystic kidney disease phenotype, the complex diagnosis including mutational analysis of several genes is needed for reliable differential diagnosis, especially in cases with ambiguous phenotype of the disease.

Fig. 4: Types of mutations found within our study



Supported by the grant project IGA MZCR NT 13090-4, GAUK 1015 and PRVOUK- P25/LF1/2

Corresponding author: **Lena.Obeidova@gmail.com**

The authors declare that there is no conflict of interest

DOI: 10.3252/pso.eu.53era.2016