

Genetic Diagnosis of a Lethal Form of Autosomal Recessive Polycystic Kidney Disease

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Abstract

Background

Autosomal recessive polycystic kidney disease (ARPKD; OMIM number 263200) is a severe early onset hereditary form of polycystic kidney and liver disease.

Case Report

In the current study, we present a consanguineous couple with a history of an affected son with polycystic kidney disease (PKD), hepatic failure and epileptic seizures who died at the age of 8 months. Both parents were heterozygote for a missense mutation in *PKHD1* gene (NM_170724, c.9107T>G, p.V3036G).

Conclusion

Unlike previous studies which showed the association between missense mutations of *PKHD1* gene and mild phenotype of ARPKD, we have demonstrated the presence of a certain heterozygote missense mutation in parents of a patient affected with lethal form of disorder. Such phenotypic variations should be considered in genetic counseling of families especially those seeking prenatal diagnosis.

Key Words: ARPKD, Gene, Mutation.

*Please cite this article as: Mirzajani S, Mohebi M, Miryounesi M, Yassae VR, Ghafouri-Fard S. Genetic Diagnosis of a Lethal Form of Autosomal Recessive Polycystic Kidney Disease. *Int J Pediatr* 2018; 6(2): 7033-37. DOI: **10.22038/ijp.2017.27282.2352**

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Received date: Oct.12, 2017; Accepted date: Dec. 12, 2017

1- INTRODUCTION

Autosomal recessive polycystic kidney disease (ARPKD; OMIM number 263200) is a severe early onset hereditary form of polycystic kidney and liver disease (1). It affects 1 in 20,000 live births (2). ARPKD is caused by mutations in *polycystic kidney and hepatic disease 1 (PKHD1)* gene which is located on chromosome 6p12 and contains over 470 kb of the genomic sequence (3). This gene codes for Fibrocystin/ Polyductin (FPC), a single-membrane spanning protein with numerous isoforms which is expressed mostly in kidney (predominantly in collecting ducts and thick ascending loops of Henle), liver (specifically in bile duct epithelia), and pancreas (4).

The clinical features of ARPKD are highly variable among affected families (5). The signs and symptoms of this condition are usually observable shortly after birth in early infancy. Frequent complications of ARPKD include pulmonary hypoplasia, hypertension, polyuria and polydipsia, problems with liver blood flow which can lead to serious internal bleeding, large bilateral flank masses (nephromegaly), and progressive loss of renal function (6). Recently, advances in next generation sequencing technologies have made whole exome sequencing (WES) a technically feasible and powerful instrument for detection of genetic mutations leading to various Mendelian disorders (7). This technique is particularly well suited for the detection of mutations in rare disease (8) such as ARPKD.

2- CASE REPORT

In the present study, we describe a couple with a history of an affected son with polycystic kidney disease and hepatic failure who died at the age of 8 months. The parents were consanguineous (**Figure.1**). Perinatal history was unremarkable. During infancy, the predominant signs were epileptic seizures,

pulmonary distress and brain atrophy which was evident in magnetic resonance imaging (MRI). Two other cases of hepatic failure have been reported in family which led to child demise at the ages of 11 and 13, respectively. They were offered to do WES to discover underlying genetic cause. Genomic DNA was isolated from blood sample of parents using the standard salting out technique after obtaining informed consent. WES was performed in the mother using paired-end sequencing method with 100X coverage in Illumina HiSeq4000 (Laboratory for Molecular Diagnosis, University of Leuven, Belgium). All exons of protein coding genes as well as some important other genomic regions were enriched. Subsequent bioinformatics analysis of the sequencing results was performed using international databases (ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) and dbSNP [<https://www.ncbi.nlm.nih.gov/projects/SNP/>]) and standard bioinformatics softwares (Polyphen -2 (Polymorphism Phenotyping v2) and Combined Annotation Dependent Depletion [CADD]).

A heterozygote mutation was found in *PKHD1* gene (NM_170724, c.9107T>G, p.V3036G) in female proband which was confirmed by Sanger sequencing. The male proband was also shown to carry the same mutation. This mutation is predicted to be possibly damaging by PolyPhen (9). CADD was used for scoring the deleteriousness of detected nucleotide change (10) which showed that this mutation is damaging with CADD score of 23. In addition, we used the UniProt databases to predict the effect of missense mutation on protein structure (11) which showed that the wild-type and mutant amino acids differ in size in a way that the mutant residue is smaller which might lead to loss of interactions. In addition, the hydrophobicity of the wild-type and mutant residue differs, so hydrophobic

interactions, either in the core of the protein or on the surface will be lost. This mutation has also been reported in ARPkd/PKHD1 Aachen database (<http://www.humgen.rwth-aachen.de/>). Consequently, according to databases and

the observed change in the protein structure, we concluded that this nucleotide change is pathogenic.

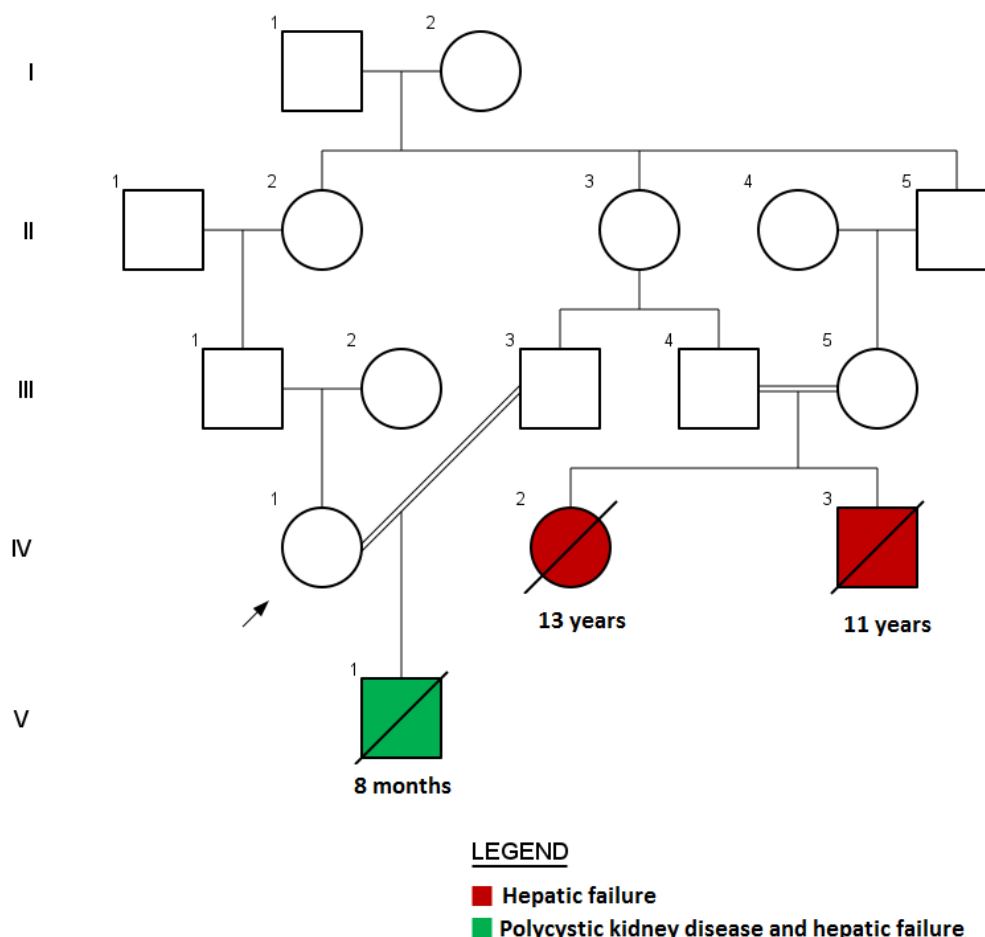


Fig.1: The family pedigree.

3- DISCUSSION

ARPKD is a heterogeneous disorder caused by mutations in *PKHD1* gene. To date, 748 variants of the *PKHD1* gene have been described in ARPkd/PKHD1 Aachen database (<http://www.humgen.rwth-aachen.de/>). Half of affected neonates die in their infancy while others stay alive until adulthood. A genotype-phenotype correlation has been suggested for this

disorder in a way that missense mutations are predicted to be associated with a nonlethal form of disorder, while chain terminating mutations are more commonly associated with neonatal death. More specifically, patients who survive the neonatal period have at least one missense mutation, implying that such nucleotide changes produce milder disease. The detected mutation in the present study has been previously found in

a Hispanic-American patient affected with childhood form of ARPKD, with no systolic hypertension, no kidney disease but portal hypertension (12). However, the detected mutation in the current study has been associated with severe infantile form of the disorder with kidney and liver involvement in addition to another complication i.e. epileptic seizure. A link between seizure and PKD has been suggested by Yao et al (13). While previous researches have shown the involvement of cilia in the pathogenesis of PKD, they have demonstrated that defective cilia might also influence the activity of the brain (13). So, further researches are needed to elaborate the link between epilepsy and PKD.

4- CONCLUSION

Unlike previous studies which showed the association between missense mutations of *PKHD1* gene and mild phenotype of ARPKD, we have demonstrated the presence of a certain heterozygote missense mutation in parents of a patient affected with lethal form of disorder. Such phenotypic variations should be considered in genetic counseling of families especially those seeking prenatal diagnosis.

5- ACKNOWLEDGMENT

The authors are grateful to the patient's family for their participation in the study.

6- CONFLICT OF INTEREST: None.

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