

# Case Report: Lethal Non-immune Hydrops Fetalis with Biallelic Inheritance of PKP2 Variants

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## Abstract

Here we describe a male infant with non-immune hydrops fetalis associated with congenital cardiomyopathy diagnosed prenatally. Whole-exome sequencing detected compound heterozygous c.1688+1G>A and p.(Asn759Ilefs\*41) variants in the PKP2 gene inherited independently from his asymptomatic parents. Our present case supports the severe phenotype of biallelic inheritance of PKP2 gene pathogenic variants

## Introduction

Hydrops fetalis occurs in approximately 1 to 1700 to 3000 pregnancies. It is defined as an abnormal fluid accumulation in two or more fetal compartments, including ascites, pleural effusion and skin edema detected in prenatal ultrasound. The widespread use of anti-D immune globin has rendered the majority of cases to be non-immune in nature (NIHF) (Almomani, R, etal 2016).

Cardiovascular etiologies, including structural cardiac anomalies, cardiac dysrhythmias, cardiac tumors, cardiomyopathy and myocarditis are the leading causes for NIHF. Cardiomyopathy in particular has been described in several genetic disorders in association with non-immune hydrops e.g. mitochondrial disorders such as Barth syndrome, RASopathies such as Noonan and Costello syndrome, lysosomal storage disorders such as mucopolysaccharidosis type VII and other single gene disorders (Bellini, C, et al 2015). Severe cardiomyopathy in association with NIHF has been described in biallelic truncating ALPK3 mutation (Almomani, R, etal 2016).

Here, we describe a severe congenital cardiomyopathy that resulted in NIHF in a male infant born to a healthy non-consanguineous Saudi Arab young couple. Whole-exome sequencing detected two heterozygous variants in the PKP2 gene; c.1688+1G>A and c.2274del p(Asn759Ilefs\*41) (Fressart, V et al, 2010) variants were inherited from the father and the mother respectively. No other variants that could have explained the patient phenotype were detected. The cardiac evaluation including EKG and echocardiogram of the parents was unremarkable.

PKP2 encodes for plakophilin-2, an essential armadillo repeat protein of the cardiac desmosome plaque and cell nucleus. Heterozygous alteration in PKP2 gene is known to cause arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) #609040 (Gerull, B et al, 2004. The estimated prevalence of ARVC/D is 1:2,500 to 1:5,000 (Burke, A. P et al, 2021). Homozygous deletion of PKP2 deletion was described in two siblings with a severe noncompaction cardiomyopathy starting prenatally and leading to rapid cardiac failure (Ramond F et al., 2017), (Katanyuwong P et al 2022)

In addition, Ballelic inheritance of PKP2 variant was reported in children presenting with acute viral myocarditis (Belkaya, S et al 2017). Hypoplastic left heart syndrome (15. Verhagen JMA,et al 2018)

A homozygous missense c.C2519Tp.A840V & compound heterozygous c.T2062C p.D829N/c.G2485Ap.D829N unreported variants were detected in those patients retrospectively. The author hypothesized that acute myocarditis is more commonly related to defect to cardiac protein structure and common viral infections merely and indirectly destabilize inherently vulnerable hearts

Our present case the supports the severe phenotype of the biallelic inheritance of PKP2 cardiac disease and extends its clinical spectrum.

### Case Presentation

The index case was the third child born to a healthy non-consanguineous Saudi Arab young couple at 36 weeks gestation by an elective cesarean section. The mother was a 24-year-old gravida 3 para 2. She was referred to the feto-maternal clinic at 36 weeks gestation with a recent diagnosis of non-immune hydrops fetalis associated with decreased fetal movements. The rest of the prenatal history and family history were unremarkable. The prenatal ultrasound showed evidence of fetal hydrops, poor cardiac function with no associated structural fetal anomalies (figure 1). The baby's birth weight was 3.59 Kg, the length was 47cm, and the head circumference was 34 cm. Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. He required an immediate intubation and mechanical ventilatory support. Physical examination revealed a male newborn with anasarca, had no active movements. Apart from distortion caused by edema, no obvious facial dysmorphism was appreciated, cardiac sounds were muffled. Liver size was normal, spleen was not palpable and genitalia were normal. Extremities showed no deformities.

Post-natal echocardiogram study showed thickened valves, severely decreased right ventricular systolic and left ventricular systolic function, moderate tricuspid valve insufficiency, prominent right ventricle muscle bundle, dilated right ventricle, mild, normal left ventricle structure and size and small restrictive membranous ventricular septal defect.

Despite the intensive hemodynamic support he received, the baby had a cardiac arrest. Repeated echocardiogram showed worsening of the contractility pericardial effusion and dilation of both ventricles (figure 2). He was declared dead post failed resuscitation.

### Patient consent

The consent was obtained from the parents for genetic study and publication

### Molecular study

Whole-Exome sequencing trio was conducted in Centogene lab, Rostock, Germany including both parents and the baby DNAs after obtaining consents. The study detected two variants in the PKP2 gene. The first variant c.1688+1G>A is predicted to disrupt the highly conserved donor splice site of exon 7 inherited from the father. According to HGMD Professional 2018.2, this variant has previously been described as disease causing for arrhythmogenic right ventricular dysplasia/cardiomyopathy by Fressart et al., 2010 (PMID: 20400443). ClinVar lists this variant as pathogenic and likely pathogenic (clinical testing, Variation ID: 45038). The second PKP2 variant c.2274del p(Asn759Ilefs\*41) creates a shift in the reading frame starting at codon 759 inherited from the mother. The new reading frame ends in a stop codon 40 positions downstream. ClinVar lists this variant as likely pathogenic (clinical testing, Variation ID: 202023). Furthermore, in Centogene's mutation database (CentoMD®5.0), this variant was previously detected in a patient with an overlapping phenotype in a homozygous state (figure 3). Neither of the two variants was detected in two older healthy siblings.

Cardiac evaluation including EKG and echocardiogram the asymptomatic parents was unremarkable.

### Discussion

Rh immunization has significantly decreased the incidence of immune hydrops fetalis. Therefore it was found that the most common association with hydrops has become fetal cardiovascular abnormalities (Bel-

lini, C et al, 2015). Which includes cardiac structural malformations, fetal, arrhythmias, high output heart failure, cardiac tumors, cardiomyopathy, myocarditis, myocardial infarction, and idiopathic arterial calcification (Knillans, T. K, et al 1995). Our patient presented with nonimmune hydrops at 36 weeks gestational age. Prenatal ultrasound detected poor cardiac contractility with no associated structural fetal anomalies. Post-natal echocardiogram showed severely decreased right and left ventricular systolic function, moderate tricuspid valve insufficiency, prominent right ventricle muscle bundle, dilated right ventricle, mild, normal left ventricle structure and size and small restrictive membranous ventricular septal defect. These findings support the pathogenicity of the right ventricular insufficiency as the most likely causative factor for the patient's hydrops.

PKP2 (#602861) gene encodes plakophilin-2, an essential armadillo repeat protein of the cardiac desmosome, on chromosome 12p11. Molecules that contribute to desmosomes' formation are: desmosomal cadherins, armadillo-repeat proteins, and plakophilins. Armadillo repeat protein function to link desmosomal cadherins with desmoplakin and the intermediate filament system (Hamosh, A et al, 2004). PKP2 gene alteration was found to cause disrupted intercellular connections resulting in myocyte cell death and an inflammatory repair process. They were also found to cause fibro-fatty replacement of the right ventricle myocardium, which results in dysfunctional dilated right ventricle. PKP2 pathogenesis is an example of pleiotropic gene that it is known to be associated in different inherited cardiac arrhythmias ranging from arrhythmogenic cardiomyopathy, Brugada syndrome, idiopathic ventricular fibrillation dilated and hypertrophic cardiomyopathy (Novelli, V et al, 2018). A study showed that several PKP2 variants could be found in high percentage of healthy controls, increasing the complexity of interpretation of the variability of this protein (Petrovski, S et al, 2013). So far more than 1000 variants have been reported in ClinVar including deletions, duplications and missense. More than 500 of those were listed as variants of unknown significance.

A study confirmed a high percentage (43 %, 25/58) of cases of ARVD/C caused by mutations in PKP2 (Dalal, D et al, 2006). In addition, earlier disease manifestation was observed in this group.

Whole Exome sequencing trio was conducted including the patient and his parents detected two heterozygous c.2274del p(Asn759)lefs\*41/ c.1688+1G>A variants in the PKP2 gene in the patient. The mother was heterozygous for the c.2274del p(Asn759)lefs\*41 variant and the father was heterozygous c.1688+1G>A variant. Both of those variants were listed as likely pathogenic according to the ClinVar in a heterozygous state. Those two variants were not detected in the older two healthy sibling. Both heterozygous parents cardiac evaluation including EKG and echocardiogram were unremarkable. Given the autosomal dominant inheritance of the ARVC/D-PKP2-related gene, incomplete penetrance and variable expressivity could well explain the parent's normal phenotype (12. Leone MP, et al 2021).

Homozygous deletion of PKP2 gene resulted in a lethal defect in cardiac morphogenesis in mice. The author concluded that plakophilin 2 is important for the assembly of junctional protein and an essential morphogenesis factor and architectural component of the heart. We assumed that the biallelic inheritance of PKP2 variants in our patient has resulted in a lethal phenotype (Grossmann, K. S, et al 2004).

## Conclusion

Congenital cardiomyopathy associated with non-immune fetal hydrops supports the severe pathogenicity of biallelic variant inheritance in the PKP2 gene. This report reinforces the power of exome sequencing in genetic diagnosis of nonimmune fetal hydrops, expanding the clinical and genetic spectrum of inherited cardiac disorders.

## Conflict of interest

None

## Acknowledgment

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