

A rare etiology of tetralogy of Fallot with pulmonary atresia: Renpenning syndrome

INTRODUCTION

Congenital heart disease (CHD) is the most frequent birth defect among live births and the leading cause of infant and perinatal mortality from a birth defect (1). Patients with CHD can now reach adulthood, but have an increased risk of having children with CHD.

Over 400 CHD genes have been discovered thus far, and nearly 90% of patients with CHD have a suspected genetic contribution (2).

Tetralogy of Fallot (TOF) is the most common cyanotic CHD accounting for 7%–10% of all CHDs (3, 4). The etiology is complex and includes environmental factors, aneuploidies, 22q11.2 deletion, and single-gene diseases. Around 15% of patients with TOF have 22q11.2 deletion syndrome (3).

Here, we present the case of a 17-year-old Turkish boy with TOF and pulmonary atresia, intellectual deficiency (ID), short stature, microcephaly and dysmorphic features. He had a frameshift mutation at the gene, polyglutamine-binding protein 1 (*PQBP1*) (NM_001167989:p.Arg153fs), which leads to Renpenning syndrome. This is also the first report of pulmonary atresia together with TOF in Renpenning syndrome.

CASE REPORT

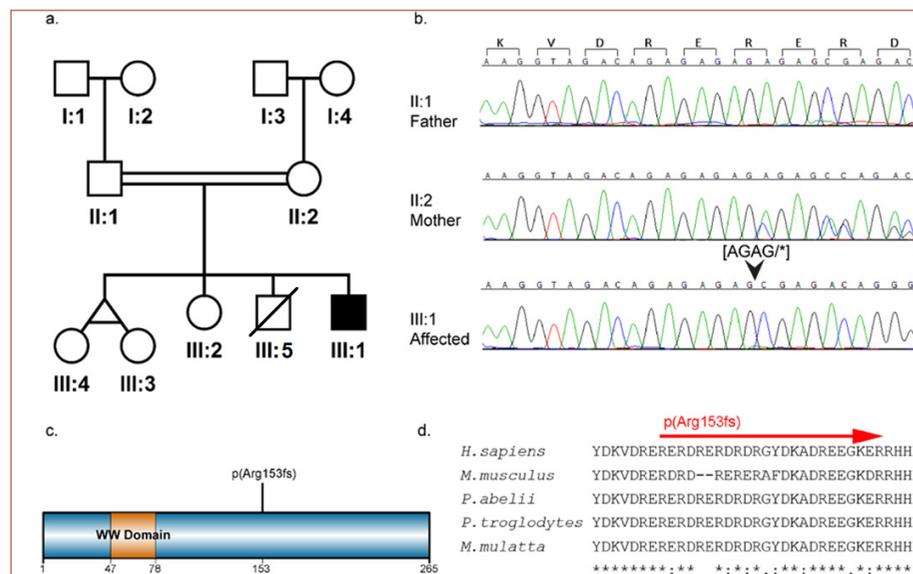


Figure 1. a: Pedigree demonstrates father, mother, and unaffected sisters with non-filled and affected child with filled symbols and a child who died because of a CHD. **b:** Sequencing results show heterozygosity in mother (II:2) and three unaffected sisters (III:4, III:3, and III:2), WT sequence of father (II:1), and homozygosity in the affected child (III:1). **c:** Variants of the *PQBP1* gene and domain locations. *PQBP1* is composed of three domains: a WW domain; a polar amino acid rich domain (PRD); an unstructured C-terminal domain (CTD) (9). **d:** Amino acid sequence alignment of *PQBP1* orthologues showing that both variants were highly conserved through evolution.

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CASE REPORT

The 17-year-old Turkish boy was seen in a pediatric genetics clinic. He was the second child of consanguineous parents whose first child died because of a CHD (details unknown) (Figures 1a and b). At one month of age, he was diagnosed with TOF and pulmonary atresia (muscular atresia) with hypoplasia of the main pulmonary artery but well-developed confluent branch pulmonary arteries fed by a patent ductus arteriosus. There was no coronary abnormality, and he underwent total correction. He had fluorescent *in situ* hybridization (FISH) for the 22q11.2 deletion syndrome, which was negative; and he was not evaluated again by a geneticist. He had slow growth and mild ID, which were attributed to his cardiac defect. His dysmorphic features were missed.

His height was 149.4 cm [−3.92 standard deviation (SD)], weight was 38.2 kg (−4.43 SD). His head circumference was 48 cm (−6.34 SD). He had a long narrow face, bulbous nose, sparse lateral eye brows, and strabismus; all typical features of Renpenning syndrome.

Whole exome sequencing analysis revealed a frame-shift hemizygous X chromosome variant inherited from an unaffected heterozygous mother at the gene, *PQBP1* (NM_001167989: p. Arg153fs). Three unaffected sisters (III:4, III:3, and III:2) also inherited the same X chromosome variant from their mother (Fig. 1a and 1b).

He had a right ventricle to pulmonary artery conduit replacement operation in 2019 because of infective endocarditis. In 2020, he was hospitalized again for a conduit infective endocarditis, but he did not respond to treatment and died.

DISCUSSION

Renpenning syndrome (OMIM#309500) is a very rare X linked disorder characterized most commonly by ID, short stature, and microcephaly, caused by mutation in the *PQBP1* gene (5). Heart defects seen most commonly are; TOF, atrial septal defect, ventricular septal defect, and rarely situs inversus. Immune deficiency is not reported (6). Our patient had infective endocarditis twice, and this was attributed to lack of hygiene. However, immune function test was not done.

He had a very long delay in diagnosis as his growth, and the developmental delay was attributed to his cardiac problems. He only had a FISH test before and was not offered a microarray analysis, which is the best first-line genetic assessment for most patients with CHD (7). The next step is whole exome sequencing (WES). Our patient did not want to do the microarray analysis; therefore, we pursued with WES.

To understand the impact of our variants on the functional proteins, conservation status of each amino acid affected by mutation was checked among different species. The sequence alignment was performed (Fig. 1c), and a highly conserved amino acid sequence was found in the 153th amino acid and contained a conserved domain WW (Fig. 1d). WW domain is frequently associated with other proteins in the signal transduction processes involved in the embryonic de-

velopment and differentiation of the central nervous system.

The mutation locates at the DR/ER repeats with six AG dinucleotides. The same AGAG deletion was reported in patients with ID (8) and a very similar 2-bp AG deletion (c.451_452del) was reported in a patient with Renpenning syndrome earlier (9).

Carrier females do not usually have clinical features owing to the favorable skewing of X-chromosome inactivation. None of the sisters nor the mother had the clinical features. They have a 50% chance of transmitting the pathogenic variant to their offsprings.

CONCLUSION

Many individuals with CHD are now of reproductive age and are at increased risk of having children with CHD and would benefit from a genetic evaluation. In our case, the eldest sister had preimplantation genetic testing and delivered a healthy son.

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Informed consent: Written informed consent was obtained from the patient's family for publication of this case report. The family did not consent for publication of images.

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