A Novel Mutated Sequence in Tbx-5 Gene, Exon-3, Repetitive Holt-Oram Syndrome

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Abstract

We report a case of 31 year-old pregnant woman that attended to our perinatology outpatient clinic because of fetal ventricular septal defect and limb reduction in upper extremities of her fetus via ultrasonography, diagnosed at 16 weeks of gestation with a history of Holt Oram Syndrome in her first child. Pregnancy was terminated and we performed mutation analysis in TBX5 gene. Sequence analysis revealed c.241A>T (p.Arg81Trp) alteration exon 3 of *TBX5* effected family members and fetus. It's a novel mutation for Holt-Oram Syndrome.

Introduction

Holt-Oram Syndrome (so called Heart and Hand Syndrome) is an autosomal dominant inherited genetic condition known as various cardiac malformations and various skeletal deformities in upper extremities could be seen. The incidence is 1 in 100.000 live born babies and it has very high penetrance. Approximately 85% of cases are attributed to a new mutation in *TBX5* gene on the long arm of chromosome 12 (12q2).[1]

Case Report

A 31 year-old pregnant woman was referred to our perinatology unit at 16 weeks' gestation, because of fetal cardiac and skeletal malformations. Ultrasonographic examination revealed a single live fetus compatible with 16 weeks. There were ventricular septal defect located in the membranous septum measured 2,1 mm in mean diameter, humeral, radial, ulnar, aplasia in the left upper extremity and right radial aplasia via ultrasonography. Her first child, is a 6 year-old girl has atrial septal defect (secundum type and corrected with an angiographic operation) and bilateral radial aplasia and agenesis of thumbs alleviated with an operation known as 'index finger pollicization'. The patient's husband has bradyarrythmia needed a pacemaker and his forearms were short. His sister also has the same defects as her brother. Pedigree analysis was presented as a diagram (Figure 1).

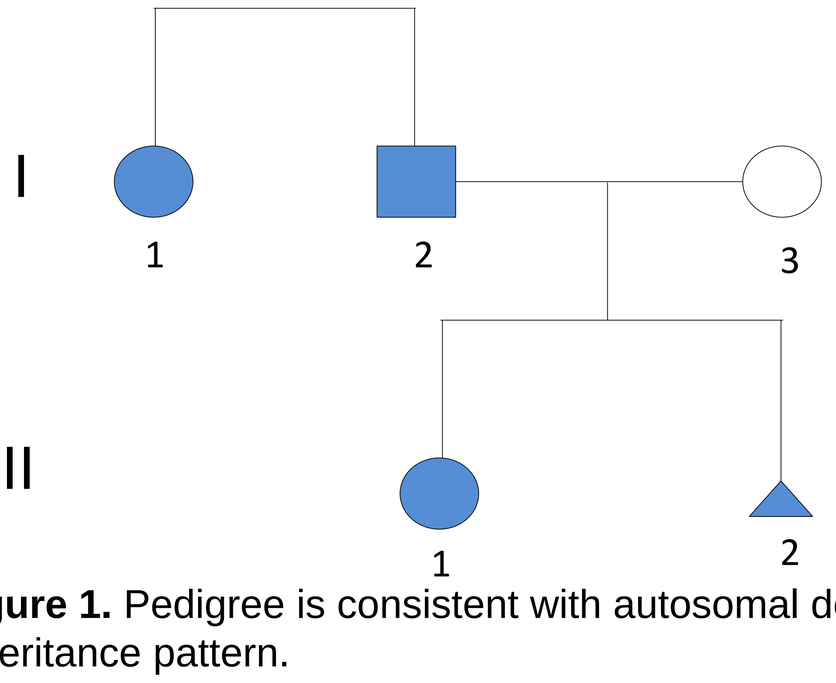

Figure 1. Pedigree is consistent with autosomal dominant inheritance pattern.

The family was informed about fetal anomalies. They wanted termination of pregnancy and further genetic evaluation. Venous blood sampling was performed in I-2, I-3, II-1 (Figure 1) and dermal tissue sampling was obtained from the terminated fetus(II-2, Figure 2). Following DNA isolation, mutation analysis in TBX5 gene was performed from these samples. Mutation analysis revealed c.241A>T alteration in exon-3 of *TBX5 gene* causing p.Arg81Trp alteration in protein(Figure 3). She was discharged two days after termination of pregnancy without any problem. We informed the family about the recurrence risk of the disease (50 per cent) and offered preimplantation genetic diagnosis (PGD) prior to future conceptions.

Figure 2. Postabortal view and X-ray radiogram of the fetus.

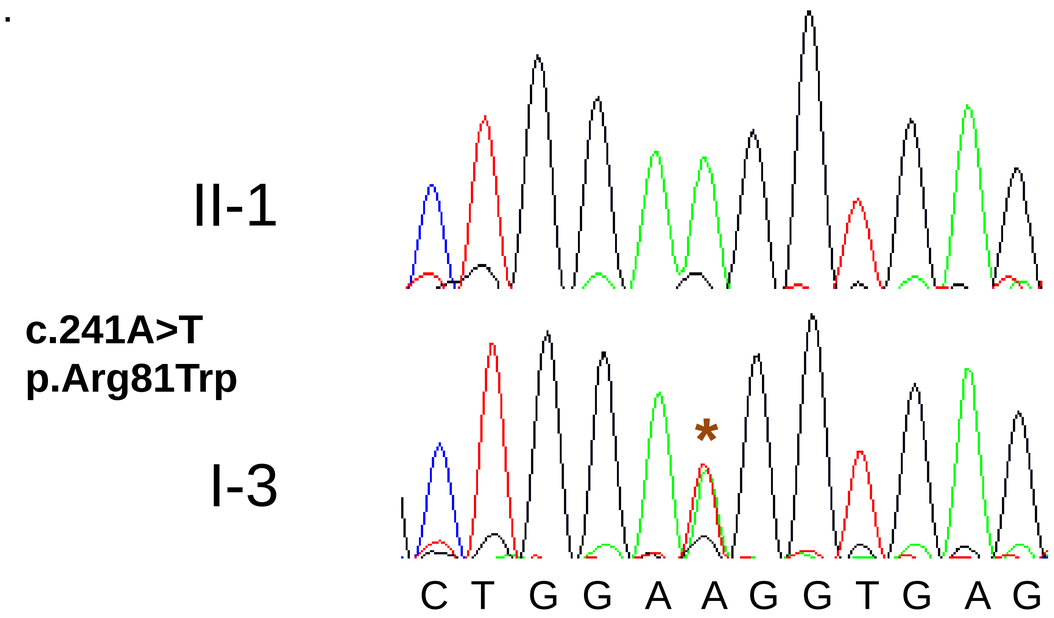

Figure 3. Mutation analysis revealed c.241A>T alteration in exon 3 of *TBX5* causing p.Arg81Trp alteration in protein.

Conclusion

Genetic analysis is helpful in the management of inherited conditions such as this family's situation. Preimplantation genetic diagnosis(PGD) is an advance and a chance to have a healthy baby who has normal genetic sequence. c.241A>T is a novel mutation found in a patient diagnosed with Holt-Oram Syndrome according to our comprehensive literature search.

References

1. Bruneau BG, Nemer G, Schmitt JP,et al: A murine model of Holt–Oram syndrome defines roles of the T-box transcription factor Tbx5 in cardiogenesis and disease. Cell 2001; 709-721).

Abbreviations: Arg: Arginine, Trp: Tryptophan, A: Adenine, T: Timine, C: Cytosine, G: Guanine