Case Report
J Genet Med 2012;9(2):98-100
http://dx.doi.org/10.5734/JGM.2012.9.2.98
ISSN 1226-1769(Print) 2233-9108(Online)

JGM Journal of Genetic Medicine

A Familial Case with Holt-Oram Syndrome with a Novel *TBX5* Mutation

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Holt-Oram syndrome (HOS) is the most common heart-hand syndrome, which is inherited in an autosomal dominant manner, but most cases are sporadic. This condition is characterized by upper-extremity malformations involving radial-ray, thenar, and carpal bones, and congenital heart malformations including atrial septal defect and ventricular septal defect. It is caused by mutations in the TBX5 gene. In this report, a Korean case with HOS is described, which is inherited from her father. A novel nonsense mutation, p.Glu294*, was identified. This is the first Korean case with HOS confirmed by genetic testing.

Key words: Holt-Oram syndrome, *TBX5*, Mutation

Introduction

Holt-Oram syndrome (HOS; OMIM 142900) is a congenital disorder, inherited in an autosomal dominant manner. HOS primarily affects heart and hand, which is characterized by upper-extremity malformations involving radial-ray, thenar, and carpal bones and congenital heart malformations including atrial septal defect and ventricular septal defect.[1, 2] Some patients have cardiac conduction defect. However, clinical manifestations of HOS have been variable among patients.[2] HOS is caused by mutations in the *TBX5* gene.[3]

Although HOS is the most common heart-hand syndrome with its estimated prevalence of 1 over 100,000 live births,[1] only a few Korean cases have been reported.[4-6] Moreover, no case has been reported in Korean population confirmed by genetic testing. In this report, a familial case with HOS is described with novel *TBX5* mutation. This is the first Korean case with HOS confirmed by genetic testing.

Case Report

The patient was the first off-spring of non-consanguineous Korean parents. She was born after 40 weeks of gestation. Her prenatal evaluation had been uneventful. Postnatal evaluation was also normal except left hand anomaly. Left thumb was triphalangeal and hypoplastic, and the other extremities were normal (Fig. 1). At 1 month of age, respiratory difficulty was noted with tachypnea, and systolic murmur was audible at left sterna border. Echocardiography revealed large secundum atrial septal defect with left-to-right shunt. In addition, perimembranous inlet-trabecular type of ventricular septal defect was found with septal aneurysm. At 2 months of age, patch closure for ventricular septal defect and atrial septal defect was done. After the operation, the diaphragm plication was performed for right diaphragmatic palsy. Of note, her father had been also given heart operation for ventricular septal defect at 10 years of age, and both

Received: 17 Nov 2012, Revised: 11 Dec 2012, Accepted: 18 Dec 2012, Published: 31 Dec 2012
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*Conflicts of interest: The authors have nothing to disclose or conflicts of interest

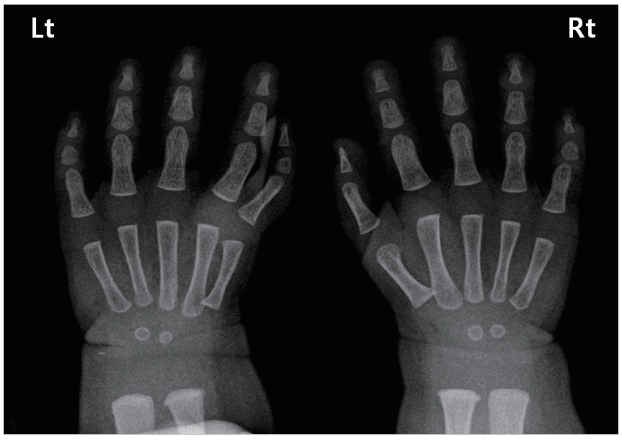

Fig. 1. Left triphalangeal thumb and normal right thumb.

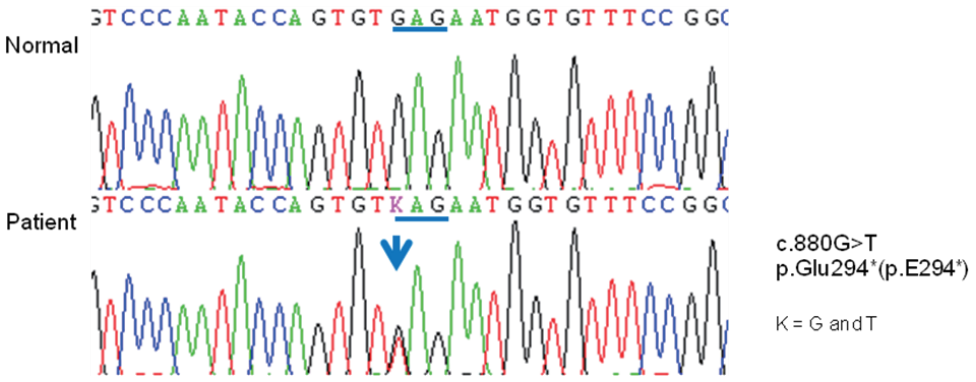

Fig. 2. Partial sequence of the *TBX5* gene. The patient and her father carries a novel nonsense mutation, c.880G>T (p.Glu294*).

his thumbs were abnormal. Under the impression of familial HOS, genetic testing for the *TBX5* gene was done, using genomic DNA from peripheral leukocytes. The patient and her father shared the novel nonsense mutation, c.880G>T (p.Glu294*) (Fig. 2). Thumb reconstruction operation was performed at two years of age. Until 5 years of age, she showed normal development with normal growth profiles; her height was 100 cm (10th percentile) and weight was 14.2 kg (25th percentile). Holter monitoring has been performed annually, which revealed intermittent sinus bradycardia, sinus node dysfunction with junctional escape beat, but no episode of atriventricular block was seen.

Discussion

Upper limb anomalies in HOS can be variable among patients. The deformities may be unilateral or bilateral, and symmetric or asymmetric. These are often more severe in left side than in right side. Hand deformities range from triphalangeal, as in our patient, or absent thumb to phocomelia. In some patients, radial aplasia or hypoplasia can be also noted.[1,2] Although most cases with HOS have upper limb anomalies, cardiac defects can be seen in 75% of the patients. The most common cardiac anomalies are atrial septal defect and ventricular septal defect, as in our case, but some patients have complex cardiac defects including conotruncal malformations.[7] The long-term prognosis of a patient with HOS usually depends on the severity of cardiac defects. Especially patients can have cardiac conduction disease, which starts as sinus bradycardia, but it can progress to high-degree atrioventricular block with or without atrial fibrillation.[5]

In the diagnostic process, the following diseases should be differentiated from HOS. *SALL4*-related disorders include radial ray malformations like HOS, Indeed, in rare cases with HOS-feature, *SALL4* mutations are found. However, ocular and renal abnormalities are exclusively involved in *SALL4*-related disorders, but not in HOS. Townes-Brocks syndrome is another disease with similar phenotype to that of HOS, but it also includes renal-ear-anal-radial anomalies, is caused by mutations in *SALL1*.[8] Other diseases to be excluded are heart-hand syndrome II/III, Fanconi anemia, VACTERL sequence, and teratogen exposure like thalidomide

and valproate. The important feature to differentiate HOS from these similar conditions is the absence of ulnar ray malformation without radial ray, anomalies including kidney, eye, vertebrae, ear, and anus in HOS.[2)]

TBX5 is a member of the T-box family of transcription factors, and the T-box domain is the DNA-binding site. TBX5 plays an important role in cardiac and limb developments.[1)] *TBX5* mutations are found in over 70% of patients with HOS. Currently, about 90 *TBX5* mutations have been identified, most of which are private and point mutations (http://www.hgmd.org/). The novel nonsense mutation found in this case is expected to lead to premature truncated protein, which may be degraded and fail to be localized in the nucleus, where TBX5 could have played its proper role.

Most cases with HOS are sporadic cases, but our case is a familial case with paternal inheritance. More cases with HOS should be identified to characterize the clinical and genetic features of Korean patients with HOS.

Acknowledgements

We thank our patient and her family members for their participation in this study. This study was supported by Grant A080588 from the Korean Ministry of Health, Welfare and Family Affairs.

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