

# Electrical disorders in atrial septal defect: genetics and heritability

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**Contributions:** (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Atrial septal defect (ASD) is one of the most common types of congenital heart diseases (CHDs). Most ASDs occur sporadically, but some are inherited and associated with cardiac conduction defects such as atrioventricular block (AVB) or bundle branch block. Mutations in genes encoding transcription factor gene *TBX5* and *NKX2-5*, were found in Holt-Oram syndrome (HOS) and ASD with atrioventricular (AV) conduction defects, respectively. HOS is characterized by upper limb anomaly in addition to ASD and AVB (heart-hand syndrome). ASD associated with *NKX2-5* is rare but is reported to cause sudden cardiac death (SCD) or cardiomyopathy. We provide a review of these two diseases.

**Keywords:** Atrial septal defect (ASD); genetics; atrioventricular block (AVB); Holt-Oram syndrome (HOS); *TBX5*; *NKX2-5*

Submitted Nov 09, 2017. Accepted for publication Feb 08, 2018.

doi: 10.21037/jtd.2018.02.53

View this article at: <http://dx.doi.org/10.21037/jtd.2018.02.53>

## Introduction

Atrial septal defect (ASD) is one of the most common types of congenital heart disease (CHD), constituting 8–10% of CHD cases in children. ASD is sometimes associated with complex CHDs or chromosomal abnormality. Although most ASDs occur sporadically, hereditary modes of inheritance have been reported. The risk of CHD in offspring of a woman with sporadic ASD has been reported to be 8–10%(1). Hereditary ASD is sometimes complicated with bradyarrhythmias such as atrioventricular block (AVB) or sick sinus syndrome (SSS); patients with surgically-repaired ASD sometimes present tachyarrhythmias such as incisional atrial tachycardia caused by operation. We herein describe the inherited ASDs associated with arrhythmias: Holt-Oram syndrome (HOS) and ASD with atrioventricular (AV) disturbance. Atrial tachycardia after ASD operational repair will be discussed in a later.

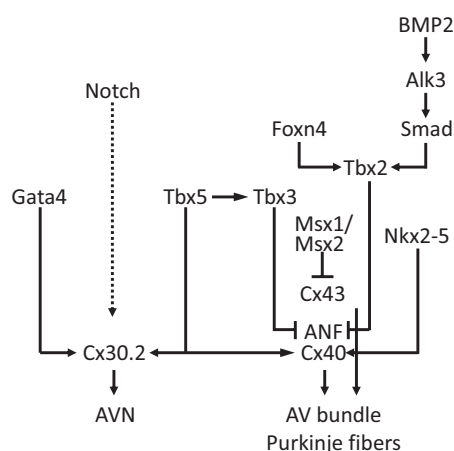
## Development of atrial septation and cardiac conduction system

### *Atrial septation*

The atrial septum is formed by three distinct structures: (I) the AV septal cushion; (II) the primary atrial septum; and (III) the dorsal mesenchymal protrusion associated with the second heart field (SHF) (2,3). Transcription factors important during the atrial septation include *GATA4*, *NKX2-5*, and *TBX5*. *TBX5* interacts with *NKX2-5* and *GATA4* and positively regulates transcription within the developing heart. *TBX5* regulates SHF *GGAS1* and *OSRI*, which are required in the posterior SHF for atrial septation (2,4,5).

### *Cardiac conduction system (Figure 1)*

Two transcriptional repressors, *TBX2* and *TBX3*, are



**Figure 1** Molecular pathways regulating the development of the fast-conducting bundle of His and its tributaries. TBX2 and TBX3 suppress the expression of chamber myocardium genes: *ANF*, *GJA5* (*Cx40*), and *GJA1* (*Cx43*), which differentiate toward rapid conduction, along with muscle-segment homeobox transcription factor *MSX1* and *MSX2*. While TBX5 and NKX2-5 activate the expression of *ANF* and *Cx40*. Together with TBX5, GATA4 activates *Cx30.2* expression, which is detected in AVN and retains the slow conduction [cited from reference (6)]. AVN, atrioventricular node.

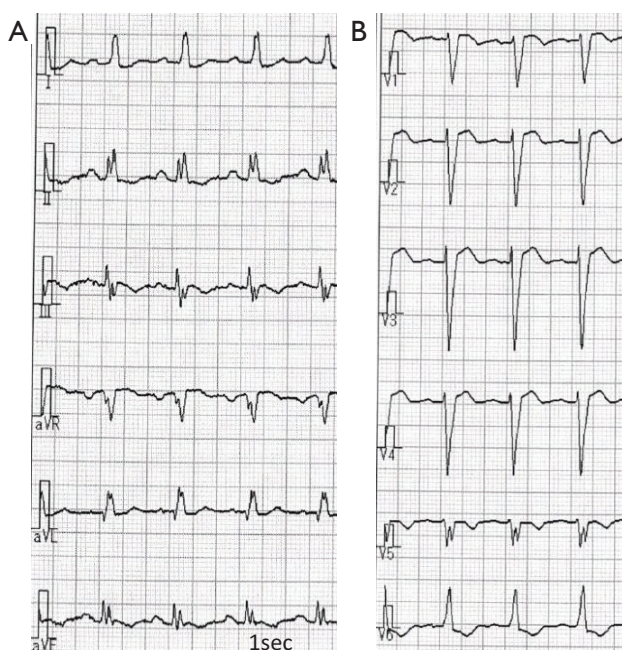
crucial in suppressing the further differentiation of the AV canal myocardium (7,8). The combined action of widely expressed transcription factors: NKX2-5, TBX5, and ID2 (inhibitor of DNA binding), the latter having a more limited domain of expression, is now known to be crucial for the development of the AV conduction system (9). TBX3 represses the chamber-specific genes *ANF*, *GJA5*, and *GJA1* along with TBX2, *MSX1*, and *MSX2*. While TBX5 and NKX2-5 activate the expression of *ANF* and *GJA5*, TBX5 also activates *Cx30.2* expression together with GATA4 (6,10) (Figure 1).

## HOS

This syndrome, characterized by thumb anomaly and ASD, was first described by Holt and Oram in 1960 (11). They reported a family in which members of four generations were affected by both CHD and skeletal anomalies, and their malformations appeared to be of similar type in all the affected members: ASD, often accompanied by bizarre arrhythmias, and the skeletal anomalies affected mainly the hands. Their electrocardiograms (Figure 2) showed sinus bradycardia, PR prolongation, and escape junctional beats. One family member had sudden cardiac death (SCD). The inheritance followed Mendelian dominant type.

The combination (ASD + finger anomaly) is the most common type of “heart-hand” syndrome (upper limb and CHDs) and is estimated to occur in 1 of 100,000 live births (12). Linkage analysis performed on families demonstrating autosomal dominant inheritance identified a disease locus at 12q24 in 1994 (13). Subsequent investigations identified *TBX5* mutations in patients with HOS at 1997 (14,15). *TBX5* is a member of a family of transcription factor genes characterized by a highly conserved binding domain called T-box (16). It is located on 12q24.1 and consists of 10 exons.

Clinical features: a congenital heart malformation is present in 75% of clinically diagnosed patients with HOS (10). Although atrial and ventricular septal defects are most commonly seen, respectively occurring in 58% and 28% of patients, additional CHDs have also been reported, including AV septal defects, tetralogy of Fallot, truncus arteriosus, partial pulmonary venous drainage, ductus arteriosus, or hypoplastic left heart syndrome (17,18). Cardiac involvement was found in 95% of familial cases. Simple CHD was found in 66% of patients and more complex CHD in 17.5%. Some cases showed only ECG



**Figure 2** ECG findings in Holt-Oram syndrome. The electrocardiography exhibited PR prolongation and left bundle branch block.

abnormalities without CHD (18).

Cardiac conduction diseases include bradycardia, AVB, atrial fibrillation, sinus node dysfunction, or right bundle branch block (13). *Tbx5* knock-out mice display a maturation failure of the conduction system morphology and function. In the AV canal of the heterozygous *Tbx5<sup>del/+</sup>* mouse heart, cells failed to mature into discrete AV node or bundle. In clinically severe cases, the discrete right bundle branch is completely absent on the right ventricular septal surface. ECG of *Tbx5<sup>del/+</sup>* mice shows the prolongation of the PR and QRS intervals, and a broad P wave. Sinus pause is frequent and prolonged with 24 hours monitoring (19,20).

Skeletal anomalies involve the preaxial radial ray and are fully penetrant. Subclinical changes may include only radiographic evidence of abnormal carpal bone, whereas others have obvious severe manifestations such as phocomelia (13,18). Upper-limb malformations include unequal arm length, fusion or anomalous development of the carpal and thenar bones, abnormal forearm pronation and supination, abnormal opposition of the thumb, and sloping shoulders and restriction of shoulder joint movement (11). Carpal abnormalities are more specific for the HOS than are changes in the thumb (21). The left side is reported to be more severely affected (22). Other skeletal anomalies were polydactyly, arachnodactyly, coxa vara, thoracic scoliosis, hemi-atrophy of the body, and hypoplastic mandible.

Other congenital malformations found in HOS are miscellaneous: lung hypoplasia, malformations of renal and cerebral arteries, hypoplastic peripheral upper extremity vasculature, hypoplasia of left radial artery, pulmonary hypertension, cardiomyopathy, Hirschsprung disease, malformation of urinary system, renal failure, cryptorchidism, the Rokitansky-Kuster-Hauser syndrome (immature or absent of vagina or uterus), multiple strokes, myopia, and malignant tumors (23).

The correlation of the genotype with the severity of clinical features: *TBX5* mutations are identified in 70% of patients with the clinical features of HOS (24,25). The genotype-phenotype correlation in HOS remains controversial. More than 90 mutations have been identified within the *TBX5* gene, including missense, nonsense, frameshift mutations, splice mutations, duplication, and chromosomal rearrangements (14,15,26-31). Most mutations were predicted to encode a truncated protein and cause haploinsufficiency leading to more severe limb and cardiac phenotype. Of 90 these mutations, missense mutations (n>50) cause a large phenotype variation

depending on their position within the DNA-binding domain. *TBX5* dosage would be crucial for the healthy development of heart and upper limb (26).

A missense mutation (p.Pro85Thr) was found to result in a switch from cis-peptide conformation to the trans-conformation bond, affecting both folding and biological function and thereby leading to loss of function (31). Amino acid alteration near the amino-terminal end of the T-box, which should affect interactions with the major groove of the target DNA sequence, produces very significant cardiac malformations and minor skeletal abnormalities. In contrast, change in amino acids at the carboxyl end of the T-box, which should affect interactions between *TBX5* and the minor groove of the DNA target sequence, produces severe limb abnormalities and less significant cardiac abnormalities (27). It has also been reported, however, that neither the type of mutation in *TBX5* nor the location of a mutation in the T-box was predictive of the expression of malformations (32). Two gain-of-function mutations were associated with HOS (33,34).

### **ASD with AV conduction defects associated with *NKX2-5* gene mutation**

Hereditary ASD with prolonged PR interval, AVB and juvenile SCD has been reported in association with *NKX2-5* mutations (35-38). While the cardiac manifestations can be similar to those found in HOS, the disease associated with *NKX2-5* mutation lacks extracardiac anomalies such as upper limb malformations.

Schott *et al.* first demonstrated *NKX2-5* mutations in four families harboring AVB and CHD, including ASD or tetralogy of Fallot (39). Their 33 affected individuals all presented AV conduction delays, for which 14 received pacemaker implantation. SCD occurred in six asymptomatic individuals without pacemakers after surgical ASD repair. *NKX2-5* mutations also have been identified in patients with dilated cardiomyopathy (40,41) or ventricular arrhythmias (42) and caused SCD (43). SCD occurred in 15% of the patients with hereditary ASD and AV conduction disturbance (44). The families with ASD and SCD have *NKX2-5* mutations in 44% (44). The autopsy study revealed the fibrotic replacement of the AV bundle (45). Intra- and inter-familial phenotype variability of *NKX2-5* mutations is noted, but so far, no correlation has been reported between the mutant alleles and the severity in phenotype (46). In cases of hereditary ASD or CHD, or ASD with AV conduction disturbances, the genetic testing of *NKX2-5* would be useful

for predicting ventricular arrhythmias or SCD. If they are mutation carriers, a preventable implantable cardioverter defibrillator would be indicated in these patients (42,44).

*NKX2-5* gene mutation: the *NKX2-5* gene is located on chromosome 5 (5q34), which contains two exons encoding a 324-amino-acid protein. As a transcription factor of the nucleotide kinase (NK)-2 class, *NKX2-5* contains three highly conserved regions: the homeodomain, the tinman domain and the NK2 domain (47). *Nkx2-5* is necessary for cardiac development as well as maintaining proper function of the AV node and myocardium throughout adult life (48).

Homozygous inactivation of *Nkx2-5* in mammals impairs cardiac looping and is embryonic lethal (49,50). Mice with a heterozygous cardiac-specific *Nkx2-5* deletion exhibited a more subtle phenotype, which consisted of ASD, abnormality of aortic valve, and, in female mice, prolongation of the PR interval (51). To date, 61 different mutations have been identified (39,41,44,52-57). Schott *et al.* (39) also reported three different *NKX2-5* mutations (Gln170Ter, Thr178Met, and Gln198Ter) in patients with ASD and AV conduction disturbance. Two mutations were located in the DNA-binding homeodomain of *NKX2.5* and are likely to alter the affinity of target DNA binding, the other two were found to result in the deletion of C-terminal amino acids aberrantly augmenting transcription of downstream genes. Most of the *NKX2-5* mutations (62%) are amino-acid substitutions. The rest are premature stop codons (46).

## Summary

Recent extensive molecular study on transcriptional factors has elucidated the genetic background of hereditary ASD accompanied with arrhythmias. We need to carefully examine not only cardiac problems, but also the whole body of patients with ASD. Especially in the case of hereditary ASD, genetic testing will prevent future unexpected SCD due to bradycardia or tachycardia in both probands and their family members.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Aoki H, Horie M. Electrical disorders in atrial septal defect: genetics and heritability. *J Thorac Dis* 2018;10(Suppl 24):S2848-S2853. doi: 10.21037/jtd.2018.02.53