Dichotomous roles of $TBX3$ in the establishment of atrioventricular conduction pathways in the human heart

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Introduction
Mutations of the transcription factor gene $TBX3$ cause ulnar-mammary syndrome, a rare, autosomal dominant condition characterized by ulnar defects, apocrine and mammary gland hypoplasia, genital and dental abnormalities, and pituitary dysfunction.1,2 We present a patient who has ulnar-mammary syndrome caused by a de novo mutation of $TBX3$. In addition to the congenital anomalies, she has ventricular preexcitation due to a left-sided accessory pathway and right bundle branch block. This unusual combination of conduction abnormalities highlights the dichotomous functions of $TBX3$ in specifying the development of the conduction system and suppressing accessory atrioventricular (AV) pathways elsewhere.

Case report
A 14-year-old female subject, who has ulnar-mammary syndrome, was referred to a pediatric cardiologist after she was discovered to have a de novo mutation of $TBX3$. Whole-exome sequencing of her and her parents revealed that she has a premature stop codon in the conserved TBX domain (E364X, c.1090 G>T) of $TBX3$. The mutation is predicted to cause loss of function. Her parents do not carry the mutation.

She had no physical findings or symptoms referable to the heart. An echocardiogram confirmed normal cardiac anatomy. The electrocardiogram, however, showed ventricular preexcitation consistent with a left-sided accessory pathway and right bundle branch block. This unusual combination of conduction abnormalities highlights the dichotomous functions of $TBX3$ in specifying the development of the conduction system and suppressing accessory atrioventricular (AV) pathways elsewhere.

KEYWORDS Accessory atrioventricular pathway; Preexcitation; Right bundle branch block; $TBX3$; Ulnar-mammary syndrome; Wolff-Parkinson-White

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The sinus rate varied from 54 to 140 beats per minute (bpm). The mean rate was 90 bpm. The heart rate variability and diurnal variation were normal. The average heart rate was 79 bpm at night and 96 bpm during the day. A second Holter study, obtained 2 years after the ablation, showed similar results.

**Discussion**

*TBX3* is a member of the T-box family of transcription factors, which regulate the embryonic development and postnatal function of diverse tissues. In the present case, a de novo loss-of-function mutation of *TBX3* is associated with ventricular preexcitation and proximal right bundle branch block. This unusual pair of abnormalities illustrates the dichotomous functions of *TBX3* in specifying the development of the conduction system and suppressing accessory AV pathways.

In a series of genetically engineered mice that have quantitative reductions in *Tbx3* activity, mutants exhibit sinus node dysfunction, high-grade AV block, widening of the QRS interval, and ventricular preexcitation.\(^5\) The conduction defects correlate with the embryonic expression of *Tbx3* in the developing sinus and AV nodes, His bundle, and proximal bundle branches.\(^6\) *Tbx3*-deficient mutants show cellular hypoplasia of the sinus node and the abnormal expression of ventricular genes in the AV bundle and bundle branches.\(^5,7,8\) The expression pattern and mutant phenotypes indicate the role of *Tbx3* in the specification and development of the sinus node and central conduction system.

**KEY TEACHING POINTS**

- *TBX3* has dichotomous role in the establishment of atrioventricular conduction pathways in the human heart. *TBX3* both specifies the development of the normal atrioventricular conduction system and suppresses abnormal, accessory atrioventricular pathways elsewhere. Patients with *TBX3* mutations should be evaluated for conduction block and ventricular preexcitation.
- *TBX3* may maintain the postnatal health of the human conduction system. Patients with *TBX3* mutations should be followed for the possibility of developing adult-onset conduction disease (eg, sinus node dysfunction and atrioventricular block).
- The electrophysiological properties of an accessory pathway could depend upon its molecular genetic basis. Genetic studies in animal models and humans could lead to noninvasive methods of risk stratification in patients who have preexcitation.

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**Figure 1**  
A: Ventricular preexcitation and a right bundle branch block were found in a 14-year-old girl who carries a de novo loss-of-function mutation of *TBX3*. The electrocardiogram (ECG) shown was her first. B: Preexcitation is no longer present after transcatheter ablation of a left-sided accessory pathway. The right bundle branch block remains. This ECG pattern has remained the same after 3 years of follow-up.
The developmental basis of ventricular preexcitation is attributed to the expression of Tbx3 in the AV canal myocardium, where it suppresses the persistence of accessory conduction pathways. In the early embryo, the atria are in electrical continuity with the ventricles around the circumference of the AV canal. Subsequently, the myocytes in the AV canal dissociate from each other, and the insulating fibrous annulus forms, leaving the His bundle as the sole AV connection.9 Tbx3-deficient mice have histologically confirmed AV myofibers.5

The patient in this case has some, but not all, of the conduction phenotypes described in Tbx3-deficient mice. For example, conditional deletion of the Tbx3 gene in adult mice causes sinus node dysfunction and AV block.5 TBX3 may maintain the postnatal health of the human conduction system as well. The possibility of adult-onset conduction disease thus remains a concern. The patient has normal sinus and AV node function, but she is still an adolescent.

Ulnar-mammary syndrome is rare. The published reports, consisting of a few dozen cases, have generally not described any evaluation of conduction or arrhythmia phenotypes. This suggests that most patients are asymptomatic, although 1 boy had Wolff-Parkinson-White syndrome and reentrant supraventricular tachycardia as an infant.1,2 Thus, the present case may be the first, detailed electrophysiologic characterization of a person who has a TBX3 mutation. In particular, our patient was deemed to be at low risk for ventricular fibrillation and malignant arrhythmia because of the long accessory pathway effective refractory period and noninducible AV reentrant tachycardia.3 These signs are properties of the accessory pathway, which we speculate are the consequence of the abnormal regulation of genes that TBX3 positively or negatively regulates. In numerous different cell types, including stem and cancer cells, TBX3 integrates and responds to multiple cellular signaling pathways. TBX3 regulates gene expression and activity through direct effects on transcription, RNA splicing, and epigenetic modifications of chromatin state.10 Ectopic expression of Tbx3 in the myocardium of transgenic mice induces the expression of genes that confer a pacemaker-like phenotype and represses ventricular genes.1,11,12 Similarly, Tbx3 knockout or deficiency causes loss of expression of genes specific to the sinus node and central conduction system and repression of atrial or ventricular genes.5,7 Taken together, the observations suggest that the electrophysiologic properties of an accessory pathway could depend upon its molecular genetic basis. Genetic studies in animal models and humans could lead to noninvasive methods of risk stratification in patients who have preexcitation.

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