Mol Cell Biochem (2013) 382:121–126
DOI 10.1007/s11010-013-1725-4

# Novel and functional variants within the TBX18 gene promoter in ventricular septal defects

**Liming Ma · Jianjun Li · Yumei Liu · Shuchao Pang · Wenhui Huang · Bo Yan**

Received: 8 April 2013 / Accepted: 29 May 2013 / Published online: 8 June 2013


**Abstract** Congenital heart disease (CHD) is the most common birth defect in humans. Genetic causes for CHD remain largely unknown. T-box transcription factor 18 (TBX18) gene is expressed in the developing heart, including myocardium of the left ventricle and interventricular septum. Epicardial cells expressing TBX18 gene contribute to the cardiac fibroblast and smooth muscle cells. We speculated that the DNA sequence variants (DSVs) within TBX18 gene promoter may mediate CHD development by affecting TBX18 levels and the cardiac gene regulatory network. In this study, we genetically and functionally analyzed the TBX18 gene promoter in patients with ventricular septal defects (VSD) ($n = 326$) and ethnic-matched healthy controls ($n = 327$). Three novel heterozygous DSVs (g.85474435del, g.85474418C>T, and g.85473965C>G) and one single nucleotide polymorphism (g.85474871C>T, rs77693245) were identified in VSD patients, but none in the controls. Functional analysis revealed that the DSVs (g.85474871C>T, g.85474435del, and g.85473965C>G) significantly decreased the transcriptional activities of the TBX18 gene promoter. The effect of DSV (g.85474418C>T) on the TBX18 gene promoter was marginal, but not significant. Therefore, the DSVs within the TBX18 gene promoter identified in VSD patients may be involved in the VSD etiology.

**Keywords** Congenital heart disease · Ventricular septal defects · Transcription factor · TBX18 · Promoter · DNA sequence variants

## Introduction

Congenital heart disease (CHD) is the most common human birth defect that affects about 1–2 % of live births, and the true prevalence may be much higher [1]. Even with successful correction surgeries, morbidity and mortality of CHD patients are still significantly higher than the general populations. The main causes of death are later cardiac complications, including arrhythmias, coronary heart disease, and heart failure, likely due to genetic defects [2, 3]. To date, mutations in cardiac transcription factor genes, such as GATA transcription factor 4 (GATA4), T-box transcription factor 5 (TBX5), and NK2 transcription factor related, locus 5 (NKX2-5), have been implicated in a small portion of familial and isolated CHD [4]. However, genetic causes for isolated CHD remain largely unknown.

TBX transcription factors, which share a highly conserved DNA-binding domain, play critical roles in several processes during the embryonic development [5]. In mammals, six members of TBX transcription factor family (TBX1, TBX18, and TBX20 of the TBX1 subfamily, and TBX2, TBX3, and TBX5 of the TBX2 subfamily) are essential in the developing heart. From the linear heart tube to the chambered heart, TBX1, TBX5, and TBX20 act as transcriptional activators of chamber myocardial genes, whereas TBX2, TBX3, and TBX18 function as repressors

Liming Ma, Jianjun Li, and Yumei Liu contributed equally to the study.

L. Ma · Y. Liu · S. Pang · W. Huang · B. Yan (✉)
Shandong Provincial Key Laboratory of Cardiac Disease Diagnosis and Treatment, Jining Medical University Affiliated Hospital, Jining Medical University, 79 Guhuai Road, Jining 272029, Shandong, China
e-mail: yanbo@mail.jnmc.edu.cn; jnmcyan@gmail.com

J. Li
Division of General Surgery, Jining Medical University Affiliated Hospital, Jining Medical University, Jining 272029, Shandong, China