A Genetic Analysis for Patients with Pulmonary Arterial Hypertension

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Yu Yoshida, Keiko Uchida, Kazuki Kodo, Yoshiyuki Furutani, Toshio Nakanishi, and Hiroyuki Yamagishi

Keywords

T-box · *TBX4* · Pulmonary hypertension · Genetic analysis

Pulmonary arterial hypertension (PAH) is a lethal disease [1]. Although mutations in *BMPR2* and other genes have been reported, the genetic causes in large numbers of patients, especially with sporadic PAH, remain unknown. In 2013, Kerstjens-Frederikse et al. first reported *TBX4* mutations in patients with PAH [2]. *TBX4* is an essential transcription factor for the development of the hindlimbs and lungs [3]. In European countries, the frequency of *TBX4* mutation was reported as 2.4–4.1% in adult-onset PAH [2, 4] and as 7.5–30% in child-onset PAH [2, 5] (Fig. 27.1). However, its frequency in Asian patients with PAH has yet to be studied.

In our genetic analysis for patients with PAH, at least nine sequence variants in exons and six sequence variants in flanking introns of *TBX4* were found. The allele frequencies of variants in the Japanese population are under investigation. The detected variants will be validated using the following web databases: UCSC genome browser (<https://genome-asia.ucsc.edu>), Ensembl (<http://www.ensembl.org>), PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2>), SIFT (<http://sift.jcvi.org>), Human Splicing Finder (<http://umd.be/HSF3>), and Protein Data Bank Japan (<https://>

Y. Yoshida · K. Uchida · K. Kodo

Department of Pediatrics, Keio University School of Medicine, Shinjuku, Tokyo, Japan

Y. Furutani · T. Nakanishi

Department of Pediatric Cardiology, Tokyo Women's Medical University, Tokyo, Japan

e-mail: nakanishi.toshio@twmu.ac.jp

H. Yamagishi (✉)

Division of Pediatric Cardiology, Department of Pediatrics,
Keio University School of Medicine, Tokyo, Japan

e-mail: hyamag@keio.jp

Fig. 27.1 Summary of the position of the previously reported variants in *TBX4*. Upper labels indicate variants with child-onset PAH; lower labels indicate variants with adult-onset PAH. *NLS* nuclear localization signal

pdj.org) for their functional significance. We are further attempting to establish the experimental system of functional analysis for the identified variants of *TBX4* using cell culture with luciferase, immunoprecipitation, and immunohistochemistry assays in order to elucidate the molecular mechanism underlying PAH resulting from *TBX4* mutations.

This study suggests that *TBX4* may be a prevalent genetic cause of PAH not only in Caucasians but also within Japanese/Asian populations. Our ongoing studies would soon reveal the functional relevance and genotype–phenotype correlations in patients with PAH associated with *TBX4* mutations.

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