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A novel mutation of *GATA4* (K319E) is responsible for familial atrial septal defect and pulmonary valve stenosis

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ABSTRACT

Congenital heart disease (CHD) is the most common birth defect in humans, and the etiology of most CHD remains to be elusive. Atrial septal defect (ASD) makes up 30–40% of all adult CHDs and is thought to be genetically heterogeneous. Previous studies have demonstrated that mutations in transcription factors e.g. *NKX2.5*, *GATA4*, and *TBX5* contribute to congenital ASD. In this study, we investigate a family of three generations with seven patients with ASD and pulmonary valve stenosis (PS). A novel *GATA4* mutation, c.955A>G (p.K319E), was identified and co-segregated with the affected patients in this family. This mutation was predicted to be deleterious by three different bioinformatics programs (The polyphen2, SIFT and MutationTaster). Our finding expands the spectrum of *GATA4* mutations and provides additional support that GATA4 plays important roles in cardiac development.

1. Introduction

Congenital heart disease (CHD) is the most common birth defect and the leading non-infectious cause of mortality in newborns, affecting appropriately seven per 1000 of live births (Hoffman and Kaplan, 2002). It is estimated that about 130,000 new CHD cases increased in China annually (Zhao et al., 2013). Atrial septal defect (ASD) is defined by an anatomically deficient inter-atrial septum allowing oxygen-rich blood to flow directly from the left to the right atria. ASD makes up 30–40% of all adult CHD (Hoffman and Kaplan, 2002; Kaplan, 1993). Pulmonary valve stenosis has been reported in combination with ASD or as part of complex syndromes (e.g. Noonan syndrome) (Koretzky et al., 1969; Tartaglia et al., 2011).

To date, more than ten genes of three groups underlying ASD have been identified. (i) Transcription factors and cofactors, e.g. *GATA4*, *NKX2.5*, *GATA6*, *TBX5*, *ZIC3* and *CITED2*. (ii) Ligands–receptors, e.g. *ALK2*, *CRELD1* and *GJA1*. (iii) Structure protein of sarcomere, e.g. *MYH6*, *MYH7* and *ACTC* (Fahed et al., 2013; Wessels and Willems, 2010). However, due to significant genetic heterogeneity and scarcity of families with defined monogenic inheritance of isolated ASD, the etiology of most isolated ASD still remains to be elucidated. Over 20 mutations have been identified in previous mutation screenings of *GATA4* with familial or sporadic CHD, while the causal interrelationships remain mostly speculative and long-term follow-up observations are needed to clarify the possible responsibility (Butler et al., 2010; Posch et al., 2010; Wang et al., 2013; Xiong et al., 2013; Zhang et al., 2008).

In this study, we investigated the possible causative gene in a family with ASD and pulmonary valve stenosis (PS). We identified a de novo mutation (c.955A>G/p.K319E) in exon5 of *GATA4* in all affected members of this family. To the best of our knowledge, this mutation has not been reported in previous study or presented in our control cohorts and dbSNP as well as Exome Variant Server database (http://evs.gs.washington.edu/EVS/).

2. Material and methods

The Review Board of the Second Xiangya Hospital of the Central South University has approved this research. All subjects have consented to this study.

2.1. Patients

A family from Central-South China (Jiangxi Province) with 10 members across three generation participated in the present study. Seven patients were diagnosed of having ASD and PS (II2, II3, III1, III3, III4, III5 and IV1) (Fig. 1A, Table 1). The proband (III3) of the family was diagnosed by transthoracic echocardiograms of having ASD and PS with congestive heart failure. Patients' information is listed in

Abbreviations: CHD, congenital heart defects; PS, pulmonary valve stenosis; polyphen2, polymorphism phenotyping; SIFT, Sorting Intolerant From Tolerant; dbSNP, Single Nucleotide Polymorphism Database; ASD, atrial septal defect; VSD, ventricular septal defect; TOF, tetralogy of Fallot; HRV, hypoplastic right ventricle; TAPVR, total anomalous pulmonary venous retour; NLS, nuclear localization signals; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction.

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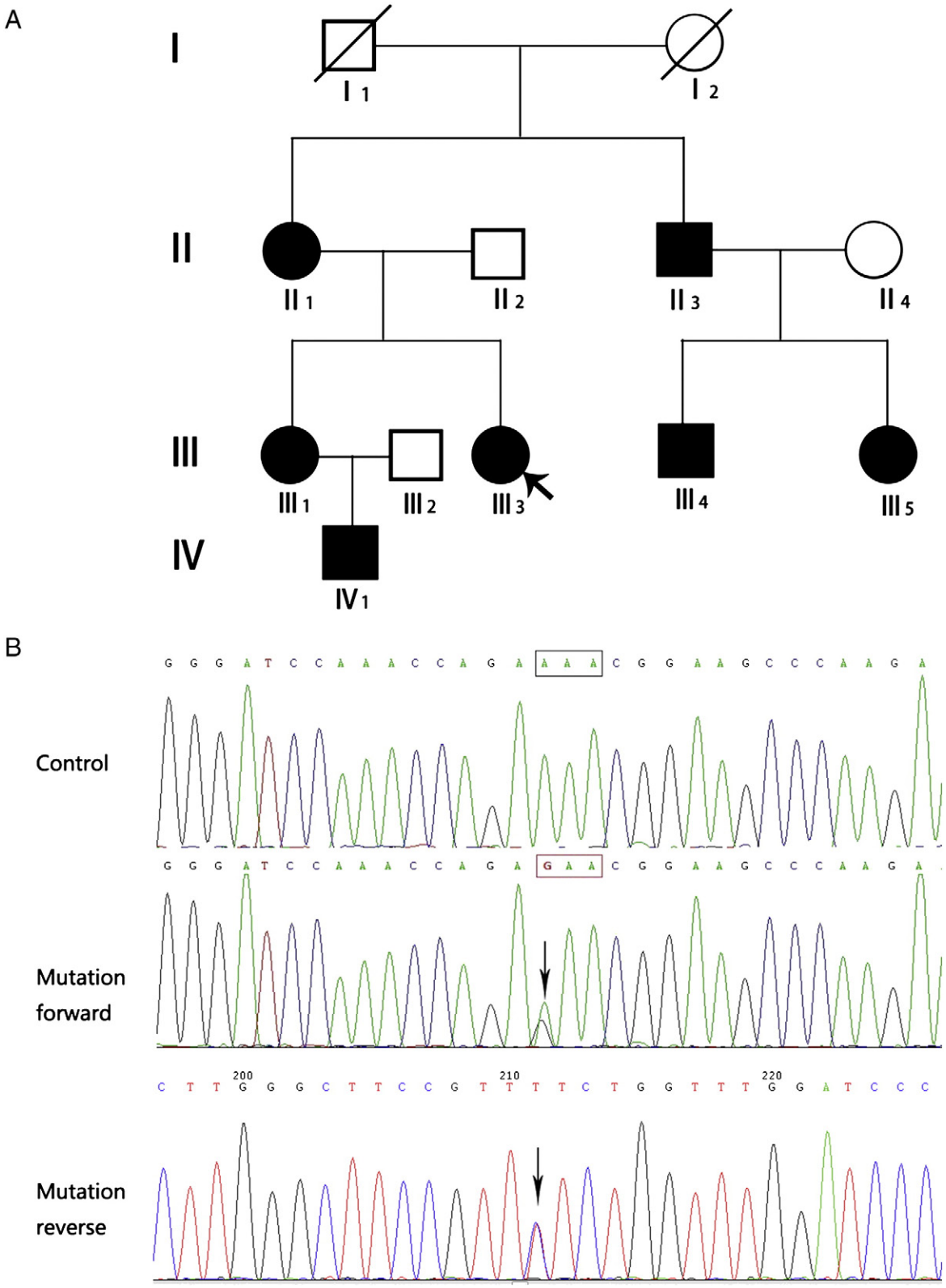

Fig. 1. (A). Pedigree of the family affected with ASD and PS. Family members are identified by generations and numbers. Squares indicate male family members; circles, female members; closed symbols, the affected members; open symbols, unaffected members; arrow, proband. (B). Sequencing results of the GATA4 mutation. Sequence chromatogram indicates an A to G transition of nucleotide 995.

Table 1. Family member IV1 was found to have ASD and PS just after birth and was surgically repaired at the age of four in the Department of Cardiothoracic Surgery of the Second Xiangya Hospital. No other malformations were observed in the seven affected members and indicated this family to be an isolated or non-syndromic CHD family with autosomal dominant pattern.