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A *novel* mutation of *GATA4* in a familial atrial septal defect

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ABSTRACT

Background: Previous studies have identified that mutations in a few genes, including *T-BOX5*, *NKX2-5*, *EVC* and *GATA4*, are associated with atrial septal defect (ASD).
Methods: A family of three generations with 4 members who were affected with ASD was investigated. To exclude the presence of any sub-microscopic chromosomal imbalance, high-resolution 1M array-based comparative genomic hybridization (aCGH) was performed. SNaPShot was used to certify the specificity of the finding mutation in the other family members. The coding region of *GATA4* and *NKX2-5* genes was screened by sequencing in another 30 cases including 10 cases of ventricular septal defect (VSD), 10 cases of atrial septal defect (ASD), 8 cases of VSD combined with ASD and 2 cases of atrioventricular septal defects (AVSD).
Results: No pathogenic copy number variant was detected by aCGH in the four affected family members with ASD. A *novel* non-synonymous variant, c.839C>T (T280M) in *GATA4*, was identified and segregated with all the ASD patients within this Chinese family. Such mutation was absent in other family members or present among sporadic CHD patients. In addition, we identified a non-synonymous variant in the *NKX2-5 gene* (P257A) associated with one congenital heart disease patient with VSD. Both mutations were not identified among healthy controls.
Conclusion: T280M mutation of *GATA4* is suggested to be associated with ASD in this Chinese family.

1. Introduction

Atrial septal defect (ASD) is one of the most common congenital heart diseases in adults, which is characterized by left-to-right shunting and an increased right ventricular output. Many children have no symptoms and seem healthy. However, if the ASD is large, permitting a large amount of blood to pass through to the right side of the heart, the right atrium, right ventricle, and lungs will become overworked, and symptoms may be noted. In this case, ASD repair may be indicated. As a group, atrial septal defects are detected in 1 child per 1500 live births. ASDs make up 30 to 40% of all congenital heart disease that is seen in adults [1].

Most ASD occur sporadically, with no clear reason for their abnormal heart development. Some congenital heart defects may have a genetic link, either occurring due to a defect in a gene, a chromosomal abnormality, or environmental exposure, causing heart problems to occur more often in certain families. Chromosomal, syndromal and teratogenic causes account for a minority of cases. It has been recognized that ASD can be caused by a few genes, including mutations in T-BOX5 (*TBX5*), NK2 Homeobox 5 (*NKX2-5*), Ellis-van Creveld syndrome gene (*EVC*) and GATA-binding protein 4 (*GATA4*). Mutation in *TBX5* may appear as Holt–Oram syndrome with ASD or ventricular septal defect (VSD). Mutation in *NKX2-5* may be related to nonsyndromic congenital heart defects including ASD and atrioventricular conduction abnormalities. Mutation in *EVC* is closely related to Ellis-van Creveld syndrome with ASD. *GATA4* is associated with familial atrial septal defect. Pehlivan et al. first proposed that the haploinsufficiency of *GATA4* may be involved in the etiology of the congenital heart disease observed in some patients with del(8)(p23.1) [2].

Here we report the results of a systemic investigation of the possible chromosomal and genetic causes in a family with ASD. We also further study the existence of *GATA4* and *NKX2-5* gene sequence variants in 30 patients with congenital heart defects (CHD).

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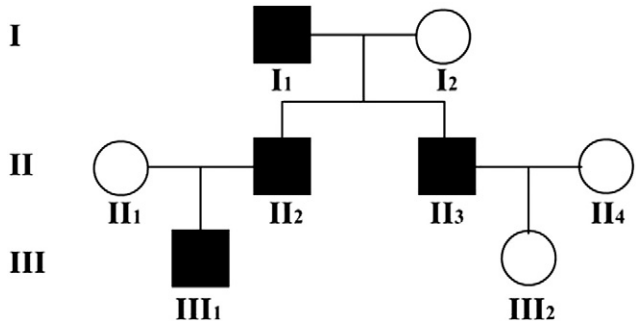

Fig. 1. Pedigram of the family affected with ASD.

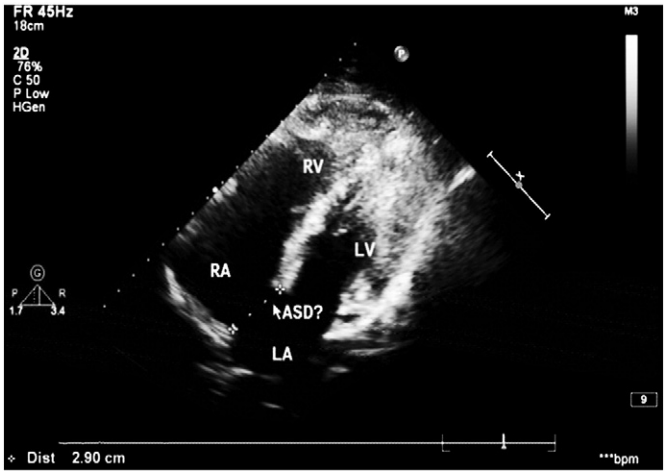

Fig. 2. Echocardiogram of the son of the proband. The white arrow points to the site of ASD.

2. Materials and methods

2.1. Patients

A Chinese family with 8 members across three generations participated in the present study. Four patients were diagnosed to have ASD and pulmonary stenosis (PS) (I_1, II_2, II_3, and III_1; Fig. 1). The proband of the family is a 60 year old man and was diagnosed by echocardiograms to have ASD and PS with congestive heart failure 10 years ago when he was 50 years old because of postexercise stifle. Two sons (II_2 and II_3) of the proband were clinically diagnosed during their 30th which showed congestive heart failure almost 20 years earlier than their father (echocardiograms see Fig. 2). III_1 was found to have ASD just after birth and was surgically repaired 6 months later after birth. There is a trend of increasing severity of phenotype with generations. None of the 4 affected members had any other abnormalities in the cardiac conduction system or other organs.

For understanding the specific role of *GATA4* and *NKX2-5* genes in human congenital heart disease, we searched for mutations in the coding regions of *GATA4* and *NKX2-5* in this family and the other 30 nonsyndromic CHD patients, including 10 cases of ventricular septal defect (VSD), 10 cases of ASD, 8 cases of VSD combined with ASD, and 2 cases of atrioventricular septal defects (AVSD). Informed consent was obtained from all the patients. The study protocol has been approved by the Ethics Committee for Human Research, Nanjing Medical University Affiliated Suzhou Hospital.

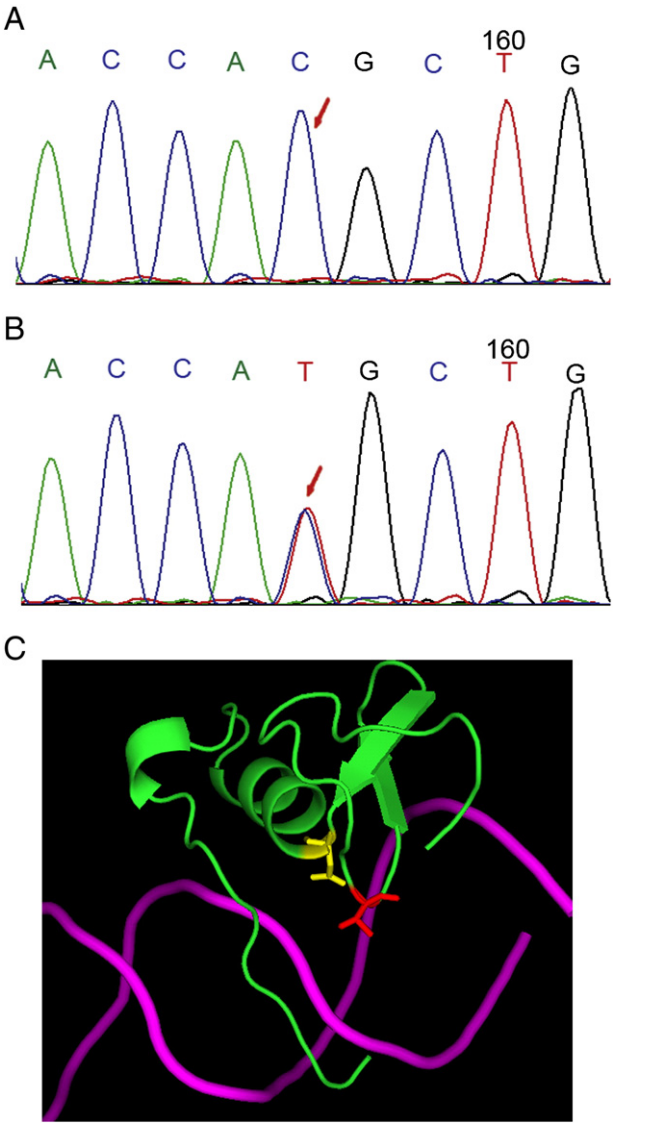

Fig. 3. Sequencing result of the *GATA4* mutation. The heterozygous c.839C>T mutation from a familiar ASD (B) and normal control (A). 3D model of the human *GATA4* fragment. Thr280 makes a direct hydrogen bond with Asn293 and interacts with the sugar phosphate backbone of the DNA (green for protein, magenta for DNA, red for Thr290, and yellow for Asn293) (C).

Table 1
Summary of genetics analysis performed on the Chinese ASD family.

ASD family members	Symptom	Age at diagnosis	CNV by aCGH	*GATA4*	*NKX2.5*
Father (I_1)	ASD, PS	50 years old	No pathogenic or unknown CNV identified	T280M	No mutation
Mother (I_2)	No	–	No pathogenic or unknown CNV identified	T280	No mutation
Son1's wife (II_1)	No	–	No pathogenic or unknown CNV identified	T280	No mutation
Son1 (II_2)	ASD, PS	30 years old	No pathogenic or unknown CNV identified	T280M	No mutation
Son2 (II_3)	ASD, PS	30 years old	No pathogenic or unknown CNV identified	T280M	No mutation
Son2's wife (II_4)	No	–	No pathogenic or unknown CNV identified	T280	No mutation
Grandson (III_1)	ASD, PS	Just after birth	No pathogenic or unknown CNV identified	T280M	No mutation
Granddaughter (III_2)	No	–	No pathogenic or unknown CNV identified	T280	No mutation

ASD = atrial septal defect; PS = pulmonary stenosis.