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Original Article

SOX7 loss-of-function variation as a cause of familial congenital heart disease

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Abstract: Introduction: As the most frequent type of birth defect in humans, congenital heart disease (CHD) leads to a large amount of morbidity and mortality as well as a tremendous socioeconomic burden. Accumulating studies have convincingly substantiated the pivotal roles of genetic defects in the occurrence of familial CHD, and deleterious variations in a great number of genes have been reported to cause various types of CHD. However, owing to pronounced genetic heterogeneity, the hereditary components underpinning CHD remain obscure in most cases. This investigation aimed to identify novel genetic determinants underlying CHD. Methods and results: A four-generation pedigree with high incidence of autosomal-dominant CHD was enrolled from the Chinese Han race population. Using whole-exome sequencing and Sanger sequencing assays of the family members available, a novel *SOX7* variation in heterozygous status, NM_031439.4: c.310C>T; p.(Gln104*), was discovered to be in co-segregation with the CHD phenotype in the whole family. The truncating variant was absent in 500 unrelated healthy subjects utilized as control individuals. Functional measurements by dual-luciferase reporter analysis revealed that Gln104*-mutant SOX7 failed to transactivate its two important target genes, *GATA4* and *BMP2*, which are both responsible for CHD. In addition, the nonsense variation invalidated the cooperative transactivation between SOX7 and NKX2.5, which is another recognized CHD-causative gene. Conclusion: The present study demonstrates for the first time that genetically defective *SOX7* predisposes to CHD, which sheds light on the novel molecular mechanism underpinning CHD, and implies significance for precise prevention and personalized treatment in a subset of CHD patients.

Keywords: Congenital heart disease, medical genetics, transcriptional regulation, SOX7, dual-luciferase analysis

Introduction

Congenital heart disease (CHD) represents the most frequent classification of human developmental deformity with an estimated prevalence of 1% in live newborns, accounting for about 30% of all major birth malformations worldwide [1, 2]. In the United States, CHD afflicts nearly 40,000 newborns per year [1, 2]. Notably, when minor cardiovascular anomalies, such as right-sided aortic arch, aneurysm of the atrial septum and bicuspid aortic valve, the most prevalent type of CHD with an incidence of 1 to 2 per 100 of the population, are encompassed, the prevalence of CHD may be as high as ~5% [3]. In terms of specific anatomic and hemodynamic lesions, CHD is classified into over 21 distinct subtypes, such as ventricular septal defect (VSD), pulmonary stenosis (PS), atrial septal defect, patent ductus arteriosus (PDA), persistent truncus arteriosus, tetralogy of Fallot, single ventricle, endocardial cushion defect, double-outlet right ventricle, pulmonary atresia, anomalous pulmonary venous connection, valvular aortic stenosis, and hypoplastic left heart [1, 2]. Although some mild cardiac anomalies can resolve spontaneously with little apparent clinical significance [4], severe CHD may give

rise to reduced health-related quality of life [5, 6], poor exercise performance [7-9], impaired neurodevelopment and structural brain abnormality [10-13], ischemic or hemorrhagic stroke [14, 15], pulmonary arterial hypertension or Eisenmenger syndrome [16-18], abnormal kidney development or kidney injury [19, 20], metabolic syndrome [21-24], infective endocarditis or central nervous system infection [25, 26], congestive heart failure [27-29], cardiac arrhythmias [30-34], and even demise [35-37]. CHD remains the most common etiology of neonatal death caused by birth deformations, with ~24% of neonates who died of congenital anomalies suffering heart defects [4], and in the American children with congenital defects, CHD leads to approximately 40% of child death [38]. Although tremendous advances have been achieved recently in surgical procedures and perioperative intensive care of CHD, which allow up to 95% of infants affected with CHD to survive into adulthood reaching fertile age, the comorbidity, morbidity and mortality increased significantly in the increasing population of adult patients suffering from CHD [2]. Consequently, CHD inflicts a vast socioeconomic burden on humans [1]. In spite of the prevalence and clinical significance, the molecular pathogenesis underpinning CHD is still incompletely understood.

In vertebrates, during the embryogenesis the heart is the first functional organ formed, and cardiac development is an extremely complex biological process, which requires the accurate spatiotemporal cooperation of various cardiogenesis-related factors, involving the intricate cross talk amongst transcription factors, signaling molecules, epigenetic modifiers, and structural proteins [2]. Previous studies have substantiated that both environmental risk factors and inheritable pathogenic components may disturb this developmental process, leading to CHD [2, 3, 39-42]. The well-known nongenetic maternal risk factors predispose to offspring's CHD include viral infections, nutritional deficiency, autoimmune disorder, diabetes mellitus, hyperhomocysteinemia, and administration of drugs as well as long-term exposures to toxicants and ionizing radiation during early gestation [39, 40]. In addition, the nongenetic paternal risk factors, encompassing advanced age, wine drinking, cigarette smoking, and exposure to chemicals, also confer an increased risk of CHD [41]. However, accumulating research highlights a strong genetic basis of CHD, especially in familial CHD, where CHD is frequently inherited in an autosomal-dominant mode, though autosomal-recessive and X-linked inheritance patterns are also covered [2, 3, 42, 43]. The earliest uncovered heritable causes of CHD are aneuploidies, the chromosomal anomalies that are preferentially associated with syndromic types of CHD, including trisomy 13 (Patau syndrome), trisomy 18 (Edwards syndrome) and monosomy X (Turner syndrome) [2, 43]. Other chromosomal abnormalities underpinning CHD include chromosomal microdeletions and microduplications, such as 1p36 deletion syndrome, 22q11.2 deletion syndrome and 22q11.2 duplication syndrome [2]. To date, in addition to chromosomal copy number variations, an increasing number of deleterious variations in over 80 genes have been discovered to cause CHD in humans, among which the majority encode cardiac transcription factors, myocardial structural proteins, chromatin modifiers, cellular signal molecules and extracellular matrix proteins [2, 3, 42-70]. However, CHD is genetically heterogeneous, with less than 30% of CHD patients having established genetic defects [42], hence the hereditary culprit components underlying CHD remain to be elusive in a large proportion of cases.

Materials and methods

Recruitment and clinical investigation of study participants

A four-generation pedigree with high incidence of CHD (Family 1) was identified from the Chinese Han-ethnicity population, where CHD was inherited as an autosomal-dominant trait. All the family members available were enlisted for the present investigation. A total of 500 unrelated healthy volunteers without family history of CHD were recruited as control people. The control subjects and CHD patients were ethnically matched. All study participants underwent a comprehensive clinical assessment by cardiologists, encompassing a thorough review of individual medical records and familial disease histories, careful physical examination, echocardiography with color Doppler and 12-lead electrocardiographic measurements. In the family members suffering from CHD, cardiac catheterization procedures and/or open-

heart surgeries were carried out when strongly indicated. Diagnosis of CHD was made as previously described [69]. Familial CHD was defined as the CHD occurring in a minimum of 2 family members from the same family. The current study was performed in conformity with the ethical tenets outlined in the Declaration of Helsinki. The protocols used in the present study were approved by the local institutional medical ethics committee (ethical approval number: LL(H)-09-07). Written specific informed consent was obtained after the interview procedures from the study subjects or the legally authorized guardians of subjects less than 18 years of age. Based on the appropriate informed assent and approval of the Medical Ethics Committee of local institution, clinical data and blood samples were collected from all study individuals.

Molecular genetic studies

Genomic deoxyribonucleic acid (DNA) was purified from the blood leukocytes of study participants by utilizing a genomic DNA extraction kit (Promega, USA). The quality as well as quantity of the DNA specimens was determined with a spectrophotometer (Thermo Fisher Scientific, USA). Whole exome sequencing (WES) were conducted on DNA samples of family members as previously described [71-75]. Briefly, for each family member subject to WES, 3 μg of genomic DNA sample was fragmented randomly into segments of 150-300 bp by sonication utilizing a sonicator (Covaris, USA) to generate an exome library. Exome libraries were enriched by ligation-mediated polymerase chain reaction (PCR) and captured employing the Human All Exon V6 Kit (Agilent Technologies, USA). Appropriate amounts of the captured exome libraries were sequenced on HiSeq 2000 Genome Analyzer (Illumina, USA) following the standard Illumina protocols. Bioinformatic analysis was made as described elsewhere [71-75]. In short, raw sequencing reads for each family member were aligned with human genome (Build GRCh37, also known as hg19) with the program BWA [76]. The GATK program was implemented to call sequence variants [77]. The ANNOVAR software was employed to make functional annotation of a genetic variant [78]. All common variants with minor allele frequencies greater than 0.1% in the population were filtered out. Variants occurring outside of coding exons and splicing donors/acceptors as well as exonic variants encoding synonymous single nucleotide polymorphisms were also excluded. Variations were further filtered according to the mode of inheritance revealed by examination of the pedigree (Family 1 was considered for autosomal dominant pattern of inheritance).

The variants that passed through the filters was further verified by Sanger sequencing and segregation assays in all available family members of Family 1. For a deleterious variation verified in a family affected with CHD, the gene carrying the variation were sequenced in 500 unrelated healthy persons, and the population genetics databases of the Human Gene Mutation Database (HGMD; http://www.hgmd.cf.ac.uk/ac/index.php), Single Nucleotide Polymorphism database (dbSNP; https://www.ncbi.nlm.nih.gov/snp/) and Genome Aggregation Database (gnomAD; http://exac.broadinstitute.org/) were retrieved to check its novelty.

Construction of expression plasmids

Total RNA was purified from human myocardial samples (collected from the discarded heart muscle tissues of the patients undergoing cardiac surgery) with TRIzol reagent (Invitrogen, USA), and cDNA was produced by reverse transcription-PCR with the OneStep RT-PCR Kit (Qiagen, Germany). The entire coding region (open read frame) of human *SOX7* gene (GenBank accession no. NM_031439.4) was PCR-amplified from cDNA utilizing DNA polymerase (Stratagene, USA) and specific primers (forward: 5'-GAAGCTAGCGACCCGTGCGAGGGCCAGGT-3'; backward: 5'-TTCTCTAGAGGCGCGAGGGCTGACCGGAC-3'). The produced 1285-bp amplicons containing entire *SOX7* cDNA was doubly cut with restriction endonucleases *Nhe*I (NEB, USA) and *Xba*I (NEB), and inserted into the plasmid pcDNA3.1 (Invitrogen) to generate the expression plasmid SOX7-pcDNA3.1. The Gln104*-mutant SOX7-pcDNA3.1 plasmid was created by site-directed mutagenesis of wild-type SOX7-pcDNA3.1 with the GeneArt® Site-Directed Mutagenesis System (Life Technologies, USA) with a complementary pair of primers (forward primer: 5'-GAGCGGCTGCGCCTGTAGCACATGCAGGACT-3'; backward primer: 5'-AGTCCTGCATGTGCTACAGGCGCAGCCGCTC-3') as per manufacturer's protocols, and was vali-

dated by Sanger sequencing. The NKX2.5-pEFSA plasmid expressing human NKX2.5 protein was generously given by Prof. Ichiro Shiojima at Chiba University, Japan [69]. The *BMP2* promoter-driven firefly luciferase reporter plasmid (BMP2-luc) was produced as described elsewhere [79]. Another firefly luciferase reporter (GATA4-luc), where expression of firefly luciferase reporter was driven by the promoter of human *GATA4* gene, was described elsewhere [69].

Cellular transfection and dual-luciferase assay

HeLa and COS-7 cells were seeded into wells of a 24-well plate (BD Biosciences, USA), and grown in Dulbecco's modified Eagle's medium (Sigma-Aldrich, USA) containing 10% fetal bovine serum (Thermo Fisher Scientific, USA) as well as 1% penicillin-streptomycin (Thermo Fisher Scientific). Cells were cultured at 37°C in an incubator with an atmosphere of 5% CO_2 and 95% air. At ~80% confluence, cells were transiently transfected with various plasmids as previously described in detail [69]. Cells were collected 24 h after transfection and subsequently lysed with 1 × lysis buffer. The luciferase activity of cellular lysates was determined with a dual-luciferase reporter assay system (Promega) on a microplate luminometer (Promega), following the manufacturers' protocols. The ratio (fold activation) of firefly to renilla luciferase activity represented the activity of a given promoter [69].

Statistics

Promoter activity values were given as mean ± standard deviation. Student's t test was applied when comparison was performed between two groups, and one-way analysis of variance accompanied by *post hoc* Fisher's test was applied for comparison among multiple groups. A two-sided *P* value < 0.05 was considered to indicate a significant difference. All statistical calculations were completed with GraphPad Prism version 8.0 (GraphPad, USA).

Results

Clinical characteristic profiles of the study family

In this study, a four-generation pedigree afflicted with CHD (**Figure 1A**) was enrolled from the Chinese Han-race population, including 34 living family members (16 female members and 18 male members) with ages ranging from 2 years to 57 years. In the whole family, all affected members had echocardiogram-documented PDA, while the unaffected members had normal echocardiographic images. Genetic analysis of the pedigree unveiled that PDA was inherited as an autosomal-dominant trait. The index patient (IV-1), a 10-year-old boy with a family history of CHD, was diagnosed with PDA and VSD, and underwent surgical closure of the defects when he was six years old. Notably in the proband's family, in addition to PDA, six affected family members (I-1, II-1, II-4, III-2, III-5 and IV-1) also suffered from VSD, and four affected members (I-1, II-4, II-7 and III-5) also suffered from PS. Besides, two affected family members (I-1 and II-4) died because of CHD-related severe heart failure in their fifties (aging 55 years and 53 years, respectively). The clinical characteristic information of the affected members is provided in **Table 1**.

Discovery of a new CHD-causative SOX7 mutation

WES was conducted on the DNA samples of six members affected with CHD (II-1, II-7, III-2, III-9, IV-1 and IV-6) and four healthy members without CHD (II-2, II-8, III-1 and III-10) from Family 1 (**Figure 1A**), yielding an average of 23-gigabase DNA sequence data per DNA sample, with an average of 98% of the DNA sequences mapped on the reference human genome (hg19). The mean read depth was ~310×, with a minimum of 78% of target regions covered to a depth greater than 20×. An average of 17,692 (ranging from 16,904 to 18,536) variations occurring in exons and splicing donors/acceptors per family member passed inheritance model filtering and had minor allele frequencies < 0.1%, among which 8 heterozygous missense and nonsense variations passed ANNOVAR filtering, and were present in the six affected family members (**Table 2**). Among the final 8 candidate CHD-causing variants (**Table 2**), merely the pathogenic variant chr8:10584105C>T (GRCh37: GenBank accession no. NC_000008.10), equal to chr8:10727684C>T (GRCh38: GenBank accession no. NC_000008.11) or NM_031439.4: c.310C>T; p.(Gln104*) in the *SOX7* gene, was verified by Sanger sequencing

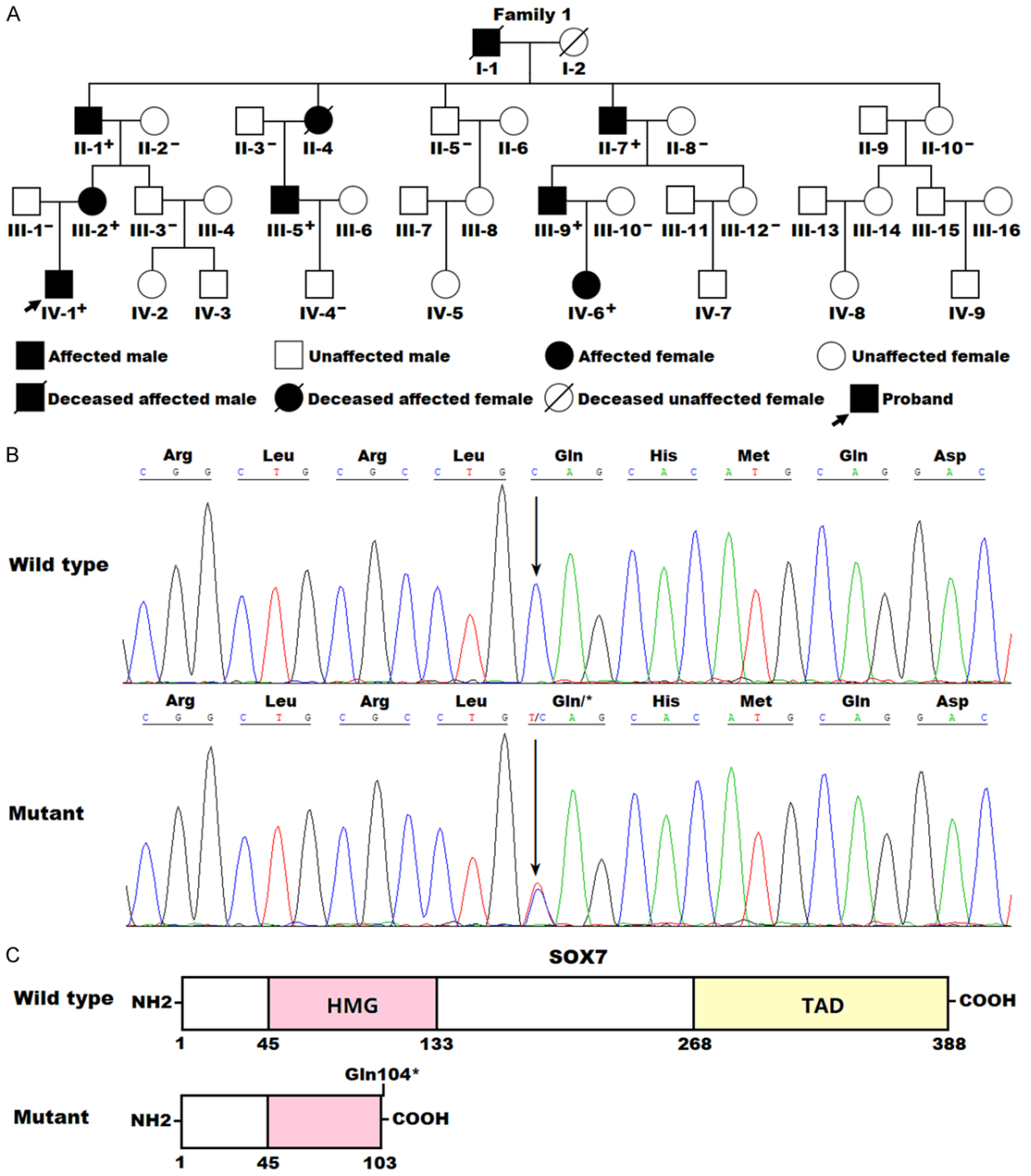

Figure 1. A SOX7 variation leading to familial congenital heart disease. A. Pedigree displaying autosomal dominant inheritance of patent ductus arteriosus in Family 1. Genotype of each family member is marked with + or -, of which + indicates a member carrying the heterozygous *SOX7* mutation, while-indicates a member without the given *SOX7* mutation. B. Sequence chromatograms of the family members. The heterozygous nucleotide change of c.310C>T in the *SOX7* gene was proved by Sanger sequencing in the members affected with CHD including the proband (IV-1, mutant), predicted to yield a truncated SOX7 protein (Gln104*) as compared to the unaffected members including the proband's father (III-1, wild type). Each codon of *SOX7* is underlined with its encoded amino acid shown above. A black arrow points to the position of the altered nucleotide or the corresponding wild-type nucleotide in the *SOX7* gene. C. Schematic representations illustrating the structural domains of human SOX7 proteins with deletion of 285 amino acids at the carboxyl-terminus of mutant SOX7 protein. TAD: transcriptional activation domain; HMG: high mobility group.

using the designed primer pairs (**Table 3**), and shown to be in co-segregation with CHD in the family as a whole. The electropherograms exhibiting the heterozygous *SOX7* variation as

Table 1. Clinical characteristic profiles of the affected pedigree members with congenital heart disease as well as the identified SOX7 variation

Individual (Family 1)	Gender	Age (years)	Cardiac structural defects	SOX7 variation (Gln104*)
I-1	Male	55*	PDA, VSD, PS	NA
II-1	Male	57	PDA, VSD	+/-
II-4	Female	53*	PDA, VSD, PS	NA
II-7	Male	50	PDA, PS	+/-
III-2	Female	33	PDA, VSD	+/-
III-5	Male	31	PDA, VSD, PS	+/-
III-9	Male	26	PDA	+/-
IV-1	Male	10	PDA, VSD	+/-
IV-6	Female	2	PDA	+/-

PDA: patent ductus arteriosus; VSD: ventricular septal defect; PS: pulmonary stenosis; NA: not applicable or available; +/-: carrier for the heterozygous SOX7 variation. *Age at death.

well as its homozygous wild-type base are illustrated in **Figure 1B**. The schematic drawings displaying pivotal structural domains of both wild-type and Gln104*-mutant SOX7 proteins are presented in **Figure 1C**. The nonsense variation was neither observed in 1000 control chromosomes nor found in the HGMD, gnomAD or dbSNP database, indicating a new CHD-causative variation.

No transactivation of the BMP2 promoter by Gln104-mutant SOX7*

As illustrated in **Figure 2**, wild-type SOX7 (SOX7) properly transactivated the *BMP2* promoter, with ~8-fold increase in luciferase activity relative to empty backbone pcDNA3.1 (pcDNA3.1) plasmid as a blank control; while Gln104*-mutant SOX7 (Gln104*) failed to transcriptionally activate the *BMP2* promoter, with a similar reporter activity with blank control (SOX7 *vs* Gln104*: t = 9.72325, P = 0.00062). In the heterozygous status with an equimolar amount of SOX7 and Gln104* co-expressed, the induced transcriptional activation of the *BMPP2* promoter was ~4-fold, a decrease by ~50% in reporter activity compared with that in homozygous status (SOX7 + pcDNA3.1 *vs* SOX7 + Gln104*: t = 4.68938, P = 0.00938).

Synergistic transcriptional activation between NKX2.5 and SOX7 abrogated by the mutation

As illustrated in **Figure 3**, SOX7 and Gln104* transactivated the *GATA4* promoter by ~4-fold and ~1-fold, respectively (SOX7 *vs* Gln104*: t = 6.21049, P = 0.00342); while in combination with NKX2.5, SOX7 and Gln104* transactivated the *GATA4* promoter by ~18-fold and ~2-fold, respectively (SOX7 + NKX2.5 *vs* Gln104* + NKX2.5: t = 9.31103, P = 0.00074).

Discussion

The current study used whole exome sequencing (WES) and informatics analyses of a Chinese family afflicted with autosomal dominant CHD. A new variation in heterozygous status, NM_031439.4: c.310C>T; p.(Gln104*), was uncovered in the *SOX7* gene, a key regulator for proper cardiovascular development [79]. The nonsense mutation was substantiated by Sanger sequencing analysis and shown to be in to co-segregation with the CHD phenotype in the whole family. The mutation was neither present in 1000 reference human chromosomes nor retrieved in such population genetics databases as HGMD, gnomAD and dbSNP. Functional studies revealed that the Gln104*-mutant SOX7 protein did not transactivate its two key downstream genes of *GATA4* and *BMPP2*, which have been both substantiated to play an important role in cardiovascular morphogenesis, and loss-of-function mutations in both *GATA4* and *BMPP2* have been found to result in CHD [80, 81].

Additionally, the mutation nullified the synergistic transcriptional activation between SOX7 and NKX2.5, another key gene for proper cardiovascular development where loss-of-function mutations have been causally linked to CHD [82]. Therefore, it is very likely that monoallelic *SOX7* mutation predicted to result in haploinsufficiency leads to CHD in this Chinese family.

SOX7 maps to human chromosome 8p23.1, which codes for a member of the high-mobility-group transcription factor family, comprizing 388 amino acids. In mammals including mice and humans, SOX7 is amply expressed in the developing heart [79]. Previous investigations have demonstrated that SOX7 functions as a transcriptional mediator of several key target

Table 2. Nonsynonymous variants in candidate genes for familial congenital heart disease discovered by whole-exome sequencing and bioinformatic analyses

Chr	Position (GRCh37)	Ref	Alt	Gene	Variant
1	11,883,887	G	C	CLCN6	NM_001286.5: c.577G>C; p.(Gly193Arg)
2	77,746,721	G	A	LRRTM4	NM_001134745.3: c.277G>A; p.(Asp93Asn)
3	114,057,953	T	C	ZBTB20	NM_001164342.2: c.1906T>C; p.(Cys636Arg)
5	15,928,503	G	T	FBXL7	NM_012304.5: c.632G>T; p.(Cys211Phe)
8	10,727,684	C	T	SOX7	NM_031439.4: c.310C>T; p.(Gln104*)
12	65,460,453	C	T	WIF1	NM_007191.5: c.698C>T; p.(Pro233Leu)
17	4,015,923	A	T	ZZEF1	NM_015113.4: c.1046A>T; p.(Asn349Ile)
19	52,376,374	G	T	ZNF577	NM_032679.3: c.869G>T; p.(Arg290Ile)

Chr: chromosome; Ref: reference; Alt: alteration.

Table 3. Primers used for amplification of the coding regions and splicing donors/acceptors of the SOX7 gene

Coding exon	Upstream (forward) primer (5'→3')	Downstream (backward) primer (5'→3')	Amplicon (bp)
1	GATAAATCAGGGGCCGGGTC	GTTTCACTTTGGACCGCGCC	567
2-a	GGGAAGAGGGTGCAAGAGAT	CTACAGTGGAGAGGGCTTGG	675
2-b	CCCACACCTCCTGAAATGTC	GTGGGAGGAAAGCTGGTGTG	660

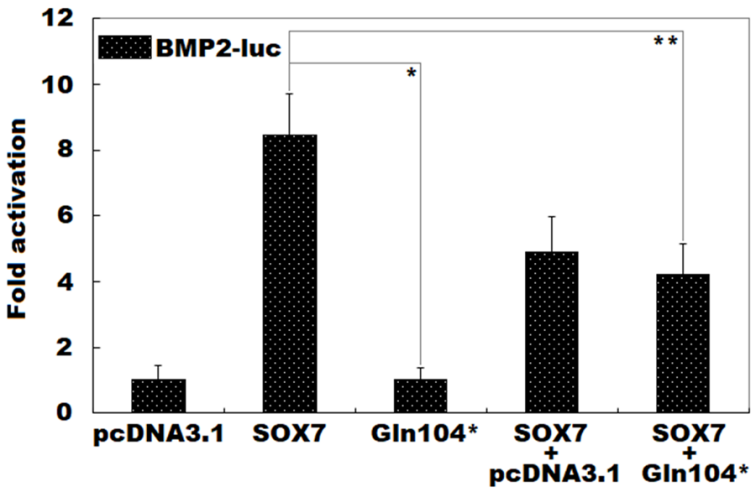

Figure 2. Nullified transactivation function of Gln104*-mutant SOX7. In cultured COS-7 cells transfected with eukaryotic expression plasmids, biologic analysis of transcriptional activation of the *BMP2* promoter-driven firefly luciferase reporter by wild-type SOX7 (SOX7) or Gln104*-mutant SOX7 (Gln104*), singly or together, revealed that SOX7 normally transactivated the promoter of the target gene *BMP2*, whereas Gln104* failed to do so. Here unpaired Student's t test was used. **Denotes $P < 0.01$, and *denotes $P < 0.001$, when compared wto an equal amount of SOX7.

genes abundantly expressed in the developing heart, such as *BMP2*, *GATA4* and *GATA6* [79, 83], alone or synergistically with such transcriptionally cooperated partner as NKX2.5 [69], and pathogenic variations in the genes *NKX2.5*, *GATA4*, *GATA6* and *BMP2* have been involved in the occurrence of CHD [80-82, 84]. In the present study, the nonsense variation was anticipated to create a truncating SOX7 protein with no transactivation domain as well as partial high-mobility-group domain. Hence, the mutation was anticipated to abolish the transactivation function of SOX7, which was validated by reporter gene assays. Taken collectively, these findings support that SOX7 loss-of-function variation predisposes to CHD, probably by downregulating expression of downstream genes required for normal cardiovascular development.

Previous studies on experimental animal models have revealed that genetically compromised SOX7 leads to CHD. In Xenopus, knockdown of either *Sox7* or *Sox18* led to partial inhibition of cardiogenesis, while knockdown of both *Sox7* and *Sox18* strongly inhibited cardiogenesis [85]. Moreover, *Sox7* RNA rescued the effects of the *Sox18* morpholino and vice versa, suggesting that

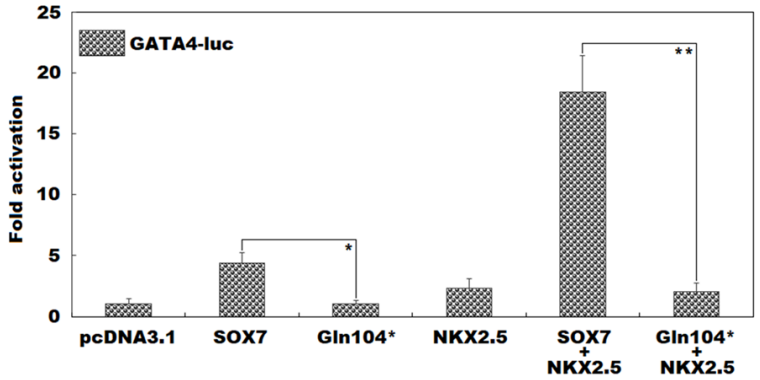

Figure 3. Synergistic transactivation between SOX7 and NKX2.5 abrogated by the variation. In transfected HeLa cells, measurement of activation of the *GATA4* promoter-driven firefly luciferase reporter by wild-type SOX7 (SOX7) or Gln104*-mutant SOX7 (Gln104*), alone or together with NKX2.5, unveiled that the synergistic transcriptional activation between NKX2.5 and SOX7 was disrupted by the Gln104* mutation. Here unpaired Student's t test was used. **Indicates $P < 0.001$, and *indicates $P < 0.005$, in comparison to their wild-type counterparts.

the two proteins share redundant functions [85]. In mice, global knockout of *Sox7* caused embryonic death with developmentally retarded embryos characteristic of dilated pericardial sacs as well as failure of yolk sac remodeling, suggesting cardiovascular failure [86]. Similarly, endothelial-specific knockout of *Sox7* led to murine embryonic lethality with cardiovascular failure and severely impaired angiogenesis [79]. In addition, conditional endocardial *Sox7* deficiency in mice caused abnormal atrioventricular cushion formation and partial atrioventricular septal defect as well as defects in closure of the atrial septum and ventricular septum [79]. Furthermore, *Sox7* was demonstrated to modulate the endothelial to mesenchymal transition process by WNT4-BMP2 signaling, essential for proper atrioventricular cushion formation [79]. In humans, both microdeletions of 8p23.1 that contains *SOX7* and duplication of *SOX7* have been associated with congenital cardiac septal defects [79, 87, 88]. Besides, as another member of the SOX-F gene family (*SOX18*, *SOX17* and *SOX7*), *SOX17* loss-of-function mutations have been discovered to give rise to CHD [69, 89, 90]. These observational results together with the present research data highlight compelling evidence suggesting that haploinsufficiency of *SOX7* contributes to the occurrence of CHD in humans and animals.

Conclusion

In summary, the current investigation first indicates *SOX7* as a causative gene of familial CHD, which sheds light on the novel molecular basis underlying CHD, and is instrumental to designing prevention and therapy for CHD.

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Disclosure of conflict of interest

None.

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