Introduction

Congenital heart disease (CHD) usually refers to abnormalities in the heart’s structure or function that arise before birth [1]. As the most frequent birth defect, CHD affects about 0.8% of live births [2,3], and it is also a leading cause of perinatal and infant mortality, causing more than 220,000 deaths globally every year [4]. In China, epidemiological studies suggest an obvious increasing trend of CHD mortality with the overall mortality rate increasing from 141 in 2003 to 229 in 2010 per 10,000,000 person-years [5]. CHD can be classified into three broad categories: cyanotic heart disease, left-sided obstruction defects and septation defects [1]. Among them, septation defects are most common and can affect septation of the atria (atrial septal defect, ASD), septation of the ventricle (ventricular septal defect, VSD) or formation of structures in the central part of the heart (atrioventricular septal defect, AVSD) [1]. CHD may occur as part of recognized chromosomal and Mendelian syndromes [6,7]; however, it manifests as a non-syndromic, non-Mendelian condition in 80% of cases and may result from a multifactorial inheritance model that involves environmental factors and genetic predisposition [8]. In the past years, several genes linked to CHD have been identified, including T-box transcription factors (TBX1, TBX5 and TBX20), homobox transcription factors (NKX2.5 and NKX2.5), basic helix-loop-helix transcription factors (HAND1 and HAND2), and GATA binding protein 4 (GATA4) [9].
Association of 4p16 Polymorphism with Congenital Heart Disease

Quality control for GWAS scan and genotyping of replication study

The GWAS scan was conducted using Illumina Omni zhonghua chips followed by a systematic quality control before association analysis [11]. In brief, we removed samples with low call rates, ambiguous gender, familial relationships, and extreme heterozygosity rate. We also detected population outliers and stratification using a PCA-based method. Our PCA analysis showed that the cases and controls were genetically matched, and the genomic control inflation factor \( \lambda \) was 1.065 [11]. SNPs were excluded if they are not mapped on autosomal chromosomes, or have a call rate <95%, minor allele frequency (MAF)<0.05 or \( \text{P} > 1.00 \times 10^{-3} \) for Hardy-Weinberg equilibrium. After quality control procedures, a total of 708,275 SNPs in 945 CHD cases and 1,246 controls were included in the final GWAS analysis [11]. The genotyping analyses in the replication study were performed by using the TaqMan allelic discrimination Assay (Applied Biosystems, Inc., USA). The information of the primers and probes were provided in Table 1. A series of methods were used to control the quality of genotyping: (i) case and control samples were mixed on each plate; (ii) genotyping was performed without knowing the case or control status; (iii) two water controls were used in each plate as blank control; (iv) five percent of the samples were randomly selected for repeat genotyping. The accurate concordance rate of genotyping for the SNP rs16835979 was 100.00% in the replication stage.

Statistical analysis

Population structure was evaluated by PCA as implemented in the software package EIGENSTRAT 3.1. The significant (\( P < 0.05 \)) top eigenvector was included in the logistic regression model as a covariate for genetic association analysis [11]. Hardy-Weinberg equilibrium was evaluated using the \( \chi^2 \) test in all of the controls. The genome-wide association analysis was performed using an additive model in a logistic regression analysis in PLINK 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/). The statistical significance was declared at \( \alpha = 0.05 \). \( P \) values were two-sided, and ORs were estimated with an additive model by logistic regression analyses. The linkage disequilibrium (LD) analysis of the 3 SNPs (rs870142, rs16835979 and rs6824295) was performed in the controls of GWAS by using PLINK 1.07. Other analyses were performed using Stata version 9.2 (StataCorp LP, TX). The chi-squared based Cochran’s Q statistic was calculated to test for heterogeneity between groups in stratified analysis. We used inverse-variance-weighted model for meta-analysis when performing combined analysis. Random-effects model was used when heterogeneity between studies exists, that is, \( P \) value for heterogeneity test was less than 0.05; otherwise, fixed-effect model was used.

Results

The characteristics of the 945 CHD cases and the 1,246 non-CHD controls in GWAS scan have been described previously [11]. Moreover, selected characteristics of the 1,709 cases and 1,962 non-CHD controls in the replication study were shown in Table 2 and there were similar distributions of age and sex between cases and controls (\( P = 0.221 \) and 0.870, respectively). The genotype distributions of these 3 SNPs in cases and controls of GWAS scan were shown in Table 3. The observed genotype frequencies were all in Hardy-Weinberg equilibrium in controls (\( P = 0.337 \) for rs870142, \( P = 0.370 \) for rs16835979 and \( P = 0.385 \) for rs6824295). Logistic regression analyses showed that no obvious associations were found between the 3 SNPs and overall
risk of CHD in an additive model (Table 3). Then, we performed stratification analysis by different diagnostic groups (ASD, VSD and ASD combined VSD) and found that all 3 SNPs showed significant associations with ASD risk (N = 334 cases) in the same direction as that observed in Cordell's study (rs870142: OR = 1.24, 95% CI = 1.04–1.49, \( P = 0.016 \); rs16835979: OR = 1.25, 95% CI = 1.05–1.50, \( P = 0.014 \); rs6824295: OR = 1.24, 95% CI = 1.04–1.48, \( P = 0.019 \)). However, no significant association was observed in the other two disease groups (Table 3).

As these 3 SNPs were in high LD (\( r^2 = 0.86–0.99 \)) in Chinese population, we selected one SNP with the lowest \( P \) value in our GWAS scan (rs16835979) to perform a replication study with additional 1,709 CHD cases of multiple phenotypes (ASD: N = 367; VSD: N = 432, Tetralogy of Fallot (TOF): N = 211, other CHDs: N = 699) and 1,962 controls. Similarly, no significant association was observed when all phenotypes were combined together. In the stratification analysis by disease groups, rs16835979 only showed significant association with the risk of ASD (OR = 1.20, 95% CI = 1.02–1.42, \( P = 0.030 \)), which was heterogeneous from the other subgroups significantly (\( P \) for heterogeneity = 0.046) (Table 4). In combined GWAS and replication samples, the minor allele of rs16835979 remained significantly associated with ASD risk (OR = 1.22, 95%CI = 1.08–1.38, \( P = 0.001 \)) (Table 5).

**Discussion**

In this study, we attempted to replicate the 4p16 ASD susceptibility loci in Han Chinese population and found that our results were consistent with the results presented by Cordell et al to a certain extent. These findings suggest that the susceptibility loci of diseases may have some similarities among different races and ethnicities.

In Cordell’s study, 3 SNPs (rs870142, rs16835979 and rs6824295) were identified to be significantly associated with ASD risk [12]. We performed a LD analysis among the 3 SNPs by the online software of SNAP (http://www.broadinstitute.org/mpg/snap/ldsearchpw.php) and found strong LD between them (\( r^2 = 0.89 \) to 0.96) in CEU (CEPH- Utah residents with European ancestry). After evaluating the LD between the 3 SNPs in the controls of our GWAS samples, we found that they were also in high LD in Chinese populations (\( r^2 = 0.86–0.99 \)). There were 28 other SNPs in the LD plot of the region containing the 3 mentioned SNPs (chr4:4665181-4698948) and we found that most SNPs were in high LD with the 3 SNPs in European population, while only about half of them were in high LD with the 3 SNPs in Chinese population. Although we included 701 ASD cases and 3,208 controls in this study (334 cases and 1,246 controls in our GWAS scan and 367 ASD cases and 1,962 controls in the replication study), the sample size, especially the case sample size was relatively smaller compared to the original Cordell’s GWAS. After performing multiple testing corrections with the Bonferroni single-step method (corrected \( \alpha \): 0.05/3 = 0.017), we found the SNPs rs870142 and rs16835979 remained association with ASD risk; however, the SNP rs6824295 lost its association with ASD. Given the high LD of the 3 SNPs, Bonferroni correction might be too strict. Additionally, owing to the genetic heterogeneity, the allele frequency of the SNP rs16835979 in both populations was different (Chinese population: MAF = 0.380 in cases, MAF = 0.334 in controls; European population: MAF = 0.314 in cases, MAF = 0.235 in controls) and the effect size in the current study was weaker than that in European population (OR = 1.22 in

**Table 1. Primers and probes of rs16835979.**

| rs16835979 |       |       |
|-----------|-------|-------|
| F-primer  | TGTGGACTCTAGATGGGACCTCCA |       |
| R-primer  | TGTCAAGATTAGGACATCTTCATCT |       |
| FAM-probe | FAM-AGTGACTTTACTGTCCTC-MGB |       |
| HEX-probe | HEX-AAGTGACTTTAATGTCC-MGB |       |

**Table 2. Characteristics of CHD cases in validation stage.**

| Variables | Case (N = 1,709) | Control (N = 1,962) | \( P \) |
|-----------|-----------------|---------------------|-------|
| Age (mean±SD) | 3.21±0.70 | 3.45±0.93 | 0.221 |
| Sex | Male | 738 (43.2%) | 842 (42.9%) | 0.870 |
| | Female | 971 (56.8%) | 1,120 (57.1%) | |
| Phenotype | ASD | 367 | | |
| | VSD | 432 | | |
| | TOF | 211 | | |
| | Other CHDs | 699 | | |

ASD: ostium secundum atrial septal defect; VSD: ventricular septal defect; TOF: tetralogy of fallot; Other CHDs included patent ductus arteriosus, ebstein anomaly, double-chambered right ventricle, bicuspid aortic valve, aortic insufficiency, aortic stenosis, mitral insufficiency, rupture of valsalva sinus aneurysm, etc.

\( P \)-values were derived from the \( \chi^2 \) test for the categorical variable (sex) and t-test for the continuous variable (age).
Table 3. Associations of the 3 SNPs with CHD in our GWA scan.

| Chr. (cytoband) | Position | SNP      | Study                 | Cases<sup>b</sup> | Controls<sup>b</sup> | MAF<sup>c</sup> (Cases) | MAF<sup>c</sup> (Controls) | OR (95% CI)<sup>d</sup> | P<sup>d</sup> |
|-----------------|----------|----------|-----------------------|-------------------|---------------------|-------------------------|---------------------------|--------------------------|----------|
| 4p16.2          | 4698948  | rs870142 | Combined All (945 cases, 1,246 controls) | 116/428/399       | 145/534/558         | 0.35                    | 0.33                      | 1.08 (0.95–1.22)        | 0.259   |
|                 |          | G/A<sup>a</sup> | ASD (334 cases, 1,246 controls) | 45/164/123        | 145/534/558         | 0.38                    | 0.33                      | 1.24 (1.04–1.49)        | 0.016   |
|                 |          |          | VSD (534 cases, 1,246 controls) | 63/230/241        | 145/534/558         | 0.33                    | 0.33                      | 1.00 (0.86–1.17)        | 0.969   |
|                 |          |          | ASD/VSD (77 cases, 1,246 controls) | 8/34/35           | 145/534/558         | 0.32                    | 0.33                      | 0.97 (0.69–1.38)        | 0.876   |
| 4p16.2          | 4686177  | rs16835979 | Combined All (945 cases, 1,246 controls) | 116/426/396       | 144/536/560         | 0.35                    | 0.33                      | 1.08 (0.95–1.23)        | 0.212   |
|                 |          | C/A<sup>a</sup> | ASD (334 cases, 1,246 controls) | 44/164/121        | 144/536/560         | 0.38                    | 0.33                      | 1.25 (1.05–1.50)        | 0.014   |
|                 |          |          | VSD (534 cases, 1,246 controls) | 64/228/241        | 144/530/560         | 0.33                    | 0.33                      | 1.01 (0.87–1.18)        | 0.896   |
|                 |          |          | ASD/VSD (77 cases, 1,246 controls) | 8/34/34           | 144/536/560         | 0.33                    | 0.33                      | 1.00 (0.70–1.41)        | 0.986   |
| 4p16.2          | 4665181  | rs6824295 | Combined All (945 cases, 1,246 controls) | 127/445/372       | 163/554/525         | 0.37                    | 0.35                      | 1.07 (0.94–1.21)        | 0.298   |
|                 |          | G/A<sup>a</sup> | ASD (334 cases, 1,246 controls) | 46/177/111        | 163/554/525         | 0.40                    | 0.35                      | 1.24 (1.04–1.48)        | 0.019   |
|                 |          |          | VSD (534 cases, 1,246 controls) | 71/232/230        | 163/554/525         | 0.35                    | 0.35                      | 0.99 (0.85–1.15)        | 0.878   |
|                 |          |          | ASD/VSD (77 cases, 1,246 controls) | 10/36/31          | 163/554/525         | 0.36                    | 0.35                      | 1.05 (0.75–1.48)        | 0.765   |

<sup>a</sup>major/minor alleles.
<sup>b</sup>variant homozygote/heterozygote/wild type homozygote.
<sup>c</sup>minor allele frequency (MAF).
<sup>d</sup>OR and P were derived from logistic regression analysis in additive model adjusting for the first principal component in GWAS.
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### Table 4. Associations of rs16835979 with CHD in replication study.

| Chr. (cytoband) | Position (bp) | SNP       | Study                  | Casesᵇ | Controlsᵇ | MAFᶜ (Cases) | MAFᶜ (Controls) | OR (95% CI)ᵈ   | Pᵈ    | Pᶠ   |
|-----------------|---------------|-----------|------------------------|--------|------------|---------------|-----------------|----------------|--------|-------|
| 4p16.2          | 4686177       | rs16835979| ASD (367 cases, 1,962 controls) | 52/165/139 | 215/888/859 | 0.38          | 0.34            | **1.20 (1.02–1.42)** | 0.030  | 0.046 |
|                 |               |           | C/Aᵃ                   |        |            |               |                 |                 |        |       |
|                 |               |           | VSD (432 cases, 1,962 controls) | 56/178/187 | 215/888/859 | 0.34          | 0.34            | 1.04 (0.89–1.22) | 0.635  |       |
|                 |               |           | TOF (211 cases, 1,962 controls) | 23/76/110 | 215/888/859 | 0.29          | 0.34            | 0.81 (0.65–1.02) | 0.070  |       |
|                 |               |           | Other CHDs (699 cases, 1,962 controls) | 91/312/287 | 215/888/859 | 0.36          | 0.34            | 1.10 (0.97–1.26) | 0.136  |       |
|                 |               |           | Combined subjectsᵃ (1,709 cases, 1,962 controls) | 222/731/723 | 215/888/859 | 0.35          | 0.34            | 1.05 (0.91–1.20) | 0.521  |       |

ᵃmajor/minor alleles.
ᵇvariant homozygote/Heterozygote/Wild type homozygote.
ᶜminor allele frequency (MAF).
ᵈestimated in additive model.
ᵉcombined via random-effects meta-analysis.
ᶠP values for heterogeneity test between groups.

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### Table 5. Associations of rs16835979 with ASD.

| Chr. (cytoband) | Position (bp) | SNP       | Study                  | Casesᵇ | Controlsᵇ | MAFᶜ (Cases) | MAFᶜ (Controls) | OR (95% CI)ᵈ   | Pᵈ    | Pᶠ   |
|-----------------|---------------|-----------|------------------------|--------|------------|---------------|-----------------|----------------|--------|-------|
| 4p16.2          | 4686177       | rs16835979| GWAS (334 ASD cases, 1,246 controls) | 44/164/121 | 144/536/560 | 0.38          | 0.33            | **1.25 (1.05–1.50)** | 0.014  | 0.742 |
|                 |               |           | C/Aᵃ                   |        |            |               |                 |                 |        |       |
|                 |               |           | Replication (367 ASD cases, 1,962 controls) | 52/165/139 | 215/888/859 | 0.38          | 0.34            | **1.20 (1.02–1.42)** | 0.030  |       |
|                 |               |           | Combined analysis (combined via fixed-effects meta-analysis) | 96/329/260 | 359/1424/1419 | 0.38          | 0.33            | **1.22 (1.08–1.38)** | 0.001  |       |

ᵃmajor/minor alleles.
ᵇvariant homozygote/heterozygote/wild type homozygote.
ᶜminor allele frequency (MAF).
ᵈestimated in additive model.
ᵉP values for heterogeneity test between group.

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Chinese population vs. OR = 1.46 in European population). Using Levin’s formula [13], we also found that the population-attributable risk of ASD for the SNP rs16835979 was relatively lower in Chinese (7%) than that in Caucasian (9%).

All 3 SNPs locate within an intron of the noncoding RNA gene LOC100507266 with unknown function. Meanwhile, they also lie in the 320-kb interval between STX18 (syntaxin 18) and MSXI (msh homeobox 1) and locate upstream of both genes. The long non-coding RNA gene LOC100507266 is known as STX18 antisense RNA 1 (STX18-AS1). STX18 is principally located in the endoplasmic reticulum, and it plays roles in transport between the endoplasmic reticulum and Golgi [14]; however, no data are available for its function in heart development. MSXI has been shown to be expressed in mesenchymal structures, including the limb buds, pharyngeal arches, neural crest, and endocardial cushions of the heart [15,16]. In Cordell’s study, MSXI was shown to be expressed in the atrial septum during development, both in mouse and chick [12]. MSXI and MSX2, which belong to the highly conserved Nk family of homeobox genes, display overlapping expression patterns and redundant functions in multiple tissues and organs during vertebrate development [15,16]. The functions of Msx1 and Msx2 in endocardial activation prior to EMT via upregulation of NFATc1 expression have been documented [13]. In addition, Msx1 has a well-documented role as both a downstream effector and an upstream regulator of Bmp signaling. It has been implicated in regulating epithelial-mesenchymal transition (EMT) during cardiac valve and septa formation [15,17]. Hand1 and Hand2 are also candidate target genes regulated by Msx1 and Msx2 [18]. Since myocardium-specific Hand1 deficiency leads to thickened atrioventricular (AV) valves, which is associated with impaired valve remodeling [19–21], decreasing Hand1 expression in the Msx1/2 double mutant AV myocardium may be associated with defects in remodeling of the AV cushions into mature valve leaflets [15]. In the mouse, loss both of Msx1 and Msx2 leads to a severe endocardial cushion and conotruncal defects [15,10]. In humans, mutations in MSXI cause orofacial clefting and tooth agenesis [22,23]. It is speculated that these 3 SNPs may affect the regulation of above genes and thus have associations with the development of ASD; however, the specific mechanisms of the 3 SNPs affecting the risk of ASD still need to be further investigated.

Like Cordell’s study, we did not observe genome-wide significant associations of 4p16 loci with overall CHD risk in our GWAS as well as replication study. The findings suggested that genetic etiology of CHD could have a considerable degree of phenotypic specificity, which was also identified by some recent studies [24–25]. For the various phenotypes of CHD originated from different part of heart, we believe different genetic factors are involved in their pathogenic process.

Interestingly, our previous GWAS has identified 2 susceptibility loci (rs2474937 at 1p12 and rs1531070 at 4p31.1) for CHD in Han Chinese. However, these variants may contribute to the risk of CHD through different pathways. As described previously, the SNP rs2474937 may affect the expression of TBX15, a member of T-box transcription factors that have key roles in the development of the embryonic mesoderm, including of the heart and skeleton. Another SNP rs1531070 is in a LD region overlapping the MAML3 (mastermind-like 3) gene and mastermind (Mam) is one of the essential components of Notch signaling pathway. In the current study, we confirmed the ASD-specific association of SNP rs16835979 in Chinese. This SNP may influence MSXI (msh homeobox 1), which belongs to the highly conserved Nk family of homeobox genes. MSXI has functions in endocardial activation prior to epithelial-mesenchymal transition (EMT) as well as Bmp signaling. Thus, the findings in the current study supplemented the existing results of our GWAS.

In conclusion, we present evidence for association between the common SNP rs16835979 at 4p16 and the ASD-specific risk in Han Chinese, which extends Cordell’s results in different populations and suggests that the susceptibility loci of disease indeed have some similarities among different races and ethnicities.

Author Contributions

Conceived and designed the experiments: HM JS HS JL. Performed the experiments: YL BN MD CD YH KZ. Analyzed the data: BZ YL. Contributed reagents/materials/analysis tools: JX YC XM S. Yang XW. Wrote the paper: BZ YL. Oversaw the study design: S. Yu JS HS JL. Contributed to interpretation of results: S. Yu JS HS JL.

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