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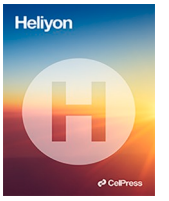

Replication of previous autism-GWAS hits suggests the association between *NAA1, SORCS3,* and *GSDME* and autism in the Han Chinese population

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ABSTRACT

Background: Autism is a severe neurodevelopmental disorder characterized by social interaction deficits, impairments in communication, and restricted and repetitive stereotyped behavior and activities. Family and twin studies suggested an essential role of genetic factors in the etiology of autism spectrum disorder (ASD). Also, other studies found *SORCS3* and *GSDME* (*DFNA5*) might be involved in brain development and susceptible to ASD.

Methods: In this study, 17 genome-wide significant SNPs reported in previous ASD genome-wide association studies (GWAS) and 7 SNPs in strong linkage disequilibrium with known ASD GWAS hits were selected to investigate the association between these SNPs and autism in the Han Chinese population. Then, 10 tagSNPs in *SORCS3* and 11 tagSNPs in *GSDME* were selected to analyze the association between these SNPs and autism. The selected 24 SNPs and tagSNPs were genotyped using the Agena MassARRAY SNP genotyping assay in 757 Han Chinese autism trios.

Results: Rs1484144 in *NAA11* was significantly associated with autism; significance remained after the Bonferroni correction ($P < 0.0022$). Also, rs79879286, rs12154597, and rs12540919 near *GSDME,* as well as rs9787523 and rs3750261 in *SORCS3,* were nominally associated with autism.

Conclusion: Our study suggests that rs1484144 in *NAA11* is a significant SNP for autism in the Han Chinese population, while *SORCS3* and *GSDME* might be the susceptibility genes for autism in this population.

1. Introduction

Autism is the most severe neurodevelopmental phenotype of autism spectrum disorder (ASD) [1,2], characterized by impaired social interaction, communication disorder, and repetitive and restrictive behavioral activities [3]. The global prevalence of ASD was

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about 1 %, and the boy-to-girl ratio is 4:1 [3,4]. Family and twin studies indicated an important role of genetic factors in the etiology of ASD, whose heritability is 80%–93 % [4,5]. Common genetic variants, particularly single-nucleotide polymorphisms (SNPs), contribute to the majority of genetic risk of ASD, and among common variants the genetic risk of single-nucleotide polymorphisms (SNPs) was to almost 50 % [5,6].

Genome-wide association studies (i.e., GWAS) help scientists identify genes associated with a particular disease by exploring the set of DNA of a large group of people and searching for SNPs [7]. Thus far, several candidate genes, including *RELN*, *MECP2*, *OXTR*, *CNTNAP2*, *EN2,* and GABA receptor subunits (*GABRB3*, *GABRA5,* and *GABRG3*) have been identified in patients with autism [8–13]. These genes have been repeatedly verified in several independent studies with large sample sizes [13], while some have been tested using GWAS. In European populations, GWAS found that SNPs in *CDH10*, *MSNP1AS,* and *MACROD2* are significantly associated with ASD and rs4307059 near *MSNP1AS* has been associated with autism in Han Chinese people [14]. In addition, studies have suggested that some genetic loci might be involved in the pathogenesis of autism in different populations [14,15]. Furthermore, four autism-related GWAS with large sample sizes recently found some new genome-wide positive loci significantly associated with ASD [16–19]. Grove et al. compared 18,381 ASD patients with 27,969 controls and found that rs71190156 in *MACROD2*, rs111931861 in *KMT2E*, rs910805 near *XRN2*, rs10099100 near *SOX7*, and rs201910565 near *PTBP2* were significantly associated with ASD [16]. Furthermore, they used Multi-Trait Analysis of GWAS (MTAG), a method for joint analysis of summary statistics from GWAS of different traits, revealed 4 loci, including rs1620977 in *NEGR1* in patients with ASD, compared to those with major depression (111, 902 patients with major depression and 312,113 controls) [16]. Another MTAG on ASD and educational attainment (328,917 persons on average) found that rs11787216 near *MROH5* and other 2 loci were associated with ASD and educational attainment of the European population at the genome level [16]. A previous study analyzed the GWAS data of Psychiatric Genomics Consortium (PGC) ASD and schizophrenia and found that 12 new loci, including rs880446 near *EEF1A2*, had genome-wide significance [17]. Another GWAS analyzed six psychiatric disorders of Integrative Psychiatric Research (iPSYCH), revealing that 4 independent loci, including rs4322805 near *PDE1A*, are significant at the genome level [18]. In addition, PGC analyzed eight psychiatric disorders and found that 23 novel loci, including rs9787523 in *SORCS3* and rs79879286 near *GSDME* (*DFNA5*), are significantly associated with at least four psychiatric disorders (including ASD) [19]. Yet, the association between these variants and autism in the Han Chinese population remains unclear.

Herein, we performed a family-based association study on 757 Han Chinese autism trios to further explore whether these ASD-related positive SNPs in European and North American populations contributed to the etiology of autism in the Han Chinese population. We found SNPs in *NAA11*, *SORCS3*, and near *GSDME* associated with autism in the Han Chinese population. SORCS3 is a vacuolar protein sorting 10 receptor family member with an important role in neuronal signal transduction and synaptic inhibition regulation [20–22]. The expression level of *SORCS3* in the brain increases during early embryonic development and remains high after birth suggested on Human Brain Transcriptome (HBT) database (http://hbatlas.org/). Also, some studies suggested that *SORCS3* might be involved in brain development [20–23]. Genetic studies showed that some SNPs in *SORCS3* were associated with neuropsychiatric disorders or related characteristics such as autism, schizophrenia, attention-deficit/hyperactivity disorder, Alzheimer's disease, and intelligence [24–28]. GSDME is a pore-forming protein that mediates pyroptosis [29,30]. Previous studies suggested that GSDME has an important role in immunity and neural development by mediating pyroptosis [29–35]. Similar to *SORCS3,* the expression level of *GSDME* in the brain increases during early human embryonic development and remains high after birth, suggesting that this gene is also involved in brain development on HBT databese. GSDME is a GSDMD-related family member that shares approximately 28 % identity with the GSDMD N-terminal domain corresponding to pyroptosis. These two proteins could be specifically cleaved by caspase-3, inducing pyroptosis [36]. The central nervous system cell pruning decreases in the brains of *Gsdmd*-deficient mice, which suggests that pyroptosis is involved in sculpting the brain [37]. Genetic studies have also suggested that a few SNPs in *GSDME* were associated with several neuropsychiatric disorders, such as schizophrenia, major depression, and bipolar disorder [23,38–44].

Replication helps ensure that a genotype-phenotype association observed in a GWA study represents a credible association and is not a chance finding or an artifact due to uncontrolled biases. Our replication results and these previous mass researches indicated that *SORCS3* and *GSDME* might be associated with autism, which needs further evidence. Furthermore, we selected some tagSNPs to investigate the association between *SORCS3, GSDME,* and autism in 757 autism trios of Han Chinese ancestry to explore the association between autism and these two genes.

2. Material and methods

2.1. Participants

A total of 757 Han Chinese autism trios (757 autistic children and their biological parents) were recruited from Peking University Sixth Hospital (Beijing, China) in this study. The sex ratio of autistic children was about 7.2:1, including 665 boys (87.8 %) and 92 girls (12.2 %). The median age of diagnosis was 4.83 (upper quartile 3.50 to lower quartile 6.43) years. In addition, these 757 trios included the 640 Han Chinese autism trios, which were assessed in a previous GWAS [14]. This study found that the reported rs4307059 near *MSNP1AS* in the European population is also a susceptibility variant for autism in the Han Chinese population.

Only individuals with typical symptoms of autism were selected to reduce heterogeneity. The inclusion criteria were: (1) children who met the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria and were independently diagnosed by two senior child psychiatrists [2]; (2) autistic children and their biological parents of Han Chinese ethnicity; (3) children affected with autism $<$18 years old with no family history of neuropsychiatric and other genetic diseases; (4) Autism Behavior Checklist score $\geq$53 [45]; (5) Childhood Autism Rating Scale score $\geq$36 [46]. The exclusion criteria were: (1) children with Asperger syndrome or pervasive

developmental disorder not otherwise specified; (2) children with phenylketonuria, fragile X syndrome, or other neurological diseases; (3) children with severe physical disease; (4) children carrying abnormal karyotypes.

2.2. Selection of replication SNPs

PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and GWAS catalog (http://www.ebi.ac.uk/gwas/) were used to search GWAS on autism using the keywords "genome-wide association study" OR "GWAS" AND "autism" OR "psychiatric disorder". Then, the autism-GWAS hits not studied in the Han Chinese population were selected.

The genotype data of SNPs in the Han Chinese general population referred to the Ensembl GRCh37 Release 93 (http://grch37.ensembl.org/index.html), the dbSNP in the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/snp), and the Han Chinese Genomes Database (https://www.biosino.org/pgghan2/index). The SNPs with minor allele frequency (MAF) in Han Chinese Beijing (CHB) > 0.05 were included in the study. The SNPs with no association ($P < 0.05$) with ASD in PGC (http://www.med.unc.edu/pgc/results-and-downloads) were excluded from this study.

2.3. Selection of tagSNPs in SORCS3 and GSDME

Priority selection was performed as follows: (1) SNPs located in the functional regions of genes [e.g., promoter region, 5′ untranslated region (UTR), exon, and 3′ UTR region]; (2) SNPs found to be associated with autism or autism-related phenotypes in previous studies; (3) SNPs with MAF in CHB being >0.05; (4) considering the physical location of SNPs in genes and then selecting and optimizing SNPs using HaploView 4.2. As a result, 10 tagSNPs in *SORCS3* (Table S5 and Fig. 1) and 11 tagSNPs in *GSDME* (Table S5 and Fig. 2) were selected for the present study.

2.4. DNA extraction and genotyping

The peripheral blood samples were obtained from children with autism and their biological parents. Genomic DNA was extracted using the Qiagen QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). The extracted DNA was quality controlled using a NanoDrop spectrophotometer (Thermo Fisher, MA, USA) to ensure that the samples met the following criteria: (1) DNA concentration >40 ng/μL; (2) the OD_{260}/OD_{280} ratio between 1.8 and 2.0; (3) the OD_{260}/OD_{230} ratio between 2.0 and 2.2.

SNP genotyping was performed using Agena MassARRAY SNP typing through the Agena Bioscience platform (Agena Bioscience, CA, USA) [47]. All primers were designed based on the sequence of forward strands provided by the NCBI human reference genome GRCh37 (hg19) (primers of 24 ASD-related genome-wide SNPs shown in Table S1; primers of 21 tagSNPs shown in Table S6). The DNA products were obtained using the following three steps: (1) polymerase chain reaction (PCR); (2) use of shrimp alkaline phosphatase to remove unincorporated nucleotides and primer extension reaction; (3) transfer of the products to SpectroCHIP for analysis through the mass spectrometer to acquire SNP genotypes.

2.5. Data analysis

The chi-square goodness-of-fit test was used to analyze whether the genotype frequency distribution deviated from Hardy–Weinberg equilibrium (HWE), and SNPs were excluded from the subsequent analysis when the *P* values were less than 0.05.

The statistical power of SNPs was calculated using the Quanto version1.2.4 [48]. The population risk was set as 0.01 [4], and the genetic effect was estimated to range from 1.3 to 1.5, according to previous studies [7,49,50]. The type I error rate was 0.05 (two-sided) under the log-additive model [51].

Family-based association tests were performed using family-based association test (FBAT) 2.0.3 software , which could detect

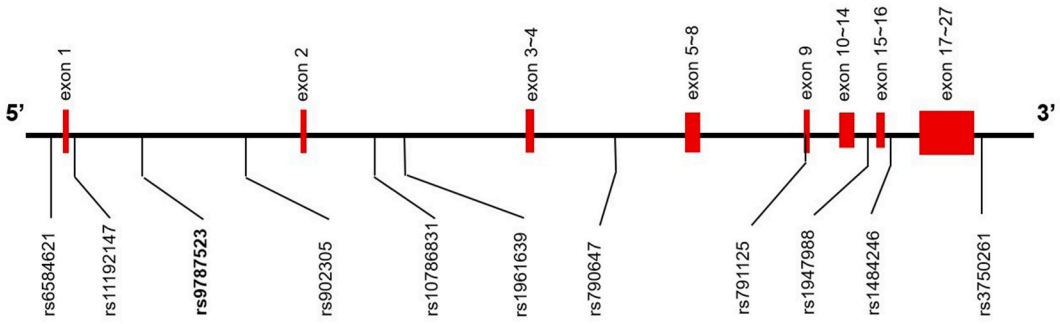

Fig. 1. A diagram of the positions of 10 tagSNPs in *SORCS3*. SNP in bold indicates nominal association with autism in the Chinese Han population; red blocks indicate exons in *SORCS3*. The distribution diagram was drawn according to information from *SORCS3* (human transcript: NM_014,978) and each tagSNP from Ensembl GRCh37 Release 93 and dbSNP in NCBI databases. Abbreviations: SNP, single nucleotide polymorphism.

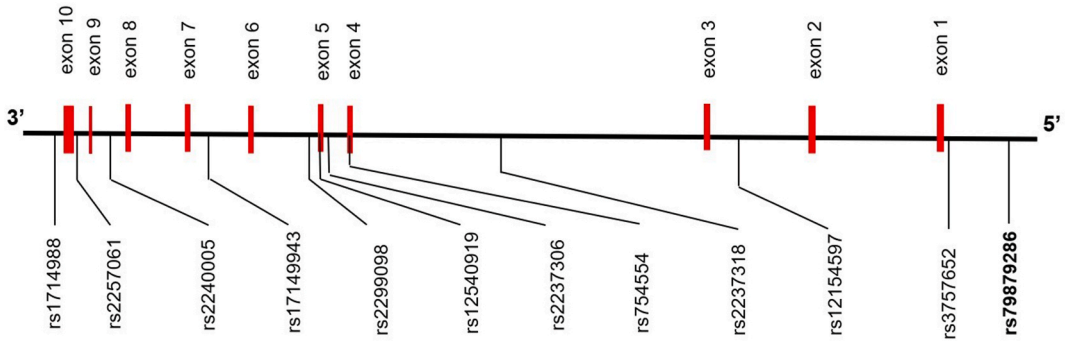

Fig. 2. A diagram of the positions of 11 tagSNPs in *GSDME*. SNP in bold indicates nominal association with autism in the Chinese Han population; red blocks indicate exons in *GSDME*. The distribution diagram was drawn according to information of *GSDME* (human transcript: NM_004403) and each tagSNP from Ensembl GRCh37 Release 93 and dbSNP in NCBI databases. Abbreviations: SNP, single nucleotide polymorphism.

Mendelian errors automatically and reset their genotypes to zero [51]. The processed data were used to analyze the association between SNPs and autism under additive and recessive genetic models separately with the FBAT program. Then, Bonferroni correction was performed to reduce the type I error rate with the significance level of $P < \alpha/n$ ($\alpha = 0.05$, n is the number of SNPs). The significance level for all statistical tests was two-tailed. The ratio of transmission to untransmission (T:U) of alleles of individual SNPs was calculated using HaploView version 4.2 (http://www.broad.mit.edu/mpg/haploview/) [52].

3. Results

3.1. Quality control

A few genome-wide SNPs were detected in seven GWAS studies with large ASD sample size. Seven autism genome-wide significant SNPs reported in four GWAS were replicated in the Han Chinese population [14]. Four GWAS reported 24 autism-GWAS hits associated with ASD in PGC ($P < 0.05$); their MAF in the Han Chinese population was more than 0.05 [16–19]. The details of all SNPs are shown in Table 1. Seven of these 24 SNPs were incompatible with other SNPs when designing primers. Therefore, SNPs in strong linkage disequilibrium with these 7 SNPs (Table S2) and compatible with other 17 autism-GWAS SNPs (Table S3) were selected for further association analysis.

All 24 ASD-related genome-wide SNPs clustered clearly on genotyping except rs2332700 (Fig. S1). The call rate of these well-clustered SNPs was better than 0.90, and the genotype distribution did not deviate from HWE in unaffected parents (Table S4). The statistical power calculated using Quanto under the log-additive model was 37%–99 %. All 21 tagSNPs SNPs clustered clearly on genotyping except rs6584621 and rs11192147 in *SORCS3* and rs2237306 in *GSDME* (Fig. S2). The call rate of these well-clustered SNPs was better than 0.90, and all SNPs were not deviated from HWE in unaffected parents except for rs3757652, rs17149888, and rs754554 (Table S7). Therefore, six SNPs that failed genotyping or deviated from HWE were not further analyzed. The statistical power calculated using Quanto under the log-additive model was 39%–99 %. During the FBAT, the data from families with Mendelian errors would reset '0' and were not calculated in the further analysis.

Table 1
The details of 24 ASD-related genome-wide SNPs.

GWAS	ASD sample size (cases/controls)	other sample size (cases/controls)	main Ancestry	positive SNPs	related mental disorders
PGC-ASD group, 2017	7387/8567	36989/113075 (SCZ)	European	12	ASD, SCZ
Grove *et al.*, 2019	18381/27969	N = 328917 (Edu) 111902/111902 (MD) 34129/45512 (SCZ)	European	12	5/12 ASD 4/12 ASD & MD 3/12 ASD & Edu
Schork *et al.*, 2019	12371/19526	46008/19526 (ASD, ADHD, SCZ, BIP, AFF, ANO)	European	4	six mental disorders
Cross-disorder group of PGC, 2019	18381/27969	232964/494162 (ASD, ADHD, SCZ, BIP, MD, OCD, TS, AN)	European	23	more than four mental disorders

Abbreviations: GWAS, genome-wide association study; SNP, single nucleotide polymorphism; ASD, autism spectrum disorder; SCZ, schizophrenia; Edu, educational attainment; MD, major depression; ADHD, attention-deficit/hyperactivity disorder; BIP, bipolar disorder; AFF, affective disorder; ANO, anorexia; OCD, obsessive-compulsive disorder; TS, Tourette syndrome; AN, anorexia nervosa.

3.2. Association analyses of ASD-related genome-wide SNPs

Single-SNP association analyses demonstrated that the T allele of rs1484144 was over-transmitted from unaffected parents to their autistic children under the additive model (T > C, $Z = 3.087$, $P = 0.0020$) and recessive model (T > C, $Z = 2.314$, $P = 0.0207$) (Table 2). The statistical significance of the additive model remained after the Bonferroni correction ($P < \alpha/n = 0.05/23 = 0.0022$). The rs79879286 near *GSDME* was nominally associated with autism under the additive model (G > C, $Z = 2.010$, $P = 0.0445$) and recessive model (G > C, $Z = 2.194$, $P = 0.0283$) (Table 2). The rs9787523 of *SORCS3* was nominally associated with autism under the recessive model (C > T, $Z = -1.963$, $P = 0.0496$) (Table 2). However, the significance of rs79879286 and rs9787523 did not remain after Bonferroni correction. The remaining 20 SNPs showed no association with autism under the additive or recessive model.

Table 2
Results of association analyses of 23 ASD-related genome-wide SNPs in 757 Han Chinese autism trios by FBAT.

SNP	Location	Gene	Allele	AFreq	T:U[a]	Addictive model			Recessive model		
						Fam	Z	P^b	Fam	Z	P^b
rs910805	20:21248116	*near XRN2*	A	0.791	249:237	404	0.544	0.5862	380	0.580	0.5618
			G	0.209	237:249	404	−0.544	0.5862	106	−0.108	0.9139
rs1452075	3:62481063	*CADPS*	C	0.296	304:310	487	−0.242	0.8087	173	0.547	0.5844
			T	0.704	310:304	487	0.242	0.8087	441	0.618	0.5366
rs325506	5:104012303	*near NUDT12*	C	0.576	358:359	552	−0.037	0.9702	415	0.388	0.6981
			G	0.424	359:358	552	0.037	0.9702	302	0.526	0.5986
rs1620977	1:72729142	*NEGR1*	A	0.163	200:186	328	0.661	0.5087	74	0.715	0.4749
			G	0.837	186:200	328	−0.661	0.5087	313	−0.434	0.6641
rs10149470	14:104017953	*near COA8*	A	0.584	346:353	519	−0.265	0.7912	410	0.105	0.9166
			G	0.416	353:346	519	0.265	0.7912	289	0.576	0.5645
rs880446	20:62133177	*near EEF1A2*	A	0.463	368:353	560	0.559	0.5764	335	−0.612	0.5408
			G	0.537	353:368	560	−0.559	0.5764	386	−1.371	0.1703
rs4904167	14:84700744	-	C	0.281	271:301	468	−1.254	0.2097	156	−1.228	0.2195
			T	0.719	301:271	468	1.254	0.2097	416	0.810	0.4178
rs4322805	2:183535884	*near PDE1A*	A	0.506	359:353	540	0.225	0.8221	357	−0.395	0.6928
			G	0.494	353:359	540	−0.225	0.8221	355	−0.736	0.4617
rs6780942	3:117828678	*near IGSF11*	C	0.644	313:316	492	−0.120	0.9048	403	−0.234	0.8147
			T	0.356	316:313	492	0.120	0.9048	226	−0.108	0.9137
rs9360557	6:73132745	*near KCNQ5*	C	0.621	309:279	457	1.237	0.2160	369	0.900	0.3682
			G	0.379	279:309	457	−1.237	0.2160	219	−0.989	0.3226
rs6125656	20:48090779	*KCNB1*	A	0.069	96:97	185	−0.072	0.9426	9	–	–
			G	0.931	97:96	185	0.072	0.9426	184	0.000	1.0000
rs11570190	11:57560452	*CTNND1*	A	0.846	176:194	316	−0.936	0.3494	309	−0.698	0.4851
			C	0.154	194:176	316	0.936	0.3494	61	0.871	0.3840
rs1484144	4:80217597	*NAA11*	C	0.244	202:269	377	−3.087	**0.0020**	118	−2.572	**0.0101**
			T	0.756	269:202	377	3.087	**0.0020**	353	2.314	**0.0207**
rs9787523	10:106460460	*SORCS3*	C	0.679	330:293	483	1.441	0.1495	420	0.535	0.5924
			T	0.321	293:330	483	−1.441	0.1495	204	−1.963	**0.0496**
rs7531118	1:72837239	*near NEGR1*	C	0.283	319:281	477	1.509	0.1312	161	0.965	0.3347
			T	0.717	281:319	477	−1.509	0.1312	440	−1.286	0.1986
rs79879286	7:24826589	*near GSDME*	C	0.048	54:77	126	−2.010	**0.0445**	5	–	**-**
			G	0.952	77:54	126	2.010	**0.0445**	126	2.194	**0.0283**
rs9375225	6:98588754	*near MMS22L*	G	0.594	323:312	465	0.437	0.6625	374	−0.384	0.7006
			T	0.406	312:323	465	−0.437	0.6625	261	−1.218	0.2233
rs746839	8:142617261	*near MROH5*	C	0.831	175:194	325	−0.880	0.3787	315	−0.402	0.6876
			G	0.169	194:175	325	0.880	0.3787	58	1.474	0.1403
rs11242522	5:103904914	–	C	0.406	370:344	542	0.973	0.3305	292	1.521	0.1283
			T	0.594	344:370	542	−0.973	0.3305	422	−0.103	0.9182
rs7499750	16:13749265	–	A	0.107	125:126	220	−0.063	0.9497	31	−0.311	0.7557
			C	0.893	126:125	220	0.063	0.9497	220	−0.034	0.9726
rs13236223	7:140666965	*near MRPS33*	C	0.103	142:131	247	0.666	0.5056	29	−0.843	0.3991
			T	0.897	131:142	247	−0.666	0.5056	244	−0.973	0.3304
rs6961430	7:110058448	–	C	0.197	217:224	377	−0.333	0.7389	86	−0.478	0.6326
			G	0.803	224:217	377	0.333	0.7389	355	0.163	0.8706
rs7188257	16:6314935	*near RBFOX1*	C	0.219	215:240	375	−1.024	0.3061	113	−0.995	0.3200
			T	0.781	240:215	375	1.024	0.3061	349	0.691	0.4896

Abbreviations: SNP, single nucleotide polymorphism; Position referenced the NCBI human reference genome GRCh37/hg19; AFreq, allele frequency; Fam, number of informative families; S, test statistics for the observed number of transmitted alleles; E(S), the expected value of S under the null hypothesis (i.e., no linkage and no association).

[a] The ratio of transmission to untransmission (T:U) for each selected SNP was calculated by the Haploview version 4.2.

[b] P value with bold character means nominally associated with autism ($P < 0.05$).

3.3. Association analyses of tagSNPs

The C allele of rs12154597 in *GSDME* was over-transmitted from unaffected parents to their autistic children under both additive (C > G, $Z = 2.008$, $P = 0.0446$) and recessive models (C > G, $Z = 2.168$, $P = 0.0301$) (Table 3). The C allele of rs12540919 in *GSDME* was nominally associated with autism under the additive model (C > T, $Z = 2.045$, $P = 0.0409$) (Table 3). The C allele of rs3750261 in *SORCS3* was over-transmitted from unaffected parents to their autistic children, and the T allele was a protective factor under the recessive model (C > T, $Z = -2.302$, $P = 0.0214$) (Table 3). All the above statistical significance was not corrected by Bonferroni correction $P < \alpha/n = 0.0033$ ($\alpha = 0.05$, $n = 15$). The remaining tagSNPs showed no association with autism under additive or recessive models.

4. Discussion

This family-based association study investigated the association between autism and 16 significantly ASD-related genome-wide SNPs and 7 SNPs in strong linkage disequilibrium with autism-GWAS hits in the 757 Han Chinese patients. Our data suggested that rs1484144 in *NAA11* was significantly associated with autism under the additive model and nominally associated with autism under the recessive model. Besides, rs79879286 near *GSDME* and rs9787523 in *SORCS3* were nominally associated with autism. The above replication results and mass findings suggest that *GSDME* and *SORCS3* might be autism susceptibility genes. We also explored the association of these two genes with autism, which showed that rs12154597 and rs12540919 in *GSDME* and rs3750261 in *SORCS3* were nominally associated with autism.

The GWAS of PGC meta-analyses on eight psychiatric disorders showed that rs1484144, rs9787523 and rs79879286 were risk gene variants shared by cross-psychiatric disorders, including ASD [19]. GWAS meta-analysis of the mood disorder spectrum (including bipolar disorder and major depressive disorder) found that rs79879286 was a positive locus [39]. Also, rs12154597 in *GSDME* was found to be associated with schizophrenia [41].

The genes containing autism-related SNPs found in this study were also associated with psychiatric disorders or related traits in other studies. GWAS showed that rs12642606 in *NAA11* was associated with depressive disorders [53]. In *SORCS3*, we found 2

Table 3
Results of association analyses of 15 tagSNPs in 757 Han Chnese autism trios by FBAT.

SNP	Location	Gene location	Allele	AFreq	T:U[a]	Addictive model			Recessive model		
						Fam	Z	P^b	Fam	Z	P^b
rs902305	10:106532224	*SORCS3*	A	0.751	265:239	403	1.331	0.1832	376	1.417	0.1565
			G	0.249	239:265	403	−1.331	0.1832	132	−0.340	0.7336
rs10786831	10:106614571	*SORCS3*	A	0.226	231:211	373	0.949	0.3425	93	−0.403	0.6866
			G	0.774	211:231	373	−0.949	0.3425	351	−1.287	0.1980
rs1961639	10:106635997	*SORCS3*	A	0.903	122:125	228	−0.254	0.7995	225	−0.337	0.7360
			G	0.097	125:122	228	0.254	0.7995	23	−0.236	0.8137
rs790647	10:106776484	*SORCS3*	A	0.224	233:235	393	0.000	1.0000	110	−0.581	0.5615
			C	0.776	235:233	393	0.000	1.0000	364	−0.297	0.7667
rs791125	10:106907440	*SORCS3*	C	0.71	278:275	440	0.127	0.8989	397	−0.235	0.8145
			T	0.29	275:278	440	−0.127	0.8989	160	−0.656	0.5119
rs1947988	10:106947006	*SORCS3*	C	0.837	180:155	291	1.253	0.2102	290	0.899	0.3687
			T	0.163	155:180	291	−1.253	0.2102	47	−1.343	0.1794
rs1484246	10:106961404	*SORCS3*	A	0.166	189:193	337	−0.102	0.9191	53	0.079	0.9372
			G	0.834	193:189	337	0.102	0.9191	335	0.139	0.8892
rs3750261	10:107023390	*SORCS3*	C	0.785	239:204	366	1.614	0.1066	349	0.771	0.4406
			T	0.215	204:239	366	−1.614	0.1066	95	−2.302	**0.0214**
rs12154597	7:24785882	*GSDME*	C	0.949	68:49:00	114	2.008	**0.0446**	114	2.168	**0.0301**
			G	0.051	49:68	114	−2.008	**0.0446**	6	–	–
rs2237318	7:24769278	*GSDME*	C	0.173	202:197	357	−0.350	0.7267	59	−0.433	0.6650
			T	0.827	197:202	357	0.350	0.7267	342	0.220	0.8260
rs12540919	7:24756951	*GSDME*	C	0.853	163:129	252	2.045	**0.0409**	248	1.719	0.0857
			T	0.147	129:163	252	−2.045	**0.0409**	45	−1.442	0.1493
rs2299098	7:24756377	*GSDME*	C	0.308	269:287	439	−0.762	0.4461	162	−0.043	0.9653
			G	0.692	287:269	439	0.762	0.4461	396	0.914	0.3605
rs17149943	7:24749199	*GSDME*	G	0.848	147:132	248	0.898	0.3692	239	0.690	0.4899
			T	0.152	132:147	248	−0.898	0.3692	40	−0.792	0.4281
rs2240005	7:24742553	*GSDME*	A	0.213	185:195	317	−0.512	0.6089	81	−0.311	0.7560
			G	0.787	195:185	317	0.512	0.6089	301	0.444	0.6567
rs2257061	7:24738372	*GSDME*	C	0.802	221:201	371	1.116	0.2646	350	1.363	0.1729
			T	0.198	201:221	371	−1.116	0.2646	75	0.255	0.7987

Abbreviations: SNP, single nucleotide polymorphism; Position referenced the NCBI human reference genome GRCh37/hg19; AFreq, allele frequency; Fam, number of informative families; S, test statistics for the observed number of transmitted alleles; E(S), the expected value of S under the null hypothesis (i.e., no linkage and no association).

[a] The ratio of transmission to untransmission (T:U) for each selected SNP was calculated by the Haploview version 4.2.

[b] P value with bold character means nominally associated with autism ($P < 0.05$).

nominally positive SNPs. A GWAS on six psychiatric disorders found that rs12265655 in *SORCS3* was a significant genome-wide positive locus [18]. Another study found that rs3896224 in *SORCS3* was associated with intelligence [28]. A few studies showed that some SNPs in *SORCS3* are associated with major depressive disorder, bipolar depression disorder, and Alzheimer's disease [24–27]. The *SORCS3* region, located at 10q25.1, was specifically shared by the three adult-onset disorders (schizophrenia, bipolar disorder, and major depressive disorder), two childhood psychiatric disorders (attention deficit hyperactivity disorder, and autism spectrum disorder) and shared by all the above five disorders; this region has also been reported to contain copy number variants (CNVs) associated with ASD [54]. A study using whole-exome sequencing and autozygome analysis found a homozygous missense variant in *SORCS3* (c.3110C > G) on two brothers with neurological phenotypes including intellectual disability, global developmental delay, and delayed myelination [55]. In addition, a study found a pair of adjacent de novo copy number variants (sizes 242 Kb and 318 Kb) in 10q25.1 duplicated regions overlapping the *SORCS3* and *SORCS1* genes in an ADHD proband [56]. This study showed that a nearby SNP and 2 SNPs in *GSDME* were associated with autism. Several studies suggested that some SNPs in *GSDME* were associated with schizophrenia, bipolar depression disorder, major depressive disorder, educational attainment and math ability [40–44,57]. The *GSDME* (*DFNA5*) region was shared by the three adult-onset disorders (schizophrenia, bipolar disorder, and major depressive disorder) and shared by five dioders (the above three disorders, ADHD and ASD); this region has also been reported with CNVs associated with ASD [54]. Another study found about 4.36 Mb heterozygous deletion at 7p15.3-p15.1, including *GSDME* gene deletion, in a child with developmental delay [38]. In addition, some SNPs in the *SORCS3* and *GSDME* regions are eQTLs in human tissues and affect the expression of *SORCS3* and *GSDME* [54].

Several studies suggested the involvement of *SORCS3* in the pathogenesis of autism and other psychiatric disorders. Wu et al. used knowledge-based algorithms to show that *SORCS3* correlates with five psychiatric disorders, including ASD, schizophrenia, ADHD, bipolar disorder and depressive disorder, through eight proteins (NGF, APP, DLG4, PICK1, INS, BDNF, AGRP and NTRK2) and a small molecule of glutamate [23]. Other studies suggested that *SORCS3* is bound with nerve growth factor on the plasma membrane and plays an important role in the postsynaptic protein network [20,21]. Another study found altered synaptic plasticity, impaired learning and fear memory in SORCS3-deficient mice [22]. These studies suggested that *SORCS3* might be a susceptibility gene for ASD and participated in the pathogenesis of autism.

However, no association was found between other ASD-related positive SNPs and autism in the Han Chinese population. The results of this study were not completely consistent with the findings of GWAS in the European population, which may be due to the following factors: first, the positive loci suggested in previous studies were not exactly pathogenic, implying that the variants in strong linkage disequilibrium with the positive SNPs might be the exact pathogenic loci; second, different ethnic genetic backgrounds should be considered that the allele frequencies of some SNPs were quite different in European and Han Chinese populations; third ASD has high genetic heterogeneity. Most foreign studies recruited patients with ASD, whereas, in this study, only patients with typical autism were selected to reduce heterogeneity.

This study had several limitations. First, previous studies showed that the copy number variants of *SORCS3* and *GSDME* and the mutations in *SORCS3* were associated with mental disorders. Thus, an association between other genetic variants of these two genes and autism should be further investigated. Second, autism is a complex polygenic disorder with high heterogeneity. Future studies should evaluate the intelligence, disease severity, and comorbidities in autism to investigate the association between autism-related SNPs in this study and autism phenotypes. Third, two autism-positive loci in the Han Chinese population were located in functional regions, while their function needs further investigation. Rs3750261, located in the 3′-UTR of *SORCS3,* was a binding target of hsa-miR-5197-5p. The C allele of rs3750261 might promote the binding of *SORCS3* and hsa-miR-5197-5p, while the T allele of rs3750261 did not promote the binding of mature miRNA to *SORCS3* [58]. Whether this variation affects the expression and function of *SORCS3* still needs further investigation. Rs12540919 (C.619 gG> A, Val207Met), located in the exon of *GSDME,* is a missense variant. The impact of this SNP and the activity of *GSDME* also needs exploration. Fourth, how these SNPs and genes are involved in the pathology of autism requires further integration of multi-omics data, such as transcriptomics, proteomics and epigenetics, to further elucidate the specific pathogenic mechanisms of these autism susceptibility SNPs or genes.

In summary, we found that rs1484144 in *NAA11* was significantly associated with autism in the Han Chinese population, and *NAA11* was a susceptibility gene for autism. In addition, rs9787523 and rs3750261 in *SORCS3* and rs12154597, rs12540919, and rs79879286 near *GSDME* were associated with autism; these two genes might be susceptibility genes for autism. The function and possible pathogenic mechanisms of these genes need further studies.

Ethics statement

The ethics committee of Peking University Sixth Hospital, China, approved this study (approval number: 2021-2-23-7). The ethics committee approving these experiments included the following authors: Hongqiang Sun, Hongyan Zhang, Lin Lu, Yufeng Wang, Jing Liu, Weihua Yue, Guizhong Yao, Huali Wang, Xueqin Wang, Qingjiu Cao, Xuehua Liu, Yali Cong, Jian Yang, Li Xu, and Yiman Ye.

Before beginning the study, the investigators informed the parents and guardians of the purpose, content, principles of participation, the risks of blood sampling and the benefits of participating in this study. Written informed consents was obtained from all the children's parents or guardians.

Data availability statement

Data associated with this study was not deposited into a publicly available repository and will be made available on request.

CRediT authorship contribution statement

Fen Lin: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jun Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Ziqi Wang:** Formal analysis, Data curation. **Tian Zhang:** Formal analysis, Data curation. **Tianlan Lu:** Formal analysis, Data curation. **Miaomiao Jiang:** Writing – review & editing, Formal analysis, Data curation. **Kang Yang:** Writing – review & editing, Formal analysis, Data curation. **Meixiang Jia:** Formal analysis, Data curation. **Dai Zhang:** Writing – review & editing, Funding acquisition, Conceptualization. **Lifang Wang:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

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