Polymorphisms in the *kinesin-like factor 1 B* gene and risk of epithelial ovarian cancer in Eastern Chinese women

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Abstract The *kinesin-like factor 1 B* (*KIF1B*) gene plays an important role in the process of apoptosis and the transformation and progression of malignant cells. Genetic variations in *KIF1B* may contribute to risk of epithelial ovarian cancer (EOC). In this study of 1,324 EOC patients and 1,386 cancer-free female controls, we investigated associations between two potentially functional single nucleotide polymorphisms in *KIF1B* and EOC risk by the conditional logistic regression analysis. General linear regression model was used to evaluate the correlation between the number of variant alleles and *KIF1B* mRNA expression levels. We found that the rs17401966 variant AG/GG genotypes were significantly associated with a decreased risk of EOC (adjusted odds ratio (OR)=0.81, 95 % confidence interval (CI)=0.68–0.97), compared with the AA genotype, but no associations were observed for rs1002076. Women who carried both rs17401966 AG/GG and rs1002076 AG/AA genotypes of *KIF1B* had a 0.82-fold decreased risk (adjusted 95 % CI=0.69–0.97), compared with others. Additionally, there was no evidence of possible interactions between about-mentioned co-variants. Further genotype-phenotype correlation analysis indicated that the number of rs17401966 variant G allele was significantly associated with *KIF1B* mRNA expression levels (*P* for GLM= 0.003 and 0.001 in all and Chinese subjects, respectively), with GG carriers having the lowest level of *KIF1B* mRNA expression. Taken together, the rs17401966 polymorphism likely regulates *KIF1B* mRNA expression and thus may be associated with EOC risk in Eastern Chinese women. Larger, independent studies are warranted to validate our findings.

Keywords *KIF1B* · Polymorphism · Ovarian cancer · Susceptibility

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Introduction

Ovarian cancer is the third most frequently diagnosed gynecologic cancer and the first leading cause of death from gynecologic malignancies, accounting for 3.7 % (225,500) of all new cancer cases and 4.2 % (140,200) of all cancer deaths among women in 2008 worldwide [1]. In China, the crude incidence and mortality of ovarian cancer in 2009 was 7.95/10^5 and 3.44/10^5, respectively [2], which seems much lower than other commonly diagnosed cancers, such as lung cancer. However, more than 90 % of these cases are epithelial ovarian cancer (EOC), of which 70 % are diagnosed with widespread intra-abdominal disease or distant metastases, partially leading

to poor prognosis [3]. The frequency of invasive and advanced EOC at diagnosis is mostly due to the lack of a sufficiently reliable screening test [4]. Despite improvements in surgical techniques and chemotherapeutic options, the 5-year survival for invasive EOC still remains at approximately 46 % [5].

Previous epidemiologic studies have demonstrated several risk factors of EOC, such as nulliparity, early menarche and late menopause, as well as a strong familial aggregation [6] with a wide inter-individual genetic variability in the susceptibility of EOC. Previously published genome-wide association studies (GWASs) also reported several single nucleotide polymorphisms (SNPs) that confer low-penetrance susceptibility to EOC [7–9]. Despite these successes in identifying genetic variations for ovarian cancer risk [10, 11], no EOC GWAS data has been reported for Chinese women. Moreover, the causal variants and/or the mechanisms underlying the risk or etiology have been determined for only few of these associations [12]. Recently, more investigations in potentially functional or causal SNPs have now been suggested across diseases.

The *kinesin-like factor 1 B* (*KIF1B*) gene, located at 1p36.2, has been explored extensively as a member of the kinesin 3 family genes that are responsible for the transport of organelles, vesicles, protein complexes, and RNAs to specific destinations [13]. *KIF1B* encodes a motor protein that transports mitochondria and synaptic vesicle precursors, through two alternatively spliced isoforms (i.e., KIF1Bα and KIF1Bβ) with distinct C-terminal cargo-binding domains [14]. KIF1Bα is one of microtubule-dependent molecular motors involved in important intracellular functions such as organelle transport and cell division [15]. KIF1Bβ might be a haplo-insufficient tumor suppressor by inducing apoptotic cell death, and its allelic loss is likely to be involved in the pathogenesis of neuroblastoma and other cancers [16]. Several studies have demonstrated that the aberrant expression of *KIF1B* contributes to tumorigenesis by regulating cell division [17]. Further reports showed that *KIF1B* strongly correlated with lymph nodes metastasis and clinical stage in gastric cancer, indicating *KIF1B* might involve in the aggressiveness of human cancers [18]. *KIF1Bβ* downregulation in advanced human cancers and its inhibitory effect on tumor cells in vivo and in vitro supports a tumor suppressive and proapoptotic function of KIF1B [19].

Few previous investigations have reported that somatic and germline loss-of-function mutations of *KIF1B* were significantly associated with the development of many cancers [19], such as neural tumors [17] and multiple sclerosis [20]. A GWAS firstly identified *KIF1B* polymorphisms to be significantly associated with the risk of hepatocellular carcinoma (HCC) [21], but several subsequent studies did not find any associations between *KIF1B* polymorphisms and HCC risk [22–24]. Nevertheless, two recent meta-analysis studies summarized all published association data and found that the *KIF1B*-rs17401966 G allele significantly reduced the risk of HCC [25, 26], which indicating a potentially important effect of *KIF1B* SNPs on the etiology of human cancers, such as ovarian cancer.

In light of the critical role of the *KIF1B* gene in maintaining proper cellular functions and inducing the process of apoptosis, together with the identification of functionally impairing *KIF1B* genetic variations in many advanced tumors, we hypothesized that *KIF1B* SNPs could affect the development of ovarian cancer. To date, no investigations were reported for the role of potentially functional SNPs in *KIF1B* and ovarian cancer susceptibility. Therefore, to test the hypothesis that potentially functional or causal SNPs in *KIF1B* are associated with EOC risk, we conducted a large, single institutional case-control study by genotyping two potentially functional SNPs in Eastern Chinese women.

Materials and methods

Study subjects

This study was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (FUSCC) and that of Jiangsu Cancer Hospital (JCH). A written informed consent was obtained from all recruited individuals. The study population consisted of 1,324 EOC patients and 1,386 cancer-free female controls. Out of the 1,324 EOC patients, 1,165 cases were consecutively recruited between March 2009 and August 2012 from FUSCC, and the other 159 cases were consecutively recruited between March 2012 and August 2012 at JCH. All tumors were histopathologically confirmed independently as primary epithelial ovarian carcinoma, mostly serous, endometrioid, and clear cell, by two gynecologic pathologists as routine diagnosis at FUSCC or at JCH. The controls were enrolled from healthy women who had come to the Outpatient Department of Breast Surgery at FUSCC for breast cancer screening, with the selection criteria of no individual history of cancer, as well as frequency-matched age (±5 years) and residential areas to the EOC cases. All subjects were unrelated ethnic Han Chinese and residents in the Eastern China. Before an in-person interview, all potential subjects were asked for their willingness to participate in research studies, and their demographic and risk-factor information was collected after their written informed consent was obtained. For the cases, each participant also signed a written informed consent for use of the leftover blood samples after the diagnostic tests (collected before the initiation of treatment for the cases by Tissue Bank of FUSCC and by JCH) for DNA extraction. An approximate response rate of 95 % and 90 % was for the cases and controls, respectively. Because most Chinese women are non-smokers and non-drinkers, our study populations were

restricted to women who did not smoke cigarettes or drink alcohol. For the EOC patients, the detailed clinico-pathologic information was extracted from the patients' electronic database, including the FIGO stage (International Federation of Gynecology and Obstetrics, 2009), tumor histopathology, cell differentiation, pelvic lymph node (LN) metastasis, and the expression of estrogen receptor (ER) and progesterone receptor (PR).

SNP selection and genotyping

We selected SNPs by searching the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP) and the International HapMap Project database (http://hapmap.ncbi.nlm.nih.gov/), based on the following criteria: (1) the minor allele frequency reported in HapMap was at least 5 % in Chinese Han, Beijing populations, (2) with low linkage disequilibrium by using an r^2 threshold of <0.8 for each other, and (3) predicted to be a potentially functional SNP by the SNP function prediction platform (http://snpinfo.niehs.nih.gov/snpfunc.htm), which may affect the activity of transcription factor binding sites or microRNA binding sites. As a result, two SNPs were selected: rs17401966A>G and rs1002076A>G. The former one located in the intron region may affect the transcription factor binding site activity, and the latter one located in the 3′-untranslated region was predicted to be the microRNA binding site. Genomic DNA extraction and genotyping were conducted as described previously [27]. The discrepancy rate in all positive controls (i.e., duplicated samples, overlapping samples from previous studies, and samples randomly selected to be sequenced) was less than 0.1 %.

Genotype and mRNA expression data of *KIF1B* from the HapMap database

The data on rs17401966 genotypes and *KIF1B* mRNA expression levels were both available for 270 HapMap individuals, including 45 Chinese subjects, by the SNPexp online tool (http://app3.titan.uio.no/biotools/help.php?app=snpexp) [28]. We used Student's *t* test and analysis of variance test to compare the differences in the relative mRNA expression levels among different genotype groups, and the general linear regression model (GLM)-trend test was performed to evaluate the correlation between the number of rs17401966 variant alleles and *KIF1B* mRNA expression levels.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was tested by χ^2 test for each SNP. We performed the Pearson's χ^2 test for the differences in selected variables between cases and controls. The strength of association between *KIF1B* genotypes and EOC risk was estimated by computing odds ratios (ORs) and their 95 % confidence intervals (CIs) from both univariate and multivariate logistic regression models. We also evaluated the associations in subgroup and combination effect analyses. The PROC HAPLOTYPE procedure in SAS software was applied to infer haplotype frequencies between these two SNPs. All statistics were performed by SAS software 9.1 version (SAS Institute, Cary, NC).

Results

Population characteristics

As shown in Table 1, the 1,324 EOC cases and 1,386 cancer-free female controls were matched by age (±5 years) with the mean age of 54.1 and 54.0 years, respectively (P=0.731). However, compared with the controls, the cases were more likely to be post-menopausal, thinner, and younger age at menophania (P<0.0001 for all). Therefore, age at menophania, menopausal status, and body mass index (BMI) were adjusted for any residual confounding effect in subsequent multivariate logistic regression analyses.

Associations of *KIF1B* SNPs with EOC risk

The genotype frequencies of the rs17401966 and rs1002076 SNPs and their associations with EOC risk are summarized in Table 2. All observed genotype distributions among the 1,386 controls were in agreement with HWE (P=0.163 and 0.298 for rs17401966 and rs1002076, respectively). Compared with the AA genotype, the rs17401966 AG/GG genotypes were significantly associated with a decreased risk of EOC (dominant genetic model, adjusted OR=0.81, 95 % CI=0.68–0.97, P=0.020), indicating an inverse association of rs17401966 G allele with EOC risk. However, this association was not observed for rs1002076 nor for the haplotype analysis of these two SNPs (Table 3). When combining these two SNPs, we found that women who carried both rs17401966 AG/GG and rs1002076 AG/AA genotypes had a 0.82-fold decreased risk (adjusted 95 % CI=0.69–0.97, P=0.012), compared with others (Table 2).

In stratification analyses, under a dominant genetic model, we found that the significantly decreased risk of EOC associated with rs17401966 AG/GG genotypes was more evident in women at age between 48 to 60 years (P=0.020), those with older age at menophania (>15.5 years, P=0.027), and thinner women (P=0.016), as well as in subgroups of advanced FIGO stage, high-grade serous EOC, negative LN metastasis, and positive expression of ER and PR (Table 4). Meanwhile, we observed a significant association between rs1002076 and EOC risk in patients with advanced FIGO stage and those with positive expression of PR. However, homogeneity tests

Table 1 Distributions of selected variables in epithelial ovarian cancer cases and cancer-free controls

Variables	Cases N (%)	Controls N (%)	P value[a]
All subjects	1,324 (100)	1,386 (100)	
Age, years (mean±SD)	54.1±10.6	54.0±10.0	0.731
≤48	393 (29.7)	426 (30.7)	
49–60	583 (44.0)	590 (42.6)	
>60	348 (26.3)	370 (26.7)	
Age at menophania, years (mean±SD)	15.2±1.8	15.8±1.8	<0.0001
≤15.5	799 (60.9)	526 (43.2)	
>15.5	514 (39.2)	693 (56.9)	
Missing	11	170	
Menopausal status			<0.0001
Pre-menopausal	435 (33.5)	746 (53.9)	
Post-menopausal	865 (66.5)	638 (46.1)	
Missing	24	2	
BMI[b], kg/m²			<0.0001
<25	850 (74.1)	912 (66.0)	
≥25	297 (25.9)	470 (34.0)	
Missing	178	4	
FIGO stage			
I	44 (5.5)		
II	66 (8.2)		
III	608 (75.7)		
IV	85 (10.6)		
Missing	521		
Histopathology			
High-grade serous	878 (66.5)		
Low-grade serous	132 (10.0)		
Endometrioid	78 (5.9)		
Clear cell	71 (5.4)		
Mucinous	55 (4.2)		
Unclassifiable	107 (8.1)		
Missing	3		
Differentiation			
High grade	931 (81.7)		
Moderate grade	187 (16.4)		
Low grade	22 (1.9)		
Missing	185		
Pelvic LN			
Negative	364 (56.5)		
Positive	280 (43.5)		
Missing	681		
ER expression			
Negative	250 (29.7)		
Positive	591 (70.3)		
Missing	485		
PR expression			
Negative	535 (62.8)		
Positive	317 (37.2)		
Missing	473		

FIGO International Federation of Gynecology and Obstetrics, *LN* lymph node, *ER* estrogen receptor, *PR* progesterone receptor

[a] Two-sided χ^2 test for distributions between cases and controls

[b] According to the current WHO recommendations

indicated that there were no differences in risk estimates between subgroups of the strata, suggesting no evidence of possible interaction. Additionally, there were no multiplicative two-factor interactions between about-mentioned co-variants (data not shown).

Association between rs17401966 variants and expression levels of the *KIF1B* mRNA

We evaluated the available *KIF1B* mRNA expression data from 270 HapMap individuals for their association with variant genotypes of *KIF1B* by using the SNPexp online database also available to us. There were 173 AA, 82 AG, and 15 GG carriers for the rs17401966 SNP, of which 27 AA, 13 AG, and five GG carriers were Chinese. The number of rs17401966 variant G allele was significantly associated with *KIF1B* mRNA expression levels either in all subjects or in Chinese populations (*P* for GLM=0.003 and 0.001, respectively; Fig. 1), with GG carriers having the lowest level of *KIF1B* mRNA expression. These findings indicated that rs17401966 A→G variation may function by down-regulating *KIF1B* expression, thus leading to the decreased risk of EOC.

Discussion

In the current relatively large case-control study, we found that rs17401966 variant AG/GG genotypes were significantly associated with a decreased risk of EOC, compared with the AA genotype, and that the rs17401966 A→G variation may function by down-regulating *KIF1B* expression, thus leading to the decreased EOC risk.

To the best of our knowledge, this is the first study that has identified *KIF1B*-rs17401966 G allele to be associated with a decreased EOC risk. *KIF1B* was firstly reported as a 10,585-base-pair kinesin 3 family cDNA clone, mapped to chromosome 1p36.22 [29]. This chromosomal region is frequently deleted or inactivated in several malignancies, including those of epithelial and neural origins [30]. Because of such commonly initiated events, loss of a tumor suppressor gene mapped to this region is critical in a broad range of human cancers [30]. Like all kinesins, KIF1B is a microtubule-dependent and end-directed monomeric motor protein, which containing a kinesin motor domain and a forkhead-associated domain, and functions in facilitating the transport of organelles, protein complexes, and RNA [29]. However, its underlying mechanisms causing tumorigenesis are still unclear, let alone for ovarian carcinogenesis. Lately, several investigators have revealed another kinesin family member gene (i.e., *KIF14*) as the potential oncogene that promotes a tumorigenic phenotype, considered an independent prognostic marker and potential therapeutic target for ovarian cancer [31]. These lead

Table 2 Associations of *KIF1B* genotypes with the risk of epithelial ovarian cancer

Variants Genotypes	Cases (N=1,324)	Controls (N=1,386)	P value[a]	Adjusted OR (95 % CI)[a]	P value[b]
KIF1B-rs17401966		HWE=0.163			
AA	696 (52.6)	687 (49.6)	0.277	1.00	
AG	500 (37.8)	562 (40.6)		*0.76 (0.63–0.92)*	*0.004*
GG	128 (9.7)	137 (9.9)		1.05 (0.78–1.42)	0.739
Additive model				0.92 (0.81–1.05)	0.217
Dominant model				*0.81 (0.68–0.97)*	*0.020*
Recessive model				1.18 (0.89–1.58)	0.257
KIF1B-rs1002076		HWE=0.298			
GG	508 (38.4)	525 (37.9)	0.963	1.00	
AG	606 (45.8)	641 (46.3)		0.84 (0.70–1.02)	0.076
AA	210 (15.9)	220 (15.9)		0.99 (0.77–1.28)	0.957
Additive model				0.96 (0.85–1.09)	0.549
Dominant model				0.88 (0.74–1.05)	0.157
Recessive model				1.09 (0.86–1.38)	0.472
Combination effects by rs17401966 AG/GG and rs1002076 AG/AA genotypes					
0–1	699 (52.8)	691 (49.9)	0.126	1.00	
2	625 (47.2)	695 (50.1)		*0.82 (0.69–0.97)*	*0.021*

OR odds ratio, *CI* confidence interval

[a] χ^2 test for genotype distributions between cases and controls

[b] Adjusted for age, age at menophania, menopausal status and BMI in logistic regress models. The result were in italic, if $P<0.05$

to a speculation that other kinesins, including KIF1B, may function in ovarian carcinogenesis and progression.

Recently, a GWAS study reported that the *KIF1B*-rs17401966 G allele was significantly associated with the decreased risk of HCC [21]. Since then, considerable efforts have been devoted to validating this association, but the underlying mechanisms remain controversial [22–24]. Also, even in different Chinese subgroups, the results were of diversity, with some data showing inverse associations and with others showing no associations [26]. It may be partly ascribed to ethnicities difference, small sample sizes, various levels of data quality, false-positive results, and publication bias. To date, no studies have been reported on its association with ovarian cancer risk. Our data provide further support for the

inverse association of rs17401966 AG/GG genotypes with ovarian cancer risk in an Eastern Chinese population. Although no definite evidence of possible interaction between about-mentioned co-variants, we did observe that a decreased trend of EOC risk for rs17401966 AG/GG carriers was more evident in thinner and older women of age at menophania, as well as in subgroups of advanced FIGO stage, high-grade serous EOC, negative LN metastasis, and positive expression of ER and PR. Therefore, prospective, larger, independent studies should be performed to unravel the possible interactions.

The rs17401966 SNP is located at the intron region of *KIF1B* and predicted to be at a transcription factor binding site that can modulate gene expression; it is reported to

Table 3 Haplotype analysis for genotypes of *KIF1B* and epithelial ovarian cancer risk

KIF1B haplotypes	Cases (N=2,648)		Controls (N=2,772)		Adjusted OR[a] (95 % CI)	P value[a]
	N	%	N	%		
A rs17401966 G rs1002076	1616	61.0	1,686	60.8	1.00	
A rs17401966 A rs1002076	276	10.4	250	9.0	1.08 (0.88–1.33)	0.466
G rs17401966 A rs1002076	750	28.3	831	30.0	0.92 (0.81–1.06)	0.264
G rs17401966 G rs1002076	6	0.2	5	0.2	1.16 (0.34–3.94)	0.807

CI confidence interval, *OR* odds ratio

[a] Obtained in logistic regression models with adjustment for age, age at menophania, menopausal status and BMI. The results were in italic, if $P<0.05$

Table 4 Stratification analysis for associations between *KIF1B* genotypes and epithelial ovarian cancer risk in Eastern Chinese women

Variables	*KIF1B*-rs17401966 (cases/controls)		Adjusted OR[a] (95 % CI)	P value[a]	P[hom]	*KIF1B*-rs1002076 (cases/controls)		Adjusted OR[a] (95 % CI)	P value[a]	P[hom]
	AA	AG/GG				GG	AG/AA			
Age, years										
≤48	198/213	213/213	0.76 (0.55–1.06)	0.104	0.238	144/158	249/268	0.78 (0.55–1.10)	0.156	0.938
49–60	312/276	271/314	0.73 (0.56–0.95)	0.020		220/216	363/374	0.87 (0.66–1.15)	0.339	
>60	186/198	162/172	0.99 (0.72–1.36)	0.950		144/151	204/219	0.96 (0.70–1.32)	0.808	
Age at menophania, years										
≤15.5	422/262	377/264	0.87 (0.68–1.11)	0.261	0.595	302/194	497/332	0.95 (0.74–1.22)	0.691	0.609
>15.5	272/331	242/362	0.75 (0.59–0.97)	0.027		205/256	309/437	0.81 (0.62–1.04)	0.098	
Menopausal status										
Pre-menopausal	223/364	212/382	0.77 (0.58–1.03)	0.076	0.859	164/281	271/465	0.85 (0.64–1.14)	0.276	0.838
Post-menopausal	464/322	401/316	0.84 (0.68–1.05)	0.127		338/244	527/394	0.91 (0.72–1.14)	0.403	
BMI[b], kg/m²										
<25	459/446	391/466	0.78 (0.63–0.95)	0.016	0.565	337/342	513/570	0.85 (0.69–1.05)	0.125	0.511
≥25	158/238	139/232	0.91 (0.66–1.25)	0.553		113/182	184/288	0.95 (0.69–1.33)	0.774	
FIGO stage										
I–II	52/687	58/699	1.04 (0.69–1.58)	0.852	0.167	37/525	73/861	1.17 (0.75–1.81)	0.497	0.121
III–IV	380/687	313/699	0.73 (0.59–0.89)	0.003		291/525	402/861	0.76 (0.61–0.94)	0.010	
Histopathology										
High-grade Serous	466/687	412/699	0.82 (0.68–0.99)	0.040	0.643	350/525	528/861	0.85 (0.70–1.04)	0.109	0.161
Others	228/687	215/699	0.80 (0.62–1.03)	0.087		156/525	287/861	0.97 (0.74–1.26)	0.813	
Differentiation										
High grade	487/687	444/699	0.83 (0.69–1.00)	0.052	0.971	359/525	572/861	0.88 (0.72–1.06)	0.176	0.518
Moderate-low grade	109/687	100/699	0.79 (0.57–1.11)	0.172		75/525	134/861	0.95 (0.68–1.34)	0.777	
Pelvic LN										
Negative	205/687	159/699	0.66 (0.50–0.87)	0.003	0.110	149/525	215/861	0.81 (0.62–1.07)	0.136	0.120
Positive	138/687	142/699	0.90 (0.67–1.21)	0.497		96/525	184/861	1.01 (0.75–1.38)	0.939	
ER expression										
Negative	127/687	123/699	0.86 (0.64–1.15)	0.303	0.282	95/525	155/861	0.89 (0.66–1.21)	0.461	0.477
Positive	327/687	264/699	0.75 (0.61–0.93)	0.009		242/525	349/861	0.81 (0.65–1.00)	0.053	
PR expression										
Negative	278/687	257/699	0.86 (0.69–1.07)	0.169	0.229	200/525	335/861	0.95 (0.75–1.19)	0.629	0.119
Positive	180/687	137/699	0.68 (0.52–0.88)	0.004		138/525	179/861	0.71 (0.55–0.93)	0.012	

BMI body mass index, *FIGO* International Federation of Gynecology and Obstetrics, *LN* Lymph Node, *ER* estrogen receptor, *PR* progesterone receptor

[a] Obtained in logistic regression models with adjustment for age, age at menophania, menopausal status, and BMI

[b] According to the current WHO recommendations; [hom] Homogeneity test. The results were in italic, if P<0.05

Fig. 1 Differential expression of *KIF1B* mRNA by different rs17401966 genotypes obtained from HapMap. The rs17401966 genotypes were significantly associated with *KIF1B* mRNA expression levels **a** in all subjects, and **b** in Chinese populations (*P* for GLM=0.003 and 0.001, respectively), with GG carriers having the lowest level of *KIF1B* mRNA expression
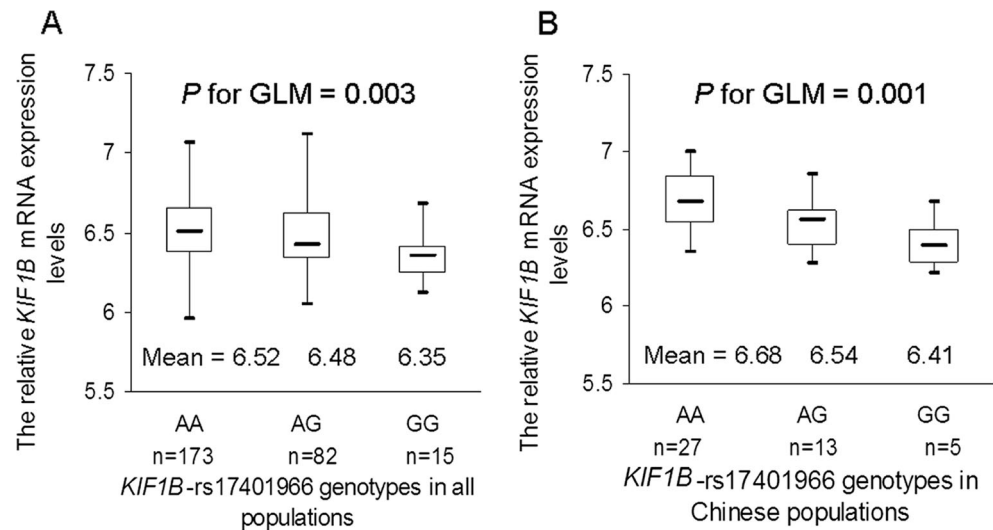
participate in gene regulatory networks [32] and may contribute to the development of human cancers [33]. Previous data indicated that some kind of spacer sequences in the intron regions might contain some unidentified functional elements, such as transcription factor binding sites for unknown or uncharacterized transcription factors or perhaps other structural features not yet understood [34]. In the present study, we used publically available online data on *KIF1B* genotypes and mRNA expression levels for the genotype-phenotype correlation analysis. It appeared that the number of rs17401966 variant G allele was significantly associated with decreased levels of *KIF1B* mRNA expression, which may lead to a decreased EOC risk in that population. This finding seems controversial because in most cases, *KIF1B* has been identified as a tumor suppressor gene, especially in neurologic tumors. For example, Schlisio et al. reported that KIF1Bα may suppress cancer growth by regulating mitochondria transportation, while KIF1Bβ could induce apoptosis and inhibit malignant transformation and progression by binding to the downstream of EglN3 [35]. However, this opinion is far from comprehensive. Chen and Yang et al. pointed out that no significant difference was observed in KIF1Bα or KIF1Bβ expression between early and advanced stage neuroblastoma by quantitative real-time PCR, suggesting that both of KIF1Bα and KIF1Bβ may not be candidate tumor suppressor [15, 36]. On the other hand, several studies showed that *KIF1B* mutation and dysfunction were common in cancers, and mutant *KIF1B* may play different roles in maintaining intercellular functions [17]. It is likely that inactive of *KIF1B* or tissue-specific gene dosage requirement may exist in the process of malignant development and progression, which may explain why rs17401966 G allele was associated with both decreased EOC risk and decreased *KIF1B* mRNA expression in the current study. Another possible explanation is that this effect may be ascribed to

unknown functional elements that may lead to the mRNA expression levels of *KIF1B* decrease.

Of note, whether or not the rs17401966 SNP is a functional one, or just a tagging one, needs to be determined by additional functional experiments, such as chromatin immunoprecipitation and perhaps direct sequencing in cancer cell lines or xenograft [32], which may reveal the mechanisms underlying the observed association with EOC risk. Moreover, cancer is recognized as a complex and multifactorial disease, and single nucleotide alteration is insufficient for the prediction of the overall risk [37]. Future studies include more genes and more SNPs, especially functional ones were needed to clarify the exact effect of each genetic factor on the development of ovarian cancer. Several other limitations of our study need to be addressed. Firstly, the hospital-based case-control study design may lead to selection bias and information bias, which may be minimized by frequency-matching for cases and controls and by adjustment for potential confounding factors in final multivariate analyses. Secondly, because of the retrospective nature of the original study design, we did not have enough information on other risk factors that could be potential confounders. Besides, although bioinformatics-based approaches, such as a number of genetic models and stratified analyses, were carried out to assess the statistical associations between *KIF1B* polymorphisms and EOC risk, further deep functional experiments are needed to clarify the underlying mechanisms.

In summary, in the current case-control study of 1,324 consecutive EOC patients and 1,386 cancer-free female controls, we found the *KIF1B*-rs17401966 SNP to be associated with EOC risk in Eastern Chinese women, and this SNP may function by regulating *KIF1B* mRNA expression. However, well-designed larger, prospective studies are warranted to validate our findings.

Conflicts of interest None

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