Cancer Management and Research

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ORIGINAL RESEARCH

Relationship between *IGF2BP2* and *IGFBP3* polymorphisms and susceptibility to non-small-cell lung cancer: a case–control study in Eastern Chinese Han population

This article was published in the following Dove Press journal:
Cancer Management and Research

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Background: *IGF2BP2* and *IGFBP3* polymorphisms may be associated with cancer risk.
Methods: With an aim to determine the association of variations in *IGF2BP2* and *IGFBP3* genes with risk of non-small-cell lung cancer (NSCLC), *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A polymorphisms were selected and genotyped in 521 NSCLC patients and 1,030 controls.
Results: We found that there was no difference in *IGF2BP2* and *IGFBP3* genotype distribution among the NSCLC patients and controls. The stratified analyses suggested that *IGF2BP2* rs1470579 A>C polymorphism decreased the risk of NSCLC in some subgroups (female subgroup: CC vs AA: adjusted P=0.032 and CC vs AC/AA: adjusted P=0.028; <60 years subgroup: CC vs AA: adjusted P=0.012 and CC vs AC/AA: adjusted P=0.013; and never drinking subgroup: CC vs AA: adjusted P=0.046 and CC vs AC/AA: adjusted P=0.031). The stratified analyses also found that *IGF2BP2* rs4402960 G>T polymorphism decreased the risk of NSCLC in some subgroups (female subgroup: TT vs GG: adjusted P=0.031 and TT vs GT/GG: adjusted P=0.026; <60 subgroup: TT vs GG: adjusted P=0.037 and TT vs GT/GG: adjusted P=0.038; and never drinking subgroup: TT vs GT/GG: adjusted P=0.046). Haplotype analysis indicated $A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}A_{rs6953668}$ haplotype decreased susceptibility of NSCLC (P=0.007).
Conclusion: Our study suggests that *IGF2BP2* rs1470579 A>C, rs4402960 G>T single-nucleotide polymorphisms are candidates for decreased susceptibility to NSCLC among female, <60 years, and never drinking subgroups. In the future, more case–control studies with functional analysis are needed to confirm these preliminary findings.

Keywords: IGFBP3, IGF2BP2, polymorphism, haplotype, risk, NSCLC

Introduction

Lung cancer (LC) is the most common malignancy worldwide. It was reported that 1.8 million new LC patients were diagnosed in 2012, which accounted for about 13% of total cancer cases.[1] Because of aging, air pollution, smoking, and exposure to occupational and/or environmental carcinogens, LC constitutes a burden all over the world. Some risk factors mentioned above might contribute to the development of LC; however, other susceptibility factors could also increase the incidence of LC. Nowadays, genetic variants were supported to influence the risk of LC, especially non-small-cell lung cancer (NSCLC), which was a common subtype of LC.

In humans, insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) is a protein which is encoded by *IGF2BP2* gene.[2,3] IGF2BP2 regulates insulin-like growth

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http://dx.doi.org/10.2147/CMAR.S169222

factor 2 (IGF2) translation by binding to the 5′ UTR of IGF2 mRNA.[3] Gu et al reported that IGF2BP2 was overexpression in both ovarian cancer and ovarian low malignant potential tumor samples compared to either normal ovary or ovarian adenomas samples.[4] A previous study also found that IGF2BP2/IGF-1/IGF-1 receptor signaling pathways might involve in cancer-mediated endothelial recruitment, which was an important feature of metastatic cancer in the tumor microenvironment.[5] In addition, Liu et al found that an lncRNA (IGF2BP2-AS1) was associated with better overall survival in lung squamous cell carcinoma.[6] In view of these previous studies, we thought that IGF2BP2 might influence the development of LC.

IGF family involves IGF ligands, IGF receptors, and IGF-binding proteins (IGFBPs). IGF-1 is a potent mitogen and regulates mitogenesis and antiapoptosis.[7] IGFBP3, a major binding protein of IGF-1, interacts with IGF-1, regulates its biological activity, and may play important roles in antiproliferation and proapoptosis.[8] Papadimitrakopoulou et al reported that IGFBP3 downregulation is an early event during head and neck carcinogenesis.[9] Adenoviral IGFBP3 and farnesyltransferase inhibitor might decrease Akt expression and promote NSCLC cell apoptosis in vitro and in vivo.[10] Results of a previous study highlighted that IGFBP3 could mediate LC progression. In addition, overexpression of IGFBP3 might induce apoptosis of NSCLC cells and promote cisplatin response in vitro.[11]

Several case–control studies focused on the association of *IGF2BP2* and *IGFBP3* polymorphisms with risk to cancer. Results of previous studies indicated that *IGF2BP2* rs4402960 G>T single-nucleotide polymorphism (SNP) was associated with the development of breast cancer.[12] Terry et al found that *IGFBP3* rs2270628 variants increased IGF1 levels in plasma and was associated with the risk of ovarian cancer.[13] In addition, *IGFBP3* rs3110697 variants were significantly associated with IGFBP-3 levels in a multiethnic populations,[14] and *IGFBP3* rs3110697 AA genotypes increased the risk of death among Chinese postmenopausal women with breast cancer.[15] However, the relationship between *IGF2BP2* and *IGFBP3* polymorphisms and NSCLC risk was unclear. With an aim to determine the potential association of genetic variations in *IGF2BP2* and *IGFBP3* genes with risk of NSCLC in Eastern Chinese Han populations, *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A SNPs were selected and genotyped in 521 NSCLC patients and 1,030 cancer-free controls.

Materials and methods

Ethics statement

This case–control study conformed to the Helsinki declaration and was approved by the Institutional Review Board of Fujian Medical University. A written consent was obtained from each participant.

Subjects

In our study, a total of 521 sporadic NSCLC cases and 1,030 age- and gender-matched controls were enrolled. All participants were recruited from the Department of Thoracic Surgery in Affiliated Union Hospital of Fujian Medical University and Affiliated People's Hospital of Jiangsu University. All NSCLC patients (mean age at 59.76±10.71 years) were diagnosed by pathology. The corresponding information was retrieved from medical files (Table 1). The cancer-free controls were well-matched to NSCLC patients by age (mean age at 60.34±9.11 years) and sex (P=0.453). Individuals without any history of personal malignancy or autoimmune disorder were included as controls. Both NSCLC cases and controls

Table 1 Distribution of selected demographic variables and risk factors in NSCLC cases and controls

Variables	Overall cases (n=521)	Overall controls (n=1,030)	*P*-value[a]
	n (%)	n (%)	
Age (years)	59.76±10.71	60.34±9.11	0.268
Age (years)			0.843
<60	238 (45.68)	476 (46.21)	
≥60	283 (54.32)	554 (53.79)	
Sex			0.453
Male	287 (55.09)	588 (57.09)	
Female	234 (44.91)	442 (42.91)	
Smoking status			**<0.001**
Never	317 (60.84)	828 (80.39)	
Ever	204 (39.16)	202 (19.61)	
Alcohol use			**<0.001**
Never	444 (85.22)	949 (92.14)	
Ever	77 (14.78)	81 (7.86)	
BMI (kg/m^2)	23.00±3.03	23.84±3.06	**<0.001**
BMI (kg/m^2)			
<24	337 (64.68)	547 (53.11)	**<0.001**
≥24	184 (35.32)	483 (46.89)	
Lymph node status			
Positive	200 (38.39)		
Negative	314 (60.27)		
Unknown	7 (1.34)		
TNM stage			
I+II	315 (60.46)		
I+IV	206 (39.54)		
Type of NSCLC			
Adenocarcinoma	415 (79.65)		
Squamous cell carcinoma	85 (16.31)		
Others	21 (4.03)		

Notes: Bold values are statistically significant (P<0.05). [a]Two-sided chi-squared test and Student's *t*-test.

Abbreviations: BMI, body mass index; NSCLC, non-small-cell lung cancer; TNM, tumor-lymph node-metastasis.

were hereditarily unrelated and were from Eastern Chinese Han population. Each participant was informed about the study protocols and a written consent was obtained. A body mass index (BMI) ≥24 kg/m^2 was considered as the criterion of Chinese individuals with obesity and overweight.[16,17] The definitions of "ever smokers" and "ever drinkers" were described in our previous study.[18]

Selection of SNPs

To assess the relationship between *IGF2BP2* and *IGFBP3* SNPs and NSCLC risk, we selected polymorphisms in *IGF2BP2* and *IGFBP3* gene according to the publications, which were associated with the development of cancer.[12,13,19–21]

DNA extraction and genotyping

Using a universal Promega DNA kit (Promega Corporation, Fitchburg, WI, USA), genomic DNA was extracted from whole blood sample which was stored with EDTA-anticoagulation tube. *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T,[22] rs3110697 G>A and rs6953668 G>A genotypes were determined by a custom-by-design 48-Plex PCR (SNPscan™ kit; Genesky Biotechnologies Inc., Shanghai, China).[23] We used ABI 3730XL sequencer to obtain genotypes. The data were read out by GeneMapper 4.1 software (Thermo Fisher Scientific, Waltham, MA, USA). For quality control, 4% samples were randomly selected from 1,551 DNA samples and analyzed again. The genotypes of *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A and rs6953668 G>A polymorphisms were not changed.

Statistical analysis

Age and BMI are expressed as mean ± SD. Student's *t*-test was used to compare these continuous variables between NSCLC cases and cancer-free controls. The categorical variables (eg, *IGF2BP2* and *IGFBP3* genotypes, BMI, gender, age, tobacco use, and drinking status) were compared by using chi-squared test (χ^2) or Fisher's exact test. Whether the *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A and rs6953668 G>A genotypes in controls conformed to Hardy–Weinberg equilibrium (HWE) was determined by an Internet-based calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl).[24–30] A $P<0.05$ (two-tailed) was accepted as the criterion of statistical significance. The relationship between *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A and rs6953668 G>A polymorphisms with NSCLC susceptibility was assessed by crude/adjusted ORs and 95% CIs. Adjusted for gender, age, tobacco use, drinking status, and BMI, multivariate linear regression was carried out to evaluate the relationship of these SNPs with susceptibility to NSCLC. We used an online SHEsis software (http://analysis.bio-x.cn/myAnalysis.php)[31] to establish haplotypes of *IGF2BP2* and *IGFBP3* genes. We used SAS 9.4 software (windows version; SAS Institute Inc., Cary, NC, USA) to do all statistical analyses.

Results

Baseline characteristics

A total of 521 NSCLC cases were included in this study. The mean age of NSCLC cases was 59.76 years (SD: 10.71 years). Among them, 415 were adenocarcinoma (79.65%), 85 were squamous cell carcinoma (16.31%), and 21 were other subtype of NSCLC (4.03%). NSCLC patients included 315 cases with stage I/II and 206 with stage III/IV. Disease staging was determined according to American Joint Committee on Cancer criteria (version 7, 2010). We recruited 1,030 non-cancer controls, involving 588 males (57.09%) and 442 females (42.91%). Their mean ± SD age was 60.34±9.11 years. Characteristics of NSCLC cases and controls included in this study are listed in Table 1. The primary information for *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A SNPs was shown in Table 2. The successful ratio was >99.00% for each SNP. Minor allele frequency (MAF) of *IGF2BP2* and *IGFBP3* SNPs was similar to the data in Chinese database (Table 2). In controls, the genotype frequencies for *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A polymorphisms were in HWE (Table 2).

Association of *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A polymorphisms with NSCLC

Table 3 showed the frequencies of *IGF2BP2* and *IGFBP3* genotypes in different NSCLC subgroups and control group. Results of the single locus analyses were summarized in Table 4. We found that there was no difference in *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A genotype distribution among overall NSCLC patients and controls. In addition, similar findings were also identified among different NSCLC subtype and controls.

Table 2 Primary information for *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A polymorphisms

Genotyped SNPs	Chromosome	Chr Pos (NCBI Build 38)	MAF for Chinese in database	MAF in our controls (n=1,030)	*P*-value for HWE test in our controls	Genotyping method	Genotyping value (%)
IGF2BP2 rs1470579 A>C	3	185811292	0.27	0.25	0.001	SNPscan	99.94
IGF2BP2 rs4402960 G>T	3	185793899	0.26	0.25	0.001	SNPscan	99.94
IGFBP3 rs2270628 C>T	7	45909971	0.21	0.19	0.672	SNPscan	99.94
IGFBP3 rs3110697 G>A	7	45915430	0.23	0.26	0.102	SNPscan	99.94
IGFBP3 rs6953668 G>A	7	45916276	0.04	0.05	0.565	SNPscan	99.87

Abbreviations: MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium; SNP, single-nucleotide polymorphism.

Table 3 The frequencies of *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A and rs6953668 G>A polymorphisms in different NSCLC subgroups

Genotype	NSCLC cases (n=521)		Adenocarcinoma (n=415)		Non-adenocarcinoma (n=106)		Controls (n=1,030)	
	n	%	n	%	n	%	n	%
IGF2BP2 rs1470579 A>C								
AA	302	58.54	241	58.07	61	57.55	593	57.63
AC	187	35.89	148	35.66	39	36.79	350	34.01
CC	32	6.14	26	6.27	6	5.66	86	8.36
C allele	251	24.09	200	24.10	51	24.06	522	25.36
IGF2BP2 rs4402960 G>T								
GG	306	58.73	244	58.80	62	58.49	603	58.60
GT	185	35.51	146	35.18	39	36.79	344	33.43
TT	30	5.76	25	6.03	5	4.72	82	7.97
T allele	245	23.51	196	23.61	49	23.11	508	24.68
IGFBP3 rs2270628 C>T								
CC	334	64.11	273	65.78	61	57.55	670	65.11
CT	163	31.29	122	29.40	41	38.68	318	30.90
TT	24	4.61	20	4.82	4	3.77	41	3.98
T allele	211	20.25	162	19.52	49	23.11	400	19.44
IGFBP3 rs3110697 G>A								
GG	286	54.89	235	56.63	51	48.11	578	56.17
GA	190	36.47	142	34.22	48	45.28	373	36.25
AA	45	8.64	38	9.16	7	6.60	78	7.58
A allele	280	26.87	218	26.27	62	29.25	529	25.70
IGFBP3 rs6953668 G>A								
GG	466	89.44	375	90.36	91	85.85	920	89.49
GA	53	10.17	39	9.40	14	13.21	104	10.12
AA	2	0.38	1	0.24	1	0.94	4	0.39
A allele	57	5.47	41	4.94	16	7.55	112	5.45

Abbreviation: NSCLC, non-small-cell lung cancer.

Association of IGF2BP2 rs1470579 A>C, rs4402960 G>T and IGFBP3 rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A polymorphisms with NSCLC in a stratification analysis

As shown in Table 5, the stratified analyses suggested that *IGF2BP2* rs1470579 A>C polymorphism decreased the risk of NSCLC in some subgroups (female subgroup: CC vs AA: adjusted OR =0.46, 95% CI =0.23–0.94, *P*=0.032 and CC vs AC/AA: adjusted OR =0.46, 95% CI =0.23–0.92, *P*=0.028; <60 years subgroup: CC vs AA: adjusted OR =0.36, 95% CI =0.16–0.80, *P*=0.012 and CC vs AC/AA: adjusted OR =0.37, 95% CI =0.17–0.81, *P*=0.013; and never drinking subgroup: CC vs AA: adjusted OR =0.61, 95% CI =0.37–0.99, *P*=0.046 and CC vs AC/AA: adjusted OR =0.59, 95% CI =0.36–0.95, *P*=0.031).

Table 4 Logistic regression analyses of association of *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A polymorphisms with risk of NSCLC

Genotype	Overall NSCLC cases (n=521) vs controls (n=1,030)				Adenocarcinoma (n=415) vs controls (n=1,030)				Non-adenocarcinoma (n=106) vs controls (n=1,030)			
	Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value	Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value	Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value
IGF2BP2 rs1470579 A>C												
Additive model	1.05 (0.84–1.32)	0.666	1.03 (0.82–1.30)	0.800	1.04 (0.82–1.33)	0.739	1.03 (0.80–1.33)	0.805	1.09 (0.71–1.66)	0.705	1.04 (0.65–1.66)	0.859
Homozygote model	0.73 (0.48–1.12)	0.154	0.72 (0.46–1.12)	0.143	0.75 (0.47–1.19)	0.214	0.73 (0.46–1.18)	0.200	0.68 (0.29–1.62)	0.383	0.67 (0.26–1.70)	0.393
Dominant model	0.99 (0.80–1.22)	0.899	0.97 (0.78–1.21)	0.775	0.98 (0.78–1.24)	0.877	0.97 (0.77–1.23)	0.814	1.00 (0.67–1.50)	0.987	0.97 (0.62–1.52)	0.893
Recessive model	0.72 (0.47–1.09)	0.122	0.71 (0.46–1.10)	0.121	0.73 (0.47–1.15)	0.180	0.73 (0.46–1.15)	0.174	0.66 (0.28–1.54)	0.336	0.65 (0.26–1.64)	0.364
IGF2BP2 rs4402960 G>T												
Additive model	1.06 (0.85–1.33)	0.604	1.03 (0.82–1.30)	0.801	1.05 (0.82–1.34)	0.692	1.03 (0.80–1.33)	0.802	1.10 (0.72–1.68)	0.644	1.03 (0.65–1.65)	0.889
Homozygote model	0.72 (0.47–1.12)	0.147	0.72 (0.46–1.14)	0.162	0.76 (0.47–1.21)	0.243	0.75 (0.47–1.22)	0.251	0.59 (0.23–1.52)	0.278	0.60 (0.22–1.65)	0.324
Dominant model	1.00 (0.80–1.23)	0.960	0.97 (0.78–1.21)	0.797	0.99 (0.79–1.25)	0.946	0.98 (0.77–1.24)	0.857	1.01 (0.67–1.51)	0.983	0.96 (0.61–1.49)	0.840
Recessive model	0.71 (0.46–1.09)	0.114	0.71 (0.46–1.12)	0.139	0.74 (0.47–1.18)	0.203	0.75 (0.46–1.20)	0.222	0.57 (0.23–1.44)	0.237	0.59 (0.22–1.60)	0.303
IGFBP3 rs2270628 C>T												
Additive model	1.03 (0.82–1.30)	0.803	1.01 (0.79–1.28)	0.945	0.94 (0.73–1.21)	0.647	0.92 (0.71–1.19)	0.504	1.42 (0.93–2.15)	0.101	1.43 (0.90–2.27)	0.127
Homozygote model	1.18 (0.70–1.98)	0.542	1.13 (0.66–1.95)	0.648	1.20 (0.69–2.08)	0.520	1.19 (0.68–2.09)	0.550	1.07 (0.37–3.10)	0.896	1.11 (0.35–3.52)	0.857
Dominant model	1.05 (0.84–1.30)	0.695	1.02 (0.81–1.29)	0.852	0.97 (0.76–1.23)	0.809	0.95 (0.74–1.21)	0.658	1.38 (0.92–2.07)	0.123	1.40 (0.89–2.18)	0.145
Recessive model	1.16 (0.70–1.95)	0.564	1.13 (0.66–1.93)	0.654	1.22 (0.71–2.11)	0.476	1.22 (0.70–2.14)	0.485	0.95 (0.33–2.69)	0.916	0.97 (0.31–3.04)	0.963
IGFBP3 rs3110697 G>A												
Additive model	1.03 (0.82–1.29)	0.789	1.02 (0.80–1.28)	0.902	0.94 (0.73–1.20)	0.609	0.93 (0.72–1.19)	0.549	1.46 (0.97–2.21)	0.073	1.53 (0.97–2.43)	0.068
Homozygote model	1.17 (0.79–1.73)	0.439	1.18 (0.79–1.79)	0.420	1.20 (0.79–1.82)	0.390	1.21 (0.79–1.85)	0.388	1.02 (0.45–2.32)	0.965	0.89 (0.36–2.19)	0.805
Dominant model	1.05 (0.85–1.30)	0.632	1.04 (0.84–1.30)	0.712	0.98 (0.78–1.24)	0.875	0.97 (0.77–1.23)	0.820	1.38 (0.93–2.06)	0.113	1.41 (0.91–2.19)	0.129
Recessive model	1.15 (0.79–1.69)	0.467	1.18 (0.79–1.75)	0.426	1.23 (0.82–1.84)	0.319	1.24 (0.82–1.89)	0.306	0.86 (0.39–1.92)	0.716	0.74 (0.31–1.77)	0.501
IGFBP3 rs6953668 G>A												
Additive model	1.01 (0.71–1.43)	0.963	1.05 (0.73–1.51)	0.808	0.92 (0.63–1.36)	0.681	0.94 (0.63–1.40)	0.772	1.36 (0.75–2.48)	0.309	1.45 (0.74–2.83)	0.277
Homozygote model	0.99 (0.18–5.42)	0.990	0.60 (0.11–3.40)	0.562	0.62 (0.07–5.52)	0.664	0.48 (0.05–4.40)	0.519	2.53 (0.28–22.91)	0.408	1.32 (0.13–13.49)	0.816
Dominant model	1.01 (0.71–1.42)	0.980	1.02 (0.71–1.46)	0.908	0.91 (0.62–1.33)	0.623	0.92 (0.62–1.36)	0.679	1.40 (0.79–2.51)	0.253	1.44 (0.75–2.76)	0.272
Recessive model	0.99 (0.18–5.40)	0.988	0.60 (0.11–3.38)	0.559	0.62 (0.07–5.55)	0.668	0.49 (0.05–4.42)	0.522	2.44 (0.27–22.02)	0.427	1.26 (0.12–12.93)	0.844

Note: [a]Adjusted for age, sex, smoking status, alcohol use, and BMI status.

Abbreviations: NSCLC, non-small-cell lung cancer; BMI, body mass index.

Table 5 Stratified analyses between *IGF2BP2* rs1470579 A>C polymorphism and NSCLC risk by sex, age, BMI, smoking status, and alcohol consumption

Variable	*IGF2BP2* rs1470579 A>C (case/control)[a]			Adjusted OR[b] (95% CI); *P*				
	AA	AC	CC	AA	AC	CC	AC /CC	CC vs (AC/AA)
Sex								
Male	165/344	101/198	21/45	1.00	1.05 (0.76–1.45); 0.789	1.00 (0.55–1.81); 0.999	1.04 (0.76–1.41); 0.824	0.98 (0.55–1.76); 0.953
Female	137/249	86/152	11/41	1.00	1.01 (0.72–1.43); 0.935	**0.46 (0.23–0.94); 0.032**	0.90 (0.65–1.24); 0.506	**0.46 (0.23–0.92); 0.028**
Age								
<60	148/273	82/159	8/43	1.00	0.94 (0.66–1.33); 0.725	**0.36 (0.16–0.80); 0.012**	0.82 (0.59–1.14); 0.237	**0.37 (0.17–0.81); 0.013**
≥60	154/320	105/191	24/43	1.00	1.12 (0.82–1.54); 0.479	1.08 (0.62–1.89); 0.787	1.11 (0.83–1.51); 0.481	1.03 (0.60–1.78); 0.909
Smoking status								
Never	185/471	113/284	19/72	1.00	1.00 (0.76–1.33); 0.978	0.64 (0.37–1.11); 0.111	0.93 (0.71–1.21); 0.585	0.64 (0.38–1.09); 0.102
Ever	117/122	74/66	13/14	1.00	1.12 (0.73–1.70); 0.610	0.89 (0.40–1.99); 0.771	1.08 (0.72–1.61); 0.720	0.85 (0.39–1.87); 0.688
Alcohol consumption								
Never	259/548	161/318	24/82	1.00	1.09 (0.85–1.40); 0.510	**0.61 (0.37–0.99); 0.046**	0.99 (0.78–1.25); 0.908	**0.59 (0.36–0.95); 0.031**
Ever	43/45	26/32	8/4	1.00	0.76 (0.38–1.51); 0.427	2.23 (0.58–8.50); 0.242	0.90 (0.47–1.72); 0.740	2.51 (0.68–9.25); 0.168
BMI (kg/m^2)								
<24	189/303	125/191	23/52	1.00	1.03 (0.76–1.39); 0.842	0.69 (0.40–1.19); 0.183	0.96 (0.72–1.27); 0.760	0.68 (0.40–1.16); 0.158
≥24	113/290	62/159	9/34	1.00	1.04 (0.72–1.52); 0.823	0.78 (0.35–1.70); 0.526	1.00 (0.70–1.43); 0.996	0.76 (0.35–1.65); 0.494

Notes: [a]For *IGF2BP2* rs1470579 A>C, the genotyping was successful in 521 (100.00%) NSCLC cases and 1,029 (99.90%) controls. [b]Adjusted for multiple comparisons (age, sex, BMI, smoking status, and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model. Bold values are statistically significant ($P<0.05$).
Abbreviations: NSCLC, non-small-cell lung cancer; BMI, body mass index.

As shown in Table 6, we also found that *IGF2BP2* rs4402960 G>T polymorphism decreased the risk of NSCLC in some subgroups (female subgroup: TT vs GG: adjusted OR =0.46, 95% CI =0.21–0.93, P=0.031 and TT vs GT/GG: adjusted OR =0.44, 95% CI =0.21–0.91, P=0.026; <60 subgroup: TT vs GG: adjusted OR =0.44, 95% CI =0.20–0.95, P=0.037 and TT vs GT/GG: adjusted OR =0.45, 95% CI =0.21–0.96, P=0.038; and never drinking subgroup: TT vs GT/GG: adjusted OR =0.61, 95% CI =0.37–0.99, P=0.046).

However, we found no significant difference in *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A genotype distribution among NSCLC cases and controls (Tables 7–9, respectively).

SNP haplotypes

We harnessed an online SHEsis software[31] to establish haplotypes of *IGF2BP2* and *IGFBP3* gene (Table 10). Finally, 19 haplotypes of *IGF2BP2* and *IGFBP3* genes were constructed. When $A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}G_{rs6953668}$ haplotype was used as reference, $A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}A_{rs6953668}$ haplotype decreased susceptibility to NSCLC (P=0.007, Table 10).

Discussion

In this study, we explored the potential relationship of *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A SNPs with susceptibility to NSCLC. We found that *IGF2BP2* rs1470579 A>C, rs4402960 G>T and *IGFBP3* rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A polymorphisms might not confer risk to overall NSCLC. However, in stratified analyses, we found significant associations between *IGF2BP2* rs1470579 A>C, rs4402960 G>T polymorphisms and decreased risk of NSCLC in female, <60 years, and never drinking subgroups. We also found that $A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}A_{rs6953668}$ haplotype decreased susceptibility to NSCLC. To our knowledge, the present study was the first investigation to identify the correlation between *IGF2BP2* rs1470579 A>C, rs4402960 G>T polymorphisms and the decreased risk of NSCLC in Asians.

Dai et al reported that IGF2BP2 is a tumor promoter which promotes malignancy proliferation through its client mRNAs IGF2 and high mobility group A1.[32] In many human malignancies, the gene encoding IGF2BP2 was found to be amplified and overexpressed. Recently, Barghash et al found that elevated expression of IGF2BP2 was associated with a shorter survival and metastasis in esophageal adenocarcinoma.[33] Several case–control studies reported that *IGF2BP2* rs4402960 G>T polymorphism was associated with the risk of T2DM and might affect the therapeutic efficacy of antidiabetic in Chinese population.[34,35] We found that the *IGF2BP2* rs4402960 TT genotype was associated with the decreased susceptibility of NSCLC among female, <60

Table 6 Stratified analyses between *IGF2BP2* rs4402960 G>T polymorphism and NSCLC risk by sex, age, BMI, smoking status, and alcohol consumption

Variable	*IGF2BP2* rs4402960 G>T (case/control)[a]			Adjusted OR[b] (95% CI); *P*				
	GG	GT	TT	GG	GT	TT	GT /TT	TT vs (GT/GG)
Sex								
Male	168/349	99/195	20/43	1.00	1.02 (0.74–1.41); 0.905	1.04 (0.57–1.90); 0.902	1.02 (0.75–1.39); 0.893	1.03 (0.57–1.86); 0.922
Female	138/254	86/149	10/39	1.00	1.03 (0.73–1.46); 0.852	**0.46 (0.21–0.93); 0.031**	0.91 (0.66–1.26); 0.574	**0.44 (0.21–0.91); 0.026**
Age (years)								
<60	147/277	82/158	9/40	1.00	0.96 (0.68–1.36); 0.817	**0.44 (0.20–0.95); 0.037**	0.86 (0.61–1.20); 0.361	**0.45 (0.21–0.96); 0.038**
≥60	159/326	103/186	21/42	1.00	1.10 (0.80–1.52); 0.555	0.99 (0.56–1.77); 0.975	1.08 (0.80–1.46); 0.615	0.96 (0.54–1.68); 0.875
Smoking status								
Never	188/480	111/278	18/69	1.00	1.00 (0.76–1.33); 0.979	0.64 (0.37–1.12); 0.117	0.93 (0.71–1.22); 0.593	0.64 (0.37–1.10); 0.109
Ever	118/123	74/66	12/13	1.00	1.12 (0.73–1.70); 0.608	0.91 (0.40–2.09); 0.823	1.08 (0.73–1.62); 0.698	0.87 (0.39–1.98); 0.744
Alcohol consumption								
Never	263/555	157/314	24/79	1.00	1.06 (0.83–1.36); 0.647	0.62 (0.38–1.02); 0.061	0.97 (0.76–1.23); 0.801	**0.61 (0.37–0.99); 0.046**
Ever	43/48	28/30	6/3	1.00	0.92 (0.46–1.82); 0.802	2.73 (0.58–12.72); 0.202	1.05 (0.54–2.02); 0.895	2.83 (0.62–12.84); 0.179
BMI (kg/m^2)								
<24	194/306	121/192	22/48	1.00	0.96 (0.71–1.30); 0.780	0.71 (0.41–1.24); 0.232	0.91 (0.68–1.21); 0.507	0.72 (0.42–1.25); 0.244
≥24	112/297	64/152	8/34	1.00	1.17 (0.80–1.71); 0.413	0.73 (0.32–1.64); 0.442	1.09 (0.76–1.57); 0.628	0.69 (0.31–1.54); 0.361

Notes: [a]For *IGF2BP2* rs4402960 G>T, the genotyping was successful in 521 (100.00%) NSCLC cases and 1,029 (99.90%) controls. [b]Adjusted for multiple comparisons (age, sex, BMI, smoking status and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model. Bold values are statistically significant ($P<0.05$).
Abbreviations: NSCLC, non-small-cell lung cancer; BMI, body mass index.

Table 7 Stratified analyses between *IGFBP3* rs2270628 C>T polymorphism and NSCLC risk by sex, age, BMI, smoking status, and alcohol consumption

Variable	*IGFBP3* rs2270628 C>T (case/control)[a]			Adjusted OR[b] (95% CI); *P*				
	CC	CT	TT	CC	CT	TT	CT /TT	TT vs (CT/CC)
Sex								
Male	188/382	84/183	15/22	1.00	0.91 (0.65–1.27); 0.573	1.39 (0.67–2.88); 0.376	0.96 (0.70–1.32); 0.794	1.43 (0.70–2.94); 0.332
Female	146/288	79/135	9/19	1.00	1.11 (0.79–1.57); 0.554	0.96 (0.42–2.20); 0.920	1.09 (0.78–1.53); 0.605	0.93 (0.41–2.10); 0.854
Age (years)								
<60	155/309	71/152	12/14	1.00	0.94 (0.66–1.34); 0.735	1.90 (0.81–4.47); 0.139	1.01 (0.72–1.43); 0.940	1.94 (0.83–4.51); 0.125
≥60	179/361	92/166	12/27	1.00	1.06 (0.77–1.47); 0.725	0.87 (0.42–1.79); 0.695	1.03 (0.76–1.41); 0.841	0.85 (0.41–1.74); 0.654
Smoking status								
Never	201/541	103/252	13/34	1.00	1.07 (0.80–1.42); 0.656	0.98 (0.50–1.92); 0.946	1.06 (0.80–1.39); 0.704	0.96 (0.49–1.86); 0.893
Ever	133/129	60/66	11/7	1.00	0.88 (0.57–1.35); 0.561	1.53 (0.57–4.08); 0.399	0.94 (0.63–1.42); 0.783	1.59 (0.60–4.21); 0.352
Alcohol consumption								
Never	283/623	139/287	22/38	1.00	1.07 (0.83–1.38); 0.594	1.18 (0.67–2.08); 0.560	1.08 (0.85–1.38); 0.515	1.16 (0.66–2.02); 0.611
Ever	51/47	24/31	2/3	1.00	0.68 (0.34–1.35); 0.268	0.78 (0.12–5.26); 0.802	0.69 (0.35–1.34); 0.269	0.90 (0.14–5.91); 0.909
BMI (kg/m^2)								
<24	210/353	107/171	20/22	1.00	1.08 (0.79–1.47); 0.642	1.58 (0.82–3.05); 0.171	1.13 (0.84–1.52); 0.407	1.54 (0.81–2.95); 0.190
≥24	124/317	56/147	4/19	1.00	0.92 (0.63–1.35); 0.670	0.54 (0.18–1.66); 0.285	0.88 (0.60–1.28); 0.493	0.56 (0.18–1.69); 0.303

Notes: [a]For *IGFBP3* rs2270628 C>T, the genotyping was successful in 521 (100%) NSCLC cases and 1,029 (99.90%) controls. [b]Adjusted for multiple comparisons (age, sex, BMI, smoking status, and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
Abbreviations: NSCLC, non-small-cell lung cancer; BMI, body mass index.

years, and never drinking patients. Previous report showed that *IGF2BP2* rs4402960 G>T polymorphism was associated with the increased risk of breast cancer in a Chinese population.[12] The other case–control study did not find any association between *IGF2BP2* rs4402960 G>T polymorphism and colorectal cancer.[36] We identified that *IGF2BP2* rs4402960 T allele might probably be a protective factor for NSCLC, which was not consistent with the findings of previous studies. It is believed that there are some LC-related driver genes possessing low frequency variant, which modify the states of chromatin or DNA.[37] In addition, intronic region could bind to some proteins and even directly alter special gene transcription.[37–39] rs4402960 G>T polymorphism is located in the intron region of *IGF2BP2* gene, which may influence

Table 8 Stratified analyses between *IGFBP3* rs3110697 G>A polymorphism and NSCLC risk by sex, age, BMI, smoking status, and alcohol consumption

Variable	*IGFBP3* rs3110697 G>A (case/control)[a]			Adjusted OR[b] (95% CI); *P*				
	GG	GA	AA	GG	GA	AA	GA /AA	AA vs (GA/GG)
Sex								
Male	155/332	109/208	23/47	1.00	1.10 (0.80–1.52); 0.571	1.00 (0.56–1.76); 0.986	1.08 (0.79–1.46); 0.634	0.96 (0.55–1.67); 0.879
Female	131/246	81/165	22/31	1.00	0.92 (0.65–1.30); 0.640	1.45 (0.80–2.63); 0.224	1.00 (0.72–1.39); 0.994	1.50 (0.84–2.67); 0.175
Age (years)								
<60	129/274	89/163	20/38	1.00	1.14 (0.81–1.62); 0.450	1.18 (0.64–2.18); 0.591	1.15 (0.83–1.60); 0.408	1.12 (0.62–2.03); 0.709
≥60	157/304	101/210	25/40	1.00	0.93 (0.67–1.28); 0.642	1.18 (0.67–2.06); 0.566	0.97 (0.72–1.31); 0.831	1.21 (0.70–2.09); 0.485
Smoking status								
Never	175/472	112/295	30/60	1.00	1.03 (0.78–1.37); 0.835	1.43 (0.88–2.32); 0.146	1.10 (0.84–1.43); 0.506	1.41 (0.88–2.26); 0.149
Ever	111/106	78/78	15/18	1.00	0.98 (0.65–1.48); 0.920	0.79 (0.38–1.65); 0.527	0.94 (0.64–1.40); 0.767	0.79 (0.39–1.63); 0.531
Alcohol consumption								
Never	243/538	163/339	38/71	1.00	1.07 (0.83–1.37); 0.621	1.26 (0.82–1.96); 0.295	1.10 (0.87–1.39); 0.441	1.23 (0.80–1.89); 0.339
Ever	43/40	27/34	7/7	1.00	0.69 (0.34–1.38); 0.294	0.80 (0.25–2.54); 0.709	0.71 (0.37–1.37); 0.306	0.94 (0.31–2.86); 0.913
BMI (kg/m^2)								
<24	194/321	118/184	25/41	1.00	1.00 (0.74–1.35); 0.999	0.71 (0.57–1.74); 0.995	1.00 (0.75–1.33); 0.993	1.00 (0.58–1.72); 0.998
≥24	92/257	72/189	20/37	1.00	1.01 (0.70–1.47); 0.960	1.47 (0.80–2.72); 0.217	1.09 (0.76–1.54); 0.647	1.47 (0.81–2.65); 0.206

Notes: [a]For *IGFBP3* rs3110697 G>A, the genotyping was successful in 521 (100%) NSCLC cases and 1,029 (99.90%) controls. [b]Adjusted for multiple comparisons (age, sex, BMI, smoking status, and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
Abbreviations: NSCLC, non-small-cell lung cancer; BMI, body mass index.

Table 9 Stratified analyses between *IGFBP3* rs6953668 G>A polymorphism and NSCLC risk by sex, age, BMI, smoking status, and alcohol consumption

Variable	*IGFBP3* rs6953668 G>A (case/control)[a]			Adjusted OR[b] (95% CI); *P*				
	GG	GA	AA	GG	GA	AA	GA /AA	AA vs (GA/GG)
Sex								
Male	254/523	31/60	2/3	1.00	1.14 (0.70–1.87); 0.593	0.63 (0.10–3.91); 0.623	1.10 (0.68–1.78); 0.700	0.63 (0.10–3.86); 0.613
Female	212/397	22/44	0/1	1.00	0.94 (0.54–1.61); 0.811	–	0.92 (0.53–1.58); 0.754	–
Age (years)								
<60	217/429	21/43	0/2	1.00	1.02 (0.57–1.80); 0.960	–	0.96 (0.54–1.69); 0.877	–
≥60	249/491	32/61	2/2	1.00	1.07 (0.66–1.71); 0.791	0.97 (0.13–7.16); 0.974	1.06 (0.67–1.69); 0.802	0.96 (0.13–7.11); 0.969
Smoking status								
Never	281/741	36/84	0/1	1.00	1.17 (0.76–1.79); 0.474	–	1.15 (0.75–1.76); 0.519	–
Ever	185/179	17/20	2/3	1.00	0.81 (0.41–1.60); 0.534	0.66 (0.11–4.07); 0.655	0.79 (0.41–1.50); 0.468	0.68 (0.11–4.16); 0.672
Alcohol consumption								
Never	399/848	44/96	1/3	1.00	1.03 (0.69–1.52); 0.897	0.47 (0.05–4.64); 0.514	1.00 (0.68–1.47); 0.998	0.46 (0.05–4.63); 0.513
Ever	67/72	9/8	1/1	1.00	1.16 (0.41–3.26); 0.778	0.82 (0.05–13.69); 0.888	1.12 (0.42–3.00); 0.823	0.80 (0.05–13.34); 0.876
BMI (kg/m^2)								
<24	301/486	34/60	2/0	1.00	0.96 (0.61–1.52); 0.862	–	1.00 (0.64–1.58); 0.991	–
≥24	165/434	19/44	0/4	1.00	1.18 (0.65–2.13); 0.584	–	1.03 (0.57–1.84); 0.930	–

Notes: [a]For *IGFBP3* rs6953668 G>A, the genotyping was successful in 521 (100%) NSCLC cases and 1,028 (99.81%) controls. [b]Adjusted for multiple comparisons (age, sex, BMI, smoking status, and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
Abbreviations: NSCLC, non-small-cell lung cancer; BMI, body mass index.

the post-transcription process. *IGF2BP2* rs4402960 G>T polymorphism may accordingly alter the risk of NSCLC through post-transcription process mechanisms, and our study suggested that *IGF2BP2* rs4402960 TT genotype and T allele play an important role in lung carcinogenesis. In the future, the function of the *IGF2BP2* rs4402960 G>T polymorphism needs to be explored in NSCLC patients. A replicated study should also be carried out.

We found that there was a significant difference in genotype distribution of *IGF2BP2* rs1470579 A>C polymorphism between NSCLC patients and controls in female, <60 years, and never drinking subgroups. The *IGF2BP2* rs1470579

Table 10 *IGF2BP2* and *IGFBP3* haplotype frequencies (%) in patients and controls and risk of NSCLC

Haplotypes	Cases (n=1042)		Controls (n=2,060)		Crude OR (95% CI)	*P*-value
	n	%	n	%		
$A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}G_{rs6953668}$	444	42.65	888	43.21	Reference	–
$A_{rs1470579}C_{rs2270628}A_{rs3110697}G_{rs4402960}G_{rs6953668}$	150	14.41	282	13.72	1.06 (0.85–1.34)	0.596
$C_{rs1470579}C_{rs2270628}G_{rs3110697}T_{rs4402960}G_{rs6953668}$	133	12.78	304	14.79	0.88 (0.69–1.11)	0.262
$A_{rs1470579}T_{rs2270628}G_{rs3110697}G_{rs4402960}G_{rs6953668}$	137	13.16	225	12.41	1.22 (0.96–1.55)	0.109
$C_{rs1470579}C_{rs2270628}A_{rs3110697}T_{rs4402960}G_{rs6953668}$	47	4.51	83	4.04	1.13 (0.78–1.65)	0.516
$C_{rs1470579}T_{rs2270628}G_{rs3110697}T_{rs4402960}G_{rs6953668}$	43	4.13	74	3.60	1.16 (0.78–1.72)	0.453
$A_{rs1470579}C_{rs2270628}A_{rs3110697}G_{rs4402960}A_{rs6953668}$	34	3.27	56	2.73	1.21 (0.78–1.89)	0.388
$A_{rs1470579}T_{rs2270628}A_{rs3110697}G_{rs4402960}G_{rs6953668}$	16	1.54	50	2.43	0.64 (0.36–1.14)	0.125
$C_{rs1470579}C_{rs2270628}A_{rs3110697}T_{rs4402960}A_{rs6953668}$	12	1.15	15	0.73	1.60 (0.74–3.45)	0.226
$A_{rs1470579}T_{rs2270628}A_{rs3110697}G_{rs4402960}A_{rs6953668}$	6	0.58	12	0.58	1.00 (0.37–2.68)	1.000
$C_{rs1470579}T_{rs2270628}A_{rs3110697}T_{rs4402960}G_{rs6953668}$	4	0.38	11	0.54	0.73 (0.23–2.30)	0.785
$C_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}G_{rs6953668}$	5	0.48	7	0.34	1.43 (0.45–4.53)	0.549
$C_{rs1470579}T_{rs2270628}A_{rs3110697}T_{rs4402960}A_{rs6953668}$	3	0.29	9	0.44	0.67 (0.18–2.48)	0.761
$C_{rs1470579}C_{rs2270628}A_{rs3110697}G_{rs4402960}G_{rs6953668}$	2	0.19	3	0.15	1.33 (0.22–8.01)	1.000
$A_{rs1470579}C_{rs2270628}A_{rs3110697}T_{rs4402960}G_{rs6953668}$	3	0.29	2	0.10	3.00 (0.50–18.03)	0.341
$A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}A_{rs6953668}$	0	0.00	13	0.63	–	**0.007**
$C_{rs1470579}T_{rs2270628}G_{rs3110697}G_{rs4402960}G_{rs6953668}$	0	0.00	8	0.39	–	0.058
$A_{rs1470579}T_{rs2270628}G_{rs3110697}G_{rs4402960}A_{rs6953668}$	0	0.00	3	0.15	–	0.555
$C_{rs1470579}T_{rs2270628}G_{rs3110697}T_{rs4402960}A_{rs6953668}$	0	0.00	3	0.15	–	0.555
Others	2	0.19	7	0.34	0.57 (0.12–2.76)	0.726

Note: Bold values are statistically significant ($P<0.05$).
Abbreviation: NSCLC, non-small-cell lung cancer.

CC genotype was less frequent in NSCLC cases compared with controls in some subgroups, suggesting that *IGF2BP2* rs1470579 CC genotype decreased the risk of NSCLC. Recent reports showed that *IGF2BP2* rs1470579 A>C SNP might play important roles in different diseases. Some previous studies suggested that *IGF2BP2* rs1470579 A>C was associated with the risk of type 2 diabetes mellitus (T2DM). For example, Horikawa et al found that this SNP was a susceptibility marker for T2DM in a Japanese population,[40] and Huang et al found that this SNP was a risk factor for T2DM in a Chinese population.[35] In addition, a quantitative assessment demonstrated that this common polymorphism was associated with the development of T2DM. Therefore, whether the A-to-C variant in the intron region of *IGF2BP2* gene does influence the expression of *IGF2BP2* gene needs to be further studied.

Using SHEsis software,[31] we constructed 19 haplotypes to assess the potential inherited patterns of *IGF2BP2* and *IGFBP3* genes. Compared with $A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}G_{rs6953668}$ haplotype, we found that $A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}A_{rs6953668}$ haplotype significantly decreased the risk of NSCLC (P=0.007, Table 10). To the best of our knowledge, we first identified the relationship of this haplotypes with susceptibility to NSCLC. However, this rare haplotype only influenced a very minor fraction (<1%) of the studied populations. In the future, more studies with a larger sample size and an adequate methodological quality should be performed to confirm or refute these primary findings.

Some limitations in the current study should be acknowledged. First, we selected only some functional polymorphisms in *IGF2BP2* and *IGFBP3* genes. In the future, a fine-mapping study should be conducted to further study the potential relationship of *GF2BP2* and *IGFBP3* polymorphisms with risk of NSCLC. Second, in this case–control study, the sample size of NSCLC patients was relatively limited, which might lead to lack of sufficient power to identify true correlation, especially in the subgroup analysis. In the future, more NSCLC cases and controls should be enrolled, and a replicated study should be carried out. Third, this case–control study was hospital-based. The cancer-free controls recruited from local hospitals might not completely represent a general Eastern Chinese Han population. Fourth, the genotype frequencies of *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms were not in HWE, which might lead to bias. Fifth, a functional experimentation was not performed. Finally, because of the lack of the information on survival of NSCLC, we did not further analyze the role of *GF2BP2* and *IGFBP3* variants on NSCLC prognosis.

Conclusion

Our study suggests that *IGF2BP2* rs1470579 A>C, rs4402960 G>T polymorphisms are candidates for decreased susceptibility to NSCLC in Eastern Chinese Han population among female, <60 years, and never drinking subgroups. Compared with $A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}G_{rs6953668}$

haplotype, $A_{rs1470579}C_{rs2270628}G_{rs3110697}G_{rs4402960}A_{rs6953668}$ haplotype significantly decreased risk of NSCLC. In the future, more case–control studies with comprehensive resequencing or SNP functional analysis are needed to confirm these preliminary findings.

Acknowledgments

We appreciate all subjects who participated in this study. We wish to thank Dr Yan Liu (Genesky Biotechnologies Inc., Shanghai, China) for technical support. This study was supported in part by the Natural Science Foundation of Fujian Province (Grant No. 2017J01291).

Disclosure

The authors report no conflicts of interest in this work.

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