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Polymorphisms of the centrosomal gene (FGFR1OP) and lung cancer risk: a meta-analysis of 14 463 cases and 44 188 controls

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Abstract

Centrosome abnormalities are often observed in premalignant lesions and *in situ* tumors and have been associated with an euploidy and tumor development. We investigated the associations of 9354 single-nucleotide polymorphisms (SNPs) in 106 centrosomal genes with lung cancer risk by first using the summary data from six published genome-wide association studies (GWASs) of the Transdisciplinary Research in Cancer of the Lung (TRICL) (12 160 cases and 16 838 controls) and then conducted *in silico* replication in two additional independent lung cancer GWASs of Harvard University (984 cases and 970 controls) and deCODE (1319 cases and 26 380 controls). A total of 44 significant SNPs with false discovery rate (FDR) \leq 0.05 were mapped to one novel gene FGFR10P and two previously reported genes (TUBB and BRCA2). After combined the results from TRICL with those from Harvard and deCODE, the most significant association ($P_{combined} = 8.032 \times 10^{-6}$) was with

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rs151606 within FGFR1OP. The rs151606 T>G was associated with an increased risk of lung cancer [odds ratio (OR) = 1.10, 95% confidence interval (95% CI) = 1.05–1.14]. Another significant tagSNP rs12212247 T>C ($P_{combined}$ = 9.589×10⁻⁶) was associated with a decreased risk of lung cancer (OR = 0.93, 95% CI = 0.90–0.96). Further *in silico* functional analyzes revealed that rs151606 might affect transcriptional regulation and result in decreased FGFR1OP expression (P_{trend} = 0.022). The findings shed some new light on the role of centrosome abnormalities in the susceptibility to lung carcinogenesis.

Abbreviations

expression quantitative trait loci
false discovery rate
genome-wide association studies
linkage disequilibrium
single-nucleotide polymorphisms

Introduction

Lung cancer represents the number one cancer-related mortality worldwide, with more than 1.6 million cases diagnosed and 1.3 million deaths per year (1). In the United States, it is the primary cause of deaths from cancers in both men and women, leading to more deaths than from breast, colorectal and prostate cancers all combined. Although lung cancer is commonly considered a disease caused by environmental exposures, genetic factors also play a role in the etiology (2). Genomic regions at chromosomes 15q25.1 (3,4), 5p15.33 (4–6), 6p21.33 (4), 3q28 (4,7,8), 13q13.1 (8) and 22q12.1 (8) have been identified to be associated with lung cancer susceptibility by genome-wide association studies (GWASs) in populations of European descent.

Centrosomes are the pivotal regulating element of cell division and act as a reaction center where the cell cycle key regulating elements assemble and play an important role in cell polarization and ciliogenesis (9,10). Recent studies have revealed that deregulation of centrosome-related proteins induce centrosome abnormalities (11), which in turn result in tumor development through the induction of chromosome instability and aneuploidy (12,13). A growing body of evidence has linked centrosome abnormalities to the developments of solid tumors and hematopoietic malignancies (10), and the underlying mechanisms are now an active area of research (14–16).

Centrosome abnormalities and chromosome instability are also frequently observed in human lung cancer (17). Genes involved in centrosome dysregulation have emerged as the candidate targets to study the mechanism of initiation and progression of lung cancer. In this study, we hypothesized that genetic variants of centrosomal genes are associated with lung cancer risk. To test this hypothesis, we performed a meta-analysis of the association results of SNPs in centrosomal genes from eight lung cancer GWASs from Transdisciplinary Research in Cancer of the Lung (TRICL) and ILCCO, including 14 463 cases and 44 188 controls.

Materials and methods

Study populations

The study populations have been detailed previously (8,18). Briefly, this study included six previously reported lung cancer GWASs of from the TRICL, which was built upon the collaborative network of the International Lung Cancer Consortium (ILCCO) (8,18) including 12 160 lung cancer cases and 16 838 controls of European descent: the MD Anderson Cancer Center (MDACC) GWAS, the Institute of Cancer Research (ICR) GWAS, the National

Cancer Institute (NCI) GWAS, the International Agency for Research on Cancer (IARC) GWAS, Toronto study from Lunenfeld-Tanenbaum Research Institute study (Toronto) GWAS and the German Lung Cancer Study (GLC) GWAS, Germany. The additional datasets of another two independent GWASs of Caucasian populations were from Harvard Lung Cancer Study (19) (984 cases and 970 controls) and Icelandic Lung Cancer Study (deCODE) (1319 cases and 26 380 controls) (20) from the ILCCO. A written informed consent was obtained from each participant, and this study was approved by the institutional review boards for each of the participating institutions.

Genotyping platforms and quality controls

For these GWASs, genotyping was performed using Illumina HumanHap 317, 317+240S, 370Duo, 550, 610 or 1M arrays. Imputation was performed by using data from the 1000 Genomes Project (phase I integrated release 3, March 2012) (21) as reference and IMPUTE2 v2.1.1 (22), MaCH v1.0 (23) or minimac (version 2012.10.3) (24) software. Poorly imputed SNPs defined as an information score < 0.40 with IMPUTE2 or an r^2 < 0.30 with MaCH were excluded from the final analyses. Standard quality control on samples was performed on all scans, excluding individuals with low call rate (< 90%) and extremely high or low heterozygosity (P < 1.0 × 10⁻⁴), as well as all individuals evaluated to be of non-European ancestry (using the HapMap phase II CEU, JPT/CHB and YRI populations as a reference).

Genes and SNPs selection

The centrosomal genes were collected from the Molecular Signatures Database (http://software.broadinstitute.org/gsea/msigdb), which is a collection of annotated gene sets for use with gene set enrichment analysis. Overall, 106 centrosomal genes located on autosomal chromosomes were selected (Supplementary Table 1, available at *Carcinogenesis* Online). The genotyped or imputed common SNPs located within 2 kB up- and downstream of centrosomal genes were extracted from the GWAS datasets and the final meta-analysis included 9354 SNPs with genotyping call rate \geq 90%, minor allele frequency \geq 5%, and Hardy Weinberg Equilibrium exact $P \geq 10^{-5}$. As previously reported (8,25), SNPs from the 1000 Genomes project release Phase 1 integrated release version 3 and filtered with only SNPs showing imputation accuracy > 0.3 were retained. The detailed workflow is shown in Supplementary Figure 1, available at *Carcinogenesis* Online.

In silico functional validation

To predict the potential functions of risk-associated SNPs and their highlinkage disequilibrium (LD) ($r^2 \ge 0.60$) variants, we used three in silico tools: SNPinfo (26), RegulomeDB (27) and F-SNP (28). Expression quantitative trait loci (eQTL) analysis was carried out using lymphoblastoid cell data from 1000 Genomes Project (21) European subpopulation (EUR, 373 individuals) (phase I integrated release 3, March 2012).

Statistical methods

For each GWAS, ORs and associated 95% CIs were calculated by unconditional logistic regression using R (v2.6), Stata (v10, State College, Texas, USA) and PLINK (v1.06) (29) software. With the inverse variance method, meta-analysis under fixed and random-effects models was conducted on the results of log-additive model of 9354 SNPs. Cochran's Q statistic to test for heterogeneity and the I² statistic to quantify the proportion of the total variation due to heterogeneity were calculated (30). Fixed effects model was applied when there was no heterogeneity among GWASs (Q-test P > 0.100 and I² < 50%); otherwise, random effects model was applied. The false discovery rate (FDR) procedure was employed to control for multiple testing (31) with FDR < 0.050. The correlation between SNPs and corresponding mRNA expression levels was estimated by using a linear regression model.

LocusZoom (32) was applied to generate regional association plots, using the 1000 Genomes European (EUR) reference data (phase I integrated release 3, March 2012) to compute LD. Haploview v4.2 (33) was employed to construct the LD plots. SNPs whose r² in linkage with any of the causal SNPs is less than 0.60 are also considered independent. All analyses were conducted with SAS (version 9.1.3; SAS Institute, Cary, NC, USA) unless specified otherwise.

Results

Meta-analysis of the main effects of SNPs in 106 centrosomal genes

The samples sizes of the used GWASs in this study are summarized in Table 1. In this study, we firstly carried out the analysis within the six TRICL GWASs, which included 12 160 lung cancer case subjects and 16 838 unaffected controls. After stringent quality control, we analyzed 9354 SNPs from 106 centrosomal genes (Figure 1). There are 843 SNPs and 96 SNPs with nominal P < 0.050 and < 0.001 under an additive (per allele) model, respectively; 44 SNPs remained significant at the FDR threshold ≤ 0.050 . These top SNPs are mapped to TUBB, FGFR1OP and BRCA2, respectively (Table 2). We removed SNPs that had a high pairwise LD with those in previously reported GWASs (4,8,34) (TUBB at 6p21.33 and BRCA2 at 13q13.1), and only SNPs mapped to FGFR1OP were included for the additional analyses. The regional association plots demonstrated that SNP rs12212247 showed high LD ($r^2 \ge 0.60$) with other 31 SNPs in FGFR1OP, except for rs151606 (Figure 2; Supplementary Table 2, available at *Carcinogenesis* Online). Finally, two tagSNPs (rs151606 and rs12212247) in FGFR1OP were selected for the further analysis. As shown in Table 3, both SNPs had a high imputation quality in each dataset.

Of these two SNPs, rs151606 A>T was shown to be associated with an increased risk of lung cancer (OR = 1.12, 95% CI = 1.07–1.17, P = 1.177×10^{-6}), while rs12212247 T>C was associated with a decreased risk (OR = 0.93, 95% CI = 0.90-0.97, P = 8.926×10^{-5}). There was no heterogeneity observed for these risk estimates in these six GWASs (Figure 3).

We sought to expand these findings in another two independent lung cancer GWASs from Harvard University (984 cases and 970 controls) and deCODE (1319 cases and 26 380 controls). When the two studies were combined, rs12212247 and its 31 high LD SNPs within FGFR10P were found with the same effect direction with a nominal P = 0.039. In addition, the protective effect of SNP rs151606 was insignificant (Table 3; Supplementary Table 3, available at *Carcinogenesis* Online). However, when we combined the summary results of all the eight studies, we observed a significant evidence for the association of rs151606 and lung cancer risk (OR = 1.10, 95% CI = 1.05–1.14, $P_{combined} = 8.032 \times 10^{-6}$) and rs12212247 (OR = 0.93, 95% CI = 0.90–0.96, $P_{combined} = 9.589 \times 10^{-6}$) (Table 3; Figure 3),

Table 1. Characteristics of the study populations included in the participating genome-wide association studies

	ICRª		MDAC	C⊳	IARC		NCId		Toron	to ^e	$GLC^{\rm f}$		Harva	ırd ^g	deCO	DE ^h
Variable	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Overall	1952	5200	1150	1134	2533	3791	5713	5736	331	499	481	478	984	970	1319	26380
AD	465	5200	619	1134	517	2824	1841	5736	90	499	186	478	597	970	547	26380
SQ	611	5200	306	1134	911	2968	1447	5736	50	499	97	478	216	970	259	26380

AD, adenocarcinoma; SQ, squamous cell carcinoma.

^aICR: the Institute of Cancer Research Genome-wide Association Study, UK.

^bMDACC: the MD Anderson Cancer Center Genome-wide Association Study, USA.

cIARC: the International Agency for Research on Cancer Genome-wide Association Study, France.

^dNCI: the National Cancer Institute Genome-wide Association Study, USA.

e Toronto: the Lunenfeld-Tanenbaum Research Institute Genome-wide Association Study, Toronto, Canada.

^fGLC: German Lung Cancer Study, Germany.

8Harvard: Harvard Lung Cancer Study, USA.

^hdeCODE: Icelandic Lung Cancer Study, Iceland.



Figure 1. Manhattan plot of genome-wide association results. SNPs are plotted on the x-axis according to their positions on each chromosome. On the y-axis, the association P values with lung cancer risk are shown (as –log10 P values). Horizontal red line represents FDR threshold 0.05. Horizontal blue line represents nominal P values of 0.05.

given only 9354 SNPs were tested for their associations with lung cancer risk in the present study.

Stratified analyses

Like many other cancers, lung cancer histologic subtypes can have dramatically different clinical behaviors. In the further analyses stratified by histology, only adenocarcinoma (AD) and squamous cell carcinoma (SQ) were included. SNP rs151606 was associated only with the risk of SQ (OR = 1.09, 95% CI = 1.02–1.16, $P_{\rm combined} = 0.011$), but not with AD (OR = 1.06, 95% CI = 1.00–1.13, $P_{\rm combined} = 0.058$); the strongest effect of rs12212247 was detected

in AD (OR = 0.94, 95%CI = 0.89–0.98, $P_{combined} = 0.007$), and then in SQ (OR = 0.95, 95%CI = 0.90–1.00, $P_{combined} = 0.043$) (Figure 3).

In silico functional validation

In silico eQTL analysis was performed by using the lymphoblastoid cell lines from 373 individuals of European descendent. The rs151606 genotypes demonstrated significant association with decreased mRNA expression of FGFR1OP in both additive ($P_{trend} = 0.022$) and recessive models ($P_{trend} = 0.031$) (Figure 4). According to the prediction results of the online tool F-SNP, SNP rs151606 might be associated with mRNA expression by

Table 2. Associations between on 5 in centrosonial genes and fully cancel now with row ~ 0.0 .	Table 2. /	Associations	between SNPs in	centrosomal	genes and lung	g cancer risk wi	ith FDR $P \le 0.05$
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TISB87636 TUBB 6 30689001 T/A 0.12 0.869 0 +++++ 1.17 (1.11-1.24) 4.23E-09 <.0001	SNP	Gene	Chr	Position (hg19)	Alleleª	EAF	Qb	I ²	Effects ^c	OR (95%CI)	Р	FDR
TB11484831 TUBB 6 30687674 C/C 0.11 0.724 0 ++++++ 1.18 (1.12-1.24) 4.988-09 <.0001	rs115897636	TUBB	6	30689001	T/A	0.12	0.869	0	+++++	1.17 (1.11–1.24)	4.23E-09	<.0001
rs11560279 TUBB 6 30668575 G/C 0.11 0.724 0 ++++++ 1.18 (1.12-1.24) 5.05E-09 <0001	rs114884831	TUBB	6	30687614	G/C	0.11	0.725	0	+++++	1.18 (1.12–1.24)	4.98E-09	<.0001
rs115812176 TUBB 6 30693816 A/G 0.20 0.456 0 ++++++ 1.12 (107-1.17) 3.60E-07 0.001 rs114380302 TUBB 6 306829565 G/A 0.20 0.448 0 ++++++ 1.12 (107-1.17) 3.78E-07 0.001 rs114840911 TUBB 6 30693633 A/G 0.20 0.522 0 ++++++ 1.11 (107-1.16) 6.09E-07 0.001 rs11460911 TUBB 6 30694374 T/C 0.18 0.4552 0 ++++++ 1.11 (107-1.17) 2.01E-06 0.002 rs115869492 TUBB 6 30693121 A/G 0.33 0.780 0 ++++++ 1.07 (104-1.11) 5.03E-05 0.025 rs239393 FGFR10P 6 167410878 A/G 0.47 0.340 12 +++++ 1.07 (104-1.11) 5.28E-05 0.025 rs32934 FCFR10P 6 167410878 A/G 0.47 0.340 12 ++++++ 1.07 (104-1.11) 5.28E-05 0.025 rs32934 FCFR10P	rs115605279	TUBB	6	30688575	G/C	0.11	0.724	0	++++++	1.18 (1.12–1.24)	5.05E-09	<.0001
rs11430902 TUBB 6 30692965 G/A 0.20 0.448 0 ++++++ 1.12 (1.07-1.17) 3.78E-07 0.001 rs1143038781 TUBB 6 30688427 G/T 0.20 0.453 0 ++++++ 1.12 (1.07-1.17) 3.78E-07 0.001 rs151606 FCFR10P 6 167430482 A/T 0.34 0.552 0 ++++++ 1.11 (1.07-1.17) 1.18E-06 0.000 rs11405700 TUBB 6 30693121 A/G 0.33 0.780 0 ++++++ 1.11 (1.07-1.17) 9.78E-06 0.002 rs139569492 TUBB 6 30693121 A/G 0.48 0.390 16 +++++ 1.07 (1.04-1.11) 5.02E-05 0.025 rs239935 FCFR10P 6 16741097 T/C 0.47 0.340 12 +++++ 1.07 (1.04-1.11) 7.28E-05 0.025 rs326997 FCFR10P 6 16742048 A/G 0.49 0.379 6 ++++++ 1.07 (1.04-1.11) 7.28E-05 0.025 rs3259374 FCFR10P 6 <td>rs116812176</td> <td>TUBB</td> <td>6</td> <td>30693816</td> <td>A/G</td> <td>0.20</td> <td>0.456</td> <td>0</td> <td>++++++</td> <td>1.12 (1.07–1.17)</td> <td>3.60E-07</td> <td>0.001</td>	rs116812176	TUBB	6	30693816	A/G	0.20	0.456	0	++++++	1.12 (1.07–1.17)	3.60E-07	0.001
rs116338781 TUBB 6 30684427 G/T 0.20 0.453 0 +++++ 1.12 (1.07-1.17) 4.88E-07 0.001 rs114460911 TUBB 6 30693633 A/G 0.20 0.522 0 ++++++ 1.11 (1.07-1.17) 4.88E-07 0.001 rs11460911 TUBB 6 30694324 T/C 0.18 0.4852 0 ++++++ 1.11 (1.07-1.17) 2.01E-06 0.002 rs115960492 TUBB 6 30694324 T/C 0.18 0.485 0 ++++++ 1.11 (1.07-1.17) 2.01E-06 0.002 rs115960492 TUBB 6 106411788 A/G 0.48 0.309 16 ++++++ 1.07 (1.04-1.11) 5.03E-05 0.025 rs239934 FGFR10P 6 167410878 G/A 0.47 0.340 12 +++++ 1.07 (1.04-1.11) 5.28E-05 0.025 rs323937 FGFR10P 6 167410248 A/G 0.46 0.320 15 0.33 (0.90-037) 7.54E-05 0.025 rs3239374 FGFR10P	rs114380302	TUBB	6	30692965	G/A	0.20	0.448	0	++++++	1.12 (1.07–1.17)	3.78E-07	0.001
rs114460911 TUBB 6 30693633 A/G 0.20 0.522 0 +++++ 1.11 (1.07-1.15) 6.09E-07 0.001 rs151606 FGFR10P 6 167430482 A/T 0.34 0.552 0 ++++++ 1.12 (1.07-1.17) 1.18E-06 0.0001 rs1159560492 TUBB 6 30693121 A/G 0.33 0.780 0 +++++ 1.07<(1.04-1.11)	rs116338781	TUBB	6	30688427	G/T	0.20	0.453	0	++++++	1.12 (1.07–1.17)	4.88E-07	0.001
TS151606 FGFR10P 6 167430482 A/T 0.34 0.552 0 +++++ 1.12 (1.07-1.17) 1.18E-06 0.001 TS114075700 TUBB 6 30694374 T/C 0.18 0.485 0 ++++++ 1.11 (1.07-1.17) 2.01E-06 0.0001 TS11950492 TUBB 6 30693121 A/G 0.33 0.780 0 ++++++ 1.01 (1.05-1.17) 2.01E-06 0.0001 TS239935 FGFR10P 6 167411088 C/T 0.47 0.338 12 ++++++ 1.07 (1.04-1.11) 6.28E-05 0.025 TS239937 FGFR10P 6 167410807 T/C 0.47 0.340 12 +++++ 1.07 (1.04-1.11) 6.78E-05 0.025 TS32097 FGFR10P 6 16742048 A/G 0.46 0.320 15 -++++ 1.07 (1.04-1.11) 6.78E-05 0.025 TS322077 FGFR10P 6 167426707 T/C 0.46 0.320 15 -+++++ 0.73 (0.90-0.97) 8.58E-05 0.025 TS9455820 FGFR	rs114460911	TUBB	6	30693633	A/G	0.20	0.522	0	++++++	1.11 (1.07–1.16)	6.09E-07	0.001
rs114075700 TUBB 6 30694374 T/C 0.18 0.485 0 +++++ 1.11 (1.07-1.17) 2.01E-06 0.002 rs115964942 TUBB 6 30693121 A/G 0.33 0.780 0 ++++++ 1.01 (1.05-1.15) 9.78E-06 0.002 rs232933 FCFR10P 6 167411788 A/G 0.48 0.309 16 +++++ 1.07 (1.04-1.11) 6.78E-05 0.025 rs424185 FCFR10P 6 167410070 T/C 0.47 0.340 12 +++++ 1.07 (1.04-1.11) 6.78E-05 0.025 rs325097 FGFR10P 6 167426707 T/C 0.46 0.320 15	rs151606	FGFR1OP	6	167430482	A/T	0.34	0.552	0	++++++	1.12 (1.07–1.17)	1.18E-06	0.001
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TR239935 FGFR1OP 6 167411788 A/G 0.48 0.309 16 ++++++ 1.07 1.04-1.11 5.03E-05 0.025 rs40837 FGFR1OP 6 167411008 C/T 0.47 0.338 12 ++++++ 1.07 (1.04-1.11) 6.78E-05 0.025 rs420837 FGFR1OP 6 1674110878 G/A 0.47 0.340 12 ++++++ 1.07 (1.04-1.11) 6.78E-05 0.025 rs239934 FGFR1OP 6 167412048 A/G 0.49 0.379 6 ++++++ 1.07 (1.04-1.11) 6.78E-05 0.025 rs3257251 FGFR1OP 6 167426438 A/G 0.46 0.320 15 0.93 (0.90-0.97) 7.58E-05 0.025 rs9457249 FGFR1OP 6 167419105 G/A 0.45 0.317 15 0.93 (0.90-0.97) 8.58E-05 0.025 rs9459841 FGFR1OP 6 167431949 G/A 0.45 0.313 16 0.93 (0.90-0.	rs115969492	TUBB	6	30693121	A/G	0.33	0.780	0	++++++	1.10 (1.05–1.15)	9.78E-06	0.009
Terretore C/T 0.47 0.38 12 ++++++ 1.07 (1.04-1.11) 6.28E-05 0.025 rs424185 FGFR10P 6 1674110087 T/C 0.47 0.330 12 ++++++ 1.07 (1.04-1.11) 6.78E-05 0.025 rs329934 FGFR10P 6 167412048 A/G 0.47 0.340 12 ++++++ 1.07 (1.04-1.11) 6.78E-05 0.025 rs329934 FGFR10P 6 16742203 T/C 0.46 0.320 15	rs239935	FGFR1OP	6	167411788	A/G	0.48	0.309	16	++++++	1.07 (1.03–1.13)	5.03E-05	0.025
Fight 20	rs400837	FGFR1OP	6	167411008	C/T	0.47	0.338	12	++++++	1.07 (1.04–1.11)	6 28E-05	0.025
15.12.103 10.1121 6 16741087 173 0.17 0.340 12 ++++++ 1.07 1.04-1.11 7.28E-05 0.025 re3239934 FGFR10P 6 167410878 A/G 0.49 0.379 6 ++++++ 1.07 1.04-1.11 7.24E-05 0.025 re323924 FGFR10P 6 167426707 T/C 0.46 0.334 13 0.93 (0.90-0.97) 7.54E-05 0.025 rs9457249 FGFR10P 6 167426707 T/C 0.46 0.320 15 0.93 (0.90-0.97) 7.54E-05 0.025 rs9459836 FGFR10P 6 16744302 C/T 0.45 0.317 15 0.93 (0.90-0.97) 8.59E-05 0.025 rs9459841 FGFR10P 6 167443194 G/A 0.45 0.315 15 0.93 (0.90-0.97) 8.59E-05 0.025 rs9459841 FGFR10P 6 167431910 G/A 0.45 0.315 15 0.93 (0.90-0.97) 8.59	rs424185	FGFR1OP	6	167410907	С, Г Т/С	0.47	0.330	12	******	1.07 (1.04_1.11)	6 78F_05	0.025
Fights Fights<	rs376097	FGFR1OP	6	167410878	G/A	0.47	0.340	12	+++++++	1.07 (1.04–1.11)	6 78E-05	0.025
First Status First Status <th< td=""><td>rs239934</td><td>FGFR1OP</td><td>6</td><td>167412048</td><td>A/G</td><td>0.49</td><td>0.379</td><td>6</td><td>++++++</td><td>1.07 (1.04–1.11)</td><td>7 24E-05</td><td>0.025</td></th<>	rs239934	FGFR1OP	6	167412048	A/G	0.49	0.379	6	++++++	1.07 (1.04–1.11)	7 24E-05	0.025
First First <th< td=""><td>rs1322077</td><td>FGFR1OP</td><td>6</td><td>167424293</td><td>T/C</td><td>0.46</td><td>0.334</td><td>13</td><td></td><td>0.93 (0.90-0.97)</td><td>7 35E-05</td><td>0.025</td></th<>	rs1322077	FGFR1OP	6	167424293	T/C	0.46	0.334	13		0.93 (0.90-0.97)	7 35E-05	0.025
Fight21 Fight224	rs9457251	FGFR1OP	6	167426707	T/C	0.46	0.320	15		0.93 (0.90-0.97)	7.54E-05	0.025
FIGHTLY FORTOP 6 167419105 G/A 0.46 0.321 15 0.93 (0.90-0.97) 8.56E-05 0.025 rs9459836 FGFR10P 6 167449102 C/T 0.45 0.317 15 0.93 (0.90-0.97) 8.56E-05 0.025 rs9459841 FGFR10P 6 167449104 G/A 0.45 0.315 15 0.93 (0.90-0.97) 8.59E-05 0.025 rs9459840 FGFR10P 6 167431910 G/A 0.45 0.315 15 0.93 (0.90-0.97) 8.77E-05 0.025 rs9459840 FGFR10P 6 167430186 A/G 0.45 0.315 15 0.93 (0.90-0.97) 8.77E-05 0.025 rs10160404 FGFR10P 6 167413139 T/C 0.46 0.329 13 0.93 (0.90-0.97) 8.98E-05 0.025 rs12212247 FGFR10P 6 167413344 C/T 0.45 0.311 16 0.93 (0.90	rs9457249	FGFR1OP	6	167426438	A/G	0.46	0.320	15		0.93 (0.90-0.97)	7 58E-05	0.025
FGFR10P 6 167443902 C/T 0.45 0.312 15 0.03 0.90-0.97) 8.59E-05 0.025 rs9459841 FGFR10P 6 167443902 C/T 0.45 0.315 15 0.93 (0.90-0.97) 8.59E-05 0.025 rs9459840 FGFR10P 6 167431949 G/A 0.45 0.315 15 0.93 (0.90-0.97) 8.77E-05 0.025 rs9459840 FGFR10P 6 167431910 G/A 0.45 0.315 15 0.93 (0.90-0.97) 8.77E-05 0.025 rs4710171 FGFR10P 6 167429467 A/G 0.45 0.315 15 0.93 (0.90-0.97) 8.39E-05 0.025 rs120212247 FGFR10P 6 16743948 C/T 0.45 0.311 16 0.93 (0.90-0.97) 9.39E-05 0.025 rs6904946 FGFR10P 6 16743948 C/T 0.45 0.310 16 0.93 (0.90-0.97) 9.21E-05 0.	rs9459836	FGFR1OP	6	167419105	G/A	0.46	0.321	15		0.93 (0.90-0.97)	8 56E-05	0.025
International internatintered international international internation	rs13195812	FGFR1OP	6	167443902	C/T	0.10	0.317	15		0.93 (0.90-0.97)	8 59E-05	0.025
Horizords FGFR10P 6 1674431949 G/A 0.45 0.312 15 0.93 (0.90-0.97) 8.77E-05 0.025 rs9459840 FGFR10P 6 167431949 G/A 0.45 0.315 15 0.93 (0.90-0.97) 8.77E-05 0.025 rs9459840 FGFR10P 6 167430186 A/G 0.45 0.315 15 0.93 (0.90-0.97) 8.77E-05 0.025 rs9459840 FGFR10P 6 167429467 A/G 0.45 0.315 15 0.93 (0.90-0.97) 8.80E-05 0.025 rs12212247 FGFR10P 6 16743348 C/T 0.45 0.311 16 0.93 (0.90-0.97) 9.17E-05 0.025 rs6904946 FGFR10P 6 16743348 T/C 0.45 0.311 16 0.93 (0.90-0.97) 9.21E-05 0.025 rs9457250 FGFR10P 6 167436159 T/C 0.45 0.307 17 0.93 (0.9	rs9459849	FGFR1OP	6	167444160	G/T	0.15	0.313	16		0.93 (0.90-0.97)	8.69E-05	0.025
Instruction	rs9459841	FGFR1OP	6	167431949	G/A	0.45	0.315	15		0.93 (0.90–0.97)	8 77E-05	0.025
Instruction	rs9459840	FGFR1OP	6	167431910	G/A	0.45	0.315	15		0.93 (0.90–0.97)	8 77E-05	0.025
Instruct Instrut Instrut Instrut In	rs4710171	FGFR1OP	6	167430186	A/G	0.45	0.315	15		0.93 (0.90–0.97)	8 79E-05	0.025
Interview	rs1060404	FGFR1OP	6	167429467	A/G	0.45	0.315	15		0.93 (0.90-0.97)	8 80E-05	0.025
Instruction	rc12212247	FGFR1OP	6	167413539	TVC	0.15	0.313	13		0.93 (0.90 0.97)	8 93F_05	0.025
Instruct Instrut Instrut Instrut In	rs22272247	FGFR1OP	6	167443443	г/С С/Т	0.45	0.325	16		0.93 (0.90–0.97)	9.17E_05	0.025
INSTRUCT INSTRUCT <td< td=""><td>rs6904946</td><td>FGFR1OP</td><td>6</td><td>167433948</td><td>С/ I T/C</td><td>0.15</td><td>0.310</td><td>16</td><td></td><td>0.93 (0.90 0.97)</td><td>9.19E_05</td><td>0.025</td></td<>	rs6904946	FGFR1OP	6	167433948	С/ I T/C	0.15	0.310	16		0.93 (0.90 0.97)	9.19E_05	0.025
INTROPOSIT IGFRIOP 6 10/494434 G/R 0.45 0.307 17 0.93 0.90-0.97 9.26E-05 0.025 rs9457256 FGFRIOP 6 167436461 T/C 0.45 0.307 17 0.93 0.90-0.97 9.26E-05 0.025 rs9457252 FGFRIOP 6 167436159 T/C 0.45 0.307 17 0.93 0.90-0.97 9.26E-05 0.025 rs9457252 FGFRIOP 6 167433925 G/A 0.45 0.307 17 0.93 0.90-0.97 9.26E-05 0.025 rs9295385 FGFRIOP 6 167422922 C/T 0.45 0.307 17 0.93 0.90-0.97 9.58E-05 0.025 rs10455982 FGFRIOP 6 167448181 A/G 0.45 0.307 17 0.93 0.90-0.97 9.75E-05 0.025 rs10946204 FGFR10P 6 167446735 A/C 0.45 0.307 17 0.93 0.90-0.97 9.	re10484531	FGFR1OP	6	167454434	1/C	0.45	0.310	16		0.93 (0.90-0.97)	9.21E_05	0.025
IST 101 0 10740401 1/c 0.45 0.307 17 0.021 0.025 0.025 rs3752520 FGFR10P 6 167436159 T/C 0.45 0.307 17 0.93 0.90-0.97 9.26E-05 0.025 rs9457252 FGFR10P 6 167433925 G/A 0.45 0.307 17 0.93 (0.90-0.97) 9.27E-05 0.025 rs9295385 FGFR10P 6 167422922 C/T 0.45 0.307 17 0.93 (0.90-0.97) 9.53E-05 0.025 rs0455982 FGFR10P 6 167448181 A/G 0.45 0.307 17 0.93 (0.90-0.97) 9.53E-05 0.025 rs10455982 FGFR10P 6 167448728 C/T 0.45 0.307 17 0.93 (0.90-0.97) 9.74E-05 0.025 rs1046204 FGFR10P 6 167446735 A/C 0.45 0.308 16 0.93 (0.90-0.97) 9.88E-05 0.025 rs1945025 0.925<	re9457256	FGFR1OP	6	167436461	С/Л Т/С	0.45	0.311	17		0.93 (0.90-0.97)	9.26E_05	0.025
INSTRUCT INSTRUCT <td< td=""><td>rs3752520</td><td>FGFR1OP</td><td>6</td><td>167436159</td><td>T/C</td><td>0.15</td><td>0.307</td><td>17</td><td></td><td>0.93 (0.90 0.97)</td><td>9.26E-05</td><td>0.025</td></td<>	rs3752520	FGFR1OP	6	167436159	T/C	0.15	0.307	17		0.93 (0.90 0.97)	9.26E-05	0.025
ISTATO 0 10/43323 G/R 0.45 0.30 17 0.11 0.12	re9457252	FGFR1OP	6	167433925	1/C	0.45	0.307	17		0.93 (0.90-0.97)	9.20E-05	0.025
INSTRUCT INSTRUCT <td< td=""><td>rs6929466</td><td>FGFR1OP</td><td>6</td><td>167422922</td><td>C/T</td><td>0.15</td><td>0.307</td><td>17</td><td></td><td>0.93 (0.90 0.97)</td><td>9.53F_05</td><td>0.025</td></td<>	rs6929466	FGFR1OP	6	167422922	C/T	0.15	0.307	17		0.93 (0.90 0.97)	9.53F_05	0.025
INSTRUCT 6 167 H0101 174 0.13	rs9295385	FGFR1OP	6	167448181	A/G	0.15	0.302	16		0.93 (0.90 0.97)	9.63E-05	0.025
Intersport Intersport <td>rs10455982</td> <td>FGFR1OP</td> <td>6</td> <td>167448728</td> <td>C/T</td> <td>0.45</td> <td>0.310</td> <td>10</td> <td></td> <td>0.93 (0.90-0.97)</td> <td>9 74F_05</td> <td>0.025</td>	rs10455982	FGFR1OP	6	167448728	C/T	0.45	0.310	10		0.93 (0.90-0.97)	9 74F_05	0.025
INTROPORT INFORMED INFORED INFORED INFORED I	rs10946204	FGFR1OP	6	167451129	С/ 1 Т/С	0.15	0.307	16		0.93 (0.90 0.97)	9.75E_05	0.025
INICOLUZIO INICIC 0.107440735 INIC 0.125 <td>rc10946203</td> <td>FGFR1OP</td> <td>6</td> <td>167446735</td> <td>1/C</td> <td>0.15</td> <td>0.207</td> <td>18</td> <td></td> <td>0.93 (0.90 0.97)</td> <td>9.88F_05</td> <td>0.025</td>	rc10946203	FGFR1OP	6	167446735	1/C	0.15	0.207	18		0.93 (0.90 0.97)	9.88F_05	0.025
ISS 91205 INCRIZ IS S2532280 I/G 0.25 0.25 0.24 0.024 0.025 <td< td=""><td>rc9534269</td><td>BRCA2</td><td>13</td><td>32030286</td><td>T/C</td><td>0.45</td><td>0.257</td><td>24</td><td></td><td>0.93 (0.90-0.97)</td><td>9.88L-05</td><td>0.025</td></td<>	rc9534269	BRCA2	13	32030286	T/C	0.45	0.257	24		0.93 (0.90-0.97)	9.88L-05	0.025
Isoborol IGRATO 0 IO/454112 IOG 0.35 0.35 15 0.05	rs6900701	FCER1OP	6	167434112	A/C	0.20	0.232	13		0.93 (0.89-0.90)	1.05L-04	0.025
13227276 161 A107 0 107442113 C/T 0.45 0.295 16 0.93 (0.90-0.97) 1.14L-04 0.026 rs9457254 FGFR10P 6 167434135 G/A 0.45 0.330 13 0.93 (0.90-0.97) 1.14L-04 0.026 rs9457259 FGFR10P 6 167444281 C/T 0.45 0.323 14 0.93 (0.90-0.97) 1.38E-04 0.031 rs9943876 BRCA2 13 32927894 C/T 0.30 0.438 0 ++ 0.93 (0.90-0.97) 1.48E-04 0.032 rs9232775 FGFR10P 6 167442994 C/A 0.44 0.308 16 ++ 0.93 (0.90-0.97) 1.48E-04 0.032	rc2227276	FGFRIOP	6	16742112	C/T	0.45	0.331	10		0.93(0.90-0.97)	1.09L-04	0.020
ISTACL	re9457254	FGFR10P	6	167434135	C/A	0.45	0.299	13		0.93 (0.90-0.97)	1.14L-04 1 14F_04	0.020
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	rc9457259	FGFR10P	6	167444281	C/T	0.45	0.330	14		0.93 (0.90-0.97)	1.14L-04	0.020
1033 - 1033 -	rc00/2076	PDCA2	12	22027801	C/T	0.45	0.323	14		0.93 (0.90-0.97)	1 /05 04	0.031
	re2027075	FCER1OP	15 6	167//200/	C/A	0.30	0.400	16		0.93 (0.90-0.97)	1.40L-04 1 70F_04	0.032

Chr, chromosome; EAF, effect allele frequency; FDR, false discovery rate; OR, odds ratio; SNP, single nucleotide polymorphism.

^aReference allele/effect allele.

 b Fixed effect models were used when no heterogeneity was found between studies (Q test P > 0.10 and I² < 50.0%); otherwise, random effect models were used.

c'+' means positive association and '-' means negative association.



Figure 2. Regional association plots. Data points are colored according to their level of LD of the each SNP with the tagging SNPs. (A) SNPs in the region 500 kb up- or downstream of the marker SNP and (B) SNPs with FDR \leq 0.050. In A, the left-hand y-axis shows the association P value of individual SNPs, which is plotted as $-\log_10$ (P) against chromosomal base pair position; the right-hand y-axis shows the recombination rate estimated from the hg19/1000 Genomes European population.

influencing the binding activity of transcriptional factors (i.e. HNF-3b, XFD-2). Although rs12212247 might have an effect on the activity of transcription factor binding site (TFBS) as predicted by SNPinfo and RegulomeDB score of 2b (Supplementary Table 4, available at *Carcinogenesis* Online), which indicated that transcription factor TAF1 binding might be influenced according to the Encyclopedia of DNA Elements (ENCODE) ChIP-Seq data from human A549 cells (35), we did not find any significant association of this SNP with FGFR10P mRNA expression levels in either model (Figure 4).

Discussion

The centrosome is the crucial microtubule-organizing center in animal cells and comprises of a pair of centrioles surrounded by the pericentriolar material (36). Centrosome deficiencies, including the occurrence of extra centrioles, and increased ability to nucleate microtubules, are common in a high percentage of many tumors. While centrosome deficiencies in cancer may arise as a result of tumorigenesis, early centrosome aberrations may also lead to increased risk of malignancy (37). Our study firstly attempted to systematically examine the effects of genetic variants in the centrosomal genes on lung cancer susceptibility. Notably, we found two potentially functional SNPs in FGFR1OP to be associated with lung cancer risk in the final meta-analysis of 14 463 lung cancer patients and 44 188 control subjects. Our current study is the first to provide an important insight into the association of variants in 6q27 and carcinogenesis, suggesting that FGFR1OP (rs151606 and rs12212247) could represent a novel lung cancer locus in Caucasian populations.

FGFR1OP (fibroblast growth factor receptor 1 oncogene partner) is a centriolar satellite cargo protein, by which centriolar satellites play the role of key mediators of centrosome functions (38). It has been reported that FGFR1OP is involved in G1/S transition and thus necessary for cell-cycle progression and survival (39). Two chromosomal translocations, fusing this gene with the FGFR1 and RET genes, have been found in hematopoietic cancers (40,41). Published GWASs have identified several SNPs in the nearby region (6q27) of FGFR1OP to be associated with the risk of multiple autoimmune diseases, including Crohn's disease (rs2301436 in FGFR1OP) (42), Graves' disease (rs9355610 near RNASET2) (43), rheumatoid arthritis (rs3093024 and rs3093023 near CCR6) (44,45)

Table 3. Summary of the association results of two SNPs in the eight lung cancer GWASs

	Sample size		T	rs151606 A > T		T	rs12212247 T > C		
Study population	Cases	Controls	quality	OR (95% CI)	Р	quality	OR (95% CI)	Р	
TRICL combined ^a	12 160	16 838		1.12 (1.07–1.17)	1.18E-06		0.93 (0.90–0.97)	8.93E-05	
ICR ^b	1952	5200	0.74	1.19 (1.09–1.30)	1.24E-04	0.99	0.93 (0.86-1.00)	4.44E-02	
MDACC ^c	1150	1134	0.45	1.10 (0.92–1.32)	3.10E-01	0.96	0.95 (0.84-1.07)	3.94E-01	
IARC ^d	2533	3791	0.44	1.04 (0.93–1.17)	5.23E-01	0.98	0.97 (0.90-1.04)	3.52E-01	
NCI ^e	5713	5736	0.72	1.10 (1.03–1.18)	3.28E-03	0.99	0.94 (0.89-0.99)	1.88E-02	
Toronto ^f	331	499	0.70	1.19 (0.91–1.57)	2.06E-01	0.99	0.82 (0.66-1.02)	7.60E-02	
GLC ^g	481	478	0.52	1.16 (0.89–1.50)	2.78E-01	0.98	0.78 (0.65-0.94)	9.02E-03	
Replication combined ^a	2303	27 350		1.02 (0.93–1.11)	7.19E-01		0.93 (0.87-1.00)	3.90E-02	
Harvard ^h	984	970	0.75	1.15 (0.95–1.39)	1.50E-01	1.00	0.88 (0.76-1.01)	5.91E-02	
DeCODEi	1319	26 380	0.75	0.98 (0.89-1.08)	7.50E-01	1.00	0.95 (0.88-1.03)	1.96E-01	
All combined ^a	14 463	44 188		1.10 (1.05–1.14)	8.03E-06		0.93 (0.90–0.96)	9.59E-06	

GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.

^aThe combined OR and P value were estimated using a fixed effects model.

^bICR: the Institute of Cancer Research Genome-wide Association Study, UK.

°MDACC: the MD Anderson Cancer Center Genome-wide Association Study, USA.

dIARC: the International Agency for Research on Cancer Genome-wide Association Study, France;

eNCI: the National Cancer Institute Genome-wide Association Study, USA.

^fToronto: the Lunenfeld-Tanenbaum Research Institute Genome-wide Association Study, Toronto, Canada.

⁸GLC: German Lung Cancer Study, Germany.

^hHarvard: Harvard Lung Cancer Study, USA.

ⁱdeCODE: Icelandic Lung Cancer Study, Iceland.

Α.			В.			С.		
Study Case Control		OR (95% CI)	Study Case Control		OR (95% CI)	Study Case Control		OR (95% CI)
Discovery			Discovery			Discovery		
ICR 1952 5200		1.19 (1.09, 1.30)	ICR 465 5200	-	1.09 (0.93, 1.29)	ICR 611 5200		1.26 (1.09, 1.45)
MDACC 1150 1134		1.10 (0.92, 1.32)	MDACC 619 1134		1.11 (0.89, 1.38)	MDACC 306 1134	-	1.02 (0.76, 1.36)
IARC 2533 3791		1.04 (0.93, 1.17)	IARC 517 2824		1.06 (0.86, 1.31)	IARC 911 2968	_	1.00 (0.85, 1.19)
NCI 5713 5736		1.10 (1.03, 1.18)	NCI 1841 5736		1.06 (0.96, 1.16)	NCI 1447 5736		1.11 (1.00, 1.23)
SLRI 331 499		1.19 (0.91, 1.57)	SLRI 90 499		1.04 (0.68, 1.60)	SLRI 50 499		1.49 (0.85, 2.63)
GLC 481 478		1.16 (0.89, 1.50)	GLC 186 478 -	*	1.10 (0.78, 1.56)	GLC 97 478 -		1.15 (0.72, 1.81)
Subtotal (I-squared = 0.0%, $p = 0.552$)	\diamond	1.12 (1.07, 1.17)	Subtotal (I-squared = 0.0%, p = 0.998)	\diamond	1.07 (1.00, 1.15)	Subtotal (I-squared = 8.9%, p = 0.359)	\diamond	1.12 (1.05, 1.21)
Replication			Replication			Replication		
Harvard 984 970		1.15 (0.95, 1.39)	Harvard 597 970	-	1.15 (0.93, 1.42)	Harvard 216 970 -		0.95 (0.68, 1.32)
deCODE 1319 26380		0.98 (0.89, 1.08)	deCODE 547 26380		0.97 (0.84, 1.13)	deCODE 259 26380 -		0.88 (0.71, 1.08)
Subtotal (I-squared = 51.0%, p = 0.153)	\Diamond	1.02 (0.93, 1.11)	Subtotal (I-squared = 33.9%, p = 0.219)	\Diamond	1.03 (0.91, 1.16)	Subtotal (I-squared = 0.0%, p = 0.706)	\diamond	0.90 (0.75, 1.07)
Heterogeneity between groups: p = 0.051			Heterogeneity between groups: p = 0.562			Heterogeneity between groups: p = 0.021		
Overall (I-squared = 28.8%, p = 0.198)	\$	1.10 (1.05, 1.14)	Overall (I-squared = 0.0%, p = 0.953)	\diamond	1.06 (1.00, 1.13)	Overall (I-squared = 36.1%, p = 0.140)	\$	1.09 (1.02, 1.16)
ف	1 13	7		1 1	.8	с	1	3
D.			L.			1.		
Study Case Control		OR (95% CI)	Study Case Control		OR (95% CI)	Study Case Control		OR (95% CI)
Discovery			Discovery			Discovery		
ICR 1952 5200		0.93 (0.86, 1.00)	ICR 465 5200		0.94 (0.83, 1.08)	ICR 611 5200		0.91 (0.81, 1.02)
MDACC 1150 1134		0.95 (0.84, 1.07)	MDACC 619 1134 -		0.93 (0.80, 1.07)	MDACC 306 1134		1.02 (0.85, 1.23)
IARC 2533 3791		0.97 (0.90, 1.04)	IARC 517 2824	<u> </u>	1.08 (0.94, 1.23)	IARC 911 2968		1.00 (0.90, 1.12)
NCI 5713 5736		0.94 (0.89, 0.99)	NCI 1841 5736		0.94 (0.87, 1.01)	NCI 1447 5736		0.92 (0.85, 1.00)
SLRI 331 499		0.82 (0.66, 1.02)	SLRI 90 499	•	1.08 (0.76, 1.53)	SLRI 50 499	•	0.76 (0.49, 1.19)
GLC 481 478		0.78 (0.65, 0.94)	GLC 186 478		0.81 (0.64, 1.04)	GLC 97 478 —	•	0.71 (0.51, 1.00)
Subtotal (I-squared = 13.4%, p = 0.329)	\diamond	0.93 (0.90, 0.97)	Subtotal (I-squared = 10.0%, p = 0.352)	\diamond	0.95 (0.90, 1.01)	Subtotal (I-squared = 18.9%, p = 0.290)	\diamond	0.94 (0.89, 0.99)
Replication			Replication			Replication		
Harvard 984 970		0.88 (0.76, 1.01)	Harvard 597 970		0.89 (0.77, 1.04)	Harvard 216 970		1.02 (0.80, 1.29)
deCODE 1319 26380		0.95 (0.88, 1.03)	deCODE 547 26380 -		0.88 (0.78, 1.00)	deCODE 259 26380		1.02 (0.86, 1.22)
Subtotal (I-squared = 0.0%, p = 0.321)		0.93 (0.87, 1.00)	Subtotal (I-squared = 0.0%, p = 0.889) <	$\overline{\diamond}$	0.89 (0.81, 0.98)	Subtotal (I-squared = 0.0%, p = 0.965)	~~	1.02 (0.89, 1.18)
Contraction of the second processing	\sim			\sim				
Heterogeneity between groups: p = 0.940			Heterogeneity between groups: p = 0.194			Heterogeneity between groups: p = 0.276		
Overall (I-squared = 0.0%, p = 0.454)	\diamond	0.93 (0.90, 0.96)	Overall (I-squared = 3.6%, p = 0.402)	0	0.94 (0.89, 0.98)	Overall (I-squared = 4.8%, p = 0.393)	Ó	0.95 (0.90, 1.00)
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.5	1 1.3	2	.5	1 1	1.8	.3	1	1.5

Figure 3. Forest plots of effect size and direction for tagSNPs with all cases from TRICL consortium. FGFR10P rs151606 in all cases, $P_{combined} = 8.032 \times 10^{-6}$ (A); FGFR10P rs151606 in adenocarcinoma cases, $P_{combined} = 0.011$ (C); FGFR10P rs12212247 in all cases, $P_{combined} = 9.589 \times 10^{-6}$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (C); FGFR10P rs12212247 in all cases, $P_{combined} = 0.012$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (C); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.012$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.012$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.012$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.012$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.011$ (D); FGFR10P rs12212247 in adenocarcinoma cases, $P_{combined} = 0.043$ (F). Each box and horizontal line represent the OR point estimate and 95% CI derived from the additive model. The area of each box is proportional to the statistical weight of the study. Diamonds represent the summary ORs obtained from the combined analysis with 95% confidence intervals indicated by their widths. The meta-analysis includes eight GWASs [the Institute of Cancer Research (ICR) GWAS, the Lunenfeld-Tanenbaum Research Institute (Toronto)

and vitiligo (rs2236313 in RNASET2 and rs6902119 near CCR6) (46,47). Recent studies have also suggested a link between autoimmune diseases and some cancers (48–50). However, little is known about the association between the genetic variants in FGFR10P and cancer risk. In this study, we observed that FGFR10P rs151606 T allele was associated with decreased levels of mRNA expression and increased risk of lung cancer. These results indicate that the association between SNP rs151606 and lung cancer risk might due

to its effect on the expression of FGFR1OP, as suggested the eQTL evidence for a role of FGFR1OP in the assembling of mitotic spindle (10,13,51). However, the exact molecular mechanism underlying the associations among lower expression of FGFR1OP on spindle multipolarity, centrosome amplification and lung cancer risk warrants additional investigation.

Except for dysregulation of gene expressions, exposure to environmental risk factors has also been shown to induce centrosome abnormality (52). Several studies have reported that exposure to chrysotile asbestos fibers, chromate particles, arsenite, and benzo[a]pyrene diol epoxide, which is a carcinogen present in tobacco smoke as well as in environmental pollution, might cause centrosome abnormalities and multipolar spindles in human lung cells (53–57). Early occurrence of centrosome alterations have been found in the uninvolved lung tissues adjacent to the tumor of NSCLCs, representing an early event in pulmonary carcinogenesis by increasing chromosome instability (58,59). Based on these previous reports and our current findings, analysis of an interaction between SNPs and main environmental risk factors (i.e. smoking status) in future studies might provide novel evidence for the effects of genetic variants in centrosomal genes on lung cancer risk.

Previous studies have identified several genetic variants in centrosomal genes (NIN, TUBG1 and APC) that contributed to breast (60) or pancreatic (61) cancer susceptibility among the Caucasian populations. However, in the present study, we did not find any significance for those SNPs but identified four other SNPs within NIN (rs67977855, rs45558232, rs59096640 and rs4534750) showing moderate associations with lung cancer risk ($P \le 0.05$) based on the six TRICL GWASs results (data not shown). Such inconsistence might due to the heterogeneity among cancers or populations.

There are some potential limitations of the present study. Firstly, the gene-set selection mainly depended on the quality and integrity of curated biological pathways. As the biological understanding of the function of diverse genes in pathways has been steadily improved, the emerging new data on functions of these genes will inevitably expand the currently available lists of 'canonical' pathways. Some important centrosomal genes might be omitted in this study. Considering this, we comprehensively



Figure 4. The correlations between identified SNPs and FGFR1OP mRNA expression. rs151606 (A, additive model, P = 0.022; B, dominant model, P = 0.088; C, recessive model, P = 0.031) and rs12212247 (D, additive model, P = 0.344; E, dominant model, P = 0.465; F, recessive model, P = 0.405).

considered multiple centrosomal gene sets and managed to make an all-inclusive listing as possible as we could. Secondly, defining whether a particular SNP is of biological function was limited by the applied *in silico* tools. To overcome this limitation, we combined the prediction results of multiple bioinformatics tools to explain our data. Thirdly, our eQTL analyses were limited to lymphoblastoid cell lines with publically available data, and gene expression analysis in tissues will give biologically plausible and more convincing results of the effect of those two identified SNPs.

In summary, the present study found significant associations between SNPs in FGFR1OP and lung cancer risk. The results suggested that the SNPs within the centrosomal genes may serve as potential markers to predict lung cancer risk in European populations. Our discoveries shed some new light on the role of centrosome abnormalities in human carcinogenesis. Further validation and functional evaluation of these genetic variants are needed to verify our findings.

URLs

Transdisciplinary Research In Cancer of the Lung (TRICL), http:// u19tricl.org/; Genetic Associations and MEchanisms in ONcology (GAME-ON) consortium, http://epi.grants.cancer.gov/gameon/; International Lung Cancer Consortium (ILCCO), http://ilcco.iarc.fr/; 1000 Genomes Project, http://www.1000genomes.org/; IMPUTE2, http://mathgen.stats.ox.ac.uk/impute/impute_v2.html; MaCH, http://www.sph.umich.edu/csg/abecasis/MACH/; Minimac, http:// genome.sph.umich.edu/csg/abecasis/MACH/; Minimac, http:// www. broadinstitute.org/gsea/msigdb/index.jsp; LocusZoom, http://csg. sph.umich.edu/locuszoom/; RegulomeDB, http://regulome.stanford.edu/; SNPinfo, http://snpinfo.niehs.nih.gov/snpinfo/snpfunc. htm; F-SNP, http://compbio.cs.queensu.ca/F-SNP/.

Supplementary material

Supplementary Tables 1–4 and Figure 1 can be found at http://carcin.oxfordjournals.org/

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TRICL

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deCODE

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