Genetic Variants at 6p21.1 and 7p15.3 Are Associated with Risk of Multiple Cancers in Han Chinese

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Cancer susceptibility loci identified in reported genome-wide association studies (GWAS) are often tumor-specific; however, evidence of pleiotropy of some genes/loci has also been observed and biologically plausible. We hypothesized that there are important regions in the genome harboring genetic variants associated with risk of multiple types of cancer. In the current study, we attempted to map genetic variants that have consistent effects on risk of multiple cancers using our existing genome-wide scan data of lung cancer, noncardia gastric cancer, and esophageal squamous-cell carcinoma with overall 5,368 cases and 4,006 controls (GWAS stage), followed by a further evaluation in additional 9,001 cases with one of these cancer types and 11,436 controls (replication stage). Five variants satisfying the criteria of pleiotropy with p values from 1.10×10^{-8} to 8.96×10^{-6} for genome-wide scans of three cancer types were further evaluated in the replication stage. We found consistent associations of rs2494938 at 6p21.1 and rs2285947 at 7p15.3 with these three cancers in both GWAS and replication stages. In combined samples of GWAS and replication stages, the minor alleles of rs2494938 and rs2285947 were significantly associated with an increased risk of the cancers (odds ratio [OR] = 1.15, 95% confidence interval [CI], 1.10–1.19 and OR = 1.17, 95% CI, 1.12–1.21), with the p values being 1.20×10^{-12} and 1.26×10^{-16}, respectively, which are at a genome-wide significance level. Our findings highlight the potential importance of variants at 6p21.1 and 7p15.3 in the susceptibility to multiple cancers.

Genome-wide association studies (GWAS) have broadened our understanding of genetic variations that confer risk for different types of cancers.[1] Notably, most of risk-related loci are tumor-specific. However, pleiotropy has been observed for several loci, such as the regions of 8q24, 5p15.33 (*TERT* [MIM 187270]-*CLPTM1L* [MIM 612585]), and 9p21.3 (*ANRIL* [MIM 613149]). Among several loci at 8q24 associated with prostate cancer risk,[2–8] at least two have also been associated with risk of colorectal cancer,[9–11] ovarian cancer,[12] or breast cancer.[13] Preliminary results from functional studies have linked a cancer-related variant (rs6983267) at 8q24 to an enhancer that may interact with the known oncogene *MYC* [MIM 190080].[14,15] The *TERT-CLPTM1L* locus has initially been implicated in lung cancer risk.[16,17] In a subsequent study on 17 cancer types, the variant rs401681 allele at the *TERT-CLPTM1L* locus has been associated with increased risk of basal cell, lung, urinary bladder, prostate, and cervical cancers, whereas it conferred protection against cutaneous melanoma.[18] Furthermore, this locus is also associated with risk of cancers of glioma,[19] pancreas,[20] and breast.[21] The *ANRIL* locus at 9p21.3 is associated with risk of coronary artery disease,[22] myocardial infarction,[23] type 2 diabetes,[24] and multiple cancers (glioma,[19,25] basal cell carcinoma,[26] melanoma,[27] breast,[28] and nasopharyngeal carcinoma[29]). Importantly, mouse models have revealed a pivotal role of *Anril* in regulation of CDKN2A/B through and in proliferation and senescence.[30] Thus, evidence of pleiotropy might highlight some common etiological pathways in the development of multiple human cancers.

In light of above evidence, we hypothesized that there are other important genomic regions harboring variants that are associated with risk of multiple types of human

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cancer. To test this hypothesis, we utilized the existing GWAS data on lung cancer,[31] noncardia gastric cancer (NCGC),[32] and esophageal squamous-cell carcinoma (ESCC)[33] that have been associated with a common risk factor of cigarette smoking[34–36] and may have shared susceptibility loci, to map pleiotropic loci contributing to these three types of cancer in Han Chinese populations, followed by further replication in an additionally large case-control set.

Subjects included in the current study and the criteria for their recruitment have been described previously.[31–33] Briefly, for the GWAS stage, 1,473 cases with lung cancer, 550 cases with NCGC, and their shared 1,962 controls were recruited from central region of China (Jiangsu Province and surrounding areas); 858 cases with lung cancer, 456 cases with NCGC, 2,031 cases with ESCC, and their shared 2,044 controls were recruited from northern region of China (Beijing and surrounding areas). In the replication stage, 1,894 cases with NCGC, 3,006 cases with ESCC, and 6,525 controls were recruited from Jiangsu Province and surrounding areas; 1,534 cases with lung cancer, 1,436 cases with NCGC, and 2,922 controls were recruited from Beijing and surrounding areas. An additional set of 1,131 cases with lung cancer and 1,989 controls was recruited from southern region of China (Guangdong Province). Overall, 5,368 cancer cases and 4,006 controls were included in the GWAS stage, and 9,001 cancer cases (2,665 lung cancer, 3,330 NCGC, and 3,006 ESCC) and 11,436 controls were included in the replication stage. All of these subjects provided informed consent. This study was approved by the Institutional Review Boards of all participating institutions.

All samples in the GWAS stage were scanned using Affymetrix Genome-Wide Human SNP Array 6.0 chips (Affymetrix), as described previously.[31–33] Standard quality control procedures on the raw genotyping data were used to filter unqualified samples and SNPs. Individuals were removed from subsequent analyses if they satisfy any of the following items: (1) low call rate (overall rat $< 95\%$), (2) ambiguous gender, (3) duplicates or familial relationship (PI_HAT > 0.025), (4) extreme heterozygosity rate ($>$ mean $+$ 6 SD). SNPs were excluded if they (1) were not mapped to autosome chromosomes, (2) had a call rate $< 95\%$, (3) had minor allele frequency (MAF) < 0.05 in controls, (4) had genotype distributions that deviated from those expected as Hardy-Weinberg equilibrium in controls ($p < 1 \times 10^{-5}$), or (5) failed in any of quality control for GWAS of lung cancer, noncardia gastric cancer, and esophageal squamous-cell carcinoma. As a result, 2,331 cases with lung cancer, 1,006 cases with NCGC, 2,031 cases with ESCC and 4,006 controls retained for the association analyses in the GWAS stage.

Association analyses in the GWAS stage were first performed independently in lung cancer, NCGC and ESCC, and in the cohorts from different areas (Central and Northern). The results from different cohorts for NCGC or ESCC were combined by meta-analysis. Pleiotropic loci were then defined and selected for further confirmation in replication stage according to the following criteria: (1) SNPs had consistent associations ($p < 0.05$) between Central and Northern cohorts for each cancer, (2) consistent associations were shown for all three types of cancer, and (3) $p \leq 1.0 \times 10^{-5}$ for the combined results of three types of cancer in the GWAS stage. As a result, five SNPs were selected for genotyping (see Table S1 available online) in the replication stage using TaqMan assays (Applied Biosystems, Foster City, CA). Sample status (case or control) was blinded to laboratory technicians who performed genotyping. Ten percent of random samples were repeated for rs2494938 and rs2285947, and the overall accordance rates were 99.8% and 99.7%, respectively.

We performed logistic regression analyses independently based on additive model with adjustment for first principal component, age, sex, and smoking status on each GWAS. For NCGC and lung cancer studies in the GWAS stage, we first treated the samples from two cohorts as independent studies (Central and Northern), and then combined the results for each cancer by meta-analysis. Because the shared controls were used for Central or Northern studies in GWAS stage, the combined association results of the three cancers for filtered SNPs with consistent association results were analyzed by pooling all cancer cases together as compared with the shared controls. The same analysis approach was used in the replication stage. The results from GWAS and replication stages or from different regions (Central, Northern, and Southern) were combined by either pooling samples together or using meta-analysis. Similar results were observed for these two approaches and the former one was reported as default in this study unless specified. Meta-analysis was performed in a default fixed-effect model with inverse variance weighted and a calculation of Cochran's Q statistics for homogeneity test. A random-effects model (DerSimonian-Laird) was adopted and the corresponding results were reported if there was indication of heterogeneity between groups ($P_Q \leq 0.05$). Otherwise, the fixed effect model was maintained ($P_Q > 0.05$). PLINK 1.07 was used for genetic association analysis.[37] Analyses were also performed using SAS version 9.1.3 (SAS Institute, Cary, NC) or Stata version 9.2 (StataCorp LP, TX).

The characteristics of 5,368 cases and 4,006 controls included in the GWAS of three types of cancer are shown in Table 1. We first performed logistic regression analyses based on additive model with adjustment for the first principal component, age, sex, and smoking status on each GWAS independently. For lung cancer and NCGC studies, we treated the samples from two cohorts as independent studies (Central study and Northern study), and then estimated combined effect of each locus by meta-analysis.[31,33] Pleiotropic loci were defined as having consistent effects among three types of cancer and between Central and Northern studies in GWAS. As a result, 5 SNPs (rs2399395 at 3q13.2, rs2494938 at 6p21.1, rs2285947 at 7p15.3, rs13232645 at 7q22.1, and

Table 1. Characteristics of Cases with Lung Cancer, Noncardia Gastric Cancer, or Esophageal Squamous-Cell Carcinoma and Controls Included in GWAS and Replication Stages

Studies	Data Set	Region	No.	Age (Mean ± SD)	Sex (males, %)	Smoking Status (smokers, %)
Total cases			**14,369**	**59.53 ± 10.68**	**72.19**	**50.09**
Lung cancer	GWAS	Central	1,473	60.08 ± 10.30	71.76	44.81
	GWAS	Northern	858	60.00 ± 10.23	76.22	59.91
	Replication	Northern	1,534	58.14 ± 9.71	67.08	59.97
	Replication	Southern	1,131	60.27 ± 12.32	70.73	55.88
NCGC	GWAS	Central	550	58.24 ± 11.91	71.27	44.91
	GWAS	Northern	456	56.79 ± 12.42	70.61	28.29
	Replication	Central	1,894	58.71 ± 11.97	70.49	46.73
	Replication	Northern	1,436	57.06 ± 12.11	69.29	25.49
ESCC	GWAS	Northern	2,031	59.84 ± 9.78	80.11	65.24
	Replication	Central	3,006	61.70 ± 8.54	71.92	50.57
Total controls			**15,442**	**59.00 ± 11.73**	**70.24**	**43.70**
	GWAS	Central	1,962	59.35 ± 9.74	61.88	53.82
	GWAS	Northern	2,044	61.34 ± 8.55	83.46	38.38
	Replication	Central	6,525	58.32 ± 11.92	68.29	28.64
	Replication	Northern	2,922	58.24 ± 12.86	70.12	68.62
	Replication	Southern	1,989	59.59 ± 13.49	71.49	51.33

rs9982863 at 21q22.3) were identified (Table S1). Because similar frequency and effect on the three types of cancer were observed across studies each of these 5 SNPs, the subjects from different studies were combined directly to test the associations. We observed that the combined p values were 1.10×10^{-8} to 8.96×10^{-6} for these five SNPs (Table S1).

We next performed replications of above five promising SNPs in overall 9,001 cases with three types of cancer (2,665 lung cancer, 3,330 NCGC, and 3,006 ESCC) and 11,436 controls. We found that rs2399395 at 3q13.2 and rs13232645 at 7q22.1 were replicated only in ESCC and lung cancer (nominal $p < 0.05$), respectively, whereas rs9982863 at 21q22.3 was not significantly associated with any type of cancer (Table S2). Thus, these three SNPs were not further investigated. The remaining two SNPs, rs2494938 at 6p21.1 and rs2285947 at 7p15.3, were both associated with all three types of cancer. In combined sample, the odds ratios (ORs) for rs2494938 and rs2285947 were 1.15 (95% confidence interval [CI], 1.10–1.19; $p = 1.20 \times 10^{-12}$) and 1.17 (95% CI, 1.12–1.21; $p = 1.26 \times 10^{-16}$), respectively (Table 2). For both rs2494938 and rs2285947, no significant heterogeneity of associations was observed between the GWAS and replication studies or among the Northern, Central, and Southern cohorts (all $p_Q > 0.05$) (Figure S1).

To further characterize the loci at 6p21.1 and 7p15.3 associated with risk of multiple cancers, we imputed untyped SNPs in the flanking regions of rs2494938 and rs2285947 within a 250 kb window for subjects in the GWAS stage using the CHB+JPT data from the 1000 Genomes database (released at June 2010) as reference haplotype using Minimac software. Regional plots were generated by three cancer types according to p value of association for each SNP using LocusZoom.[38] As shown in Figure S2, SNPs with lower p values at both regions were observed for each cancer. After conditioning on lead SNP (rs2494938 or rs2285947) for respective region, none of the associations were found with a $p < 0.001$ for the remaining SNPs at 6p21.1 and 7p15.3 except for association of variants at 7p15.3 with ESCC risk, suggesting that no additional independent loci exist at these two regions for lung cancer and NCGC. However, further studies are warranted to assess the independence of associations of variants at 7p15.3 with ESCC risk.

With an effort to show potential biofeatures of association, the locus at 6p21.1 was annotated based on UCSC genome browser (Figure S3). SNPs in strong LD with rs2494938 at 6p21.1 are located in the initial region (including promoter, exon 1, and intron 1) of *LRFN2* [MIM 612808] (encoding leucine-rich repeat and fibronectin type III domain-containing protein 2), a member of synaptic adhesion-like molecules (SALMs) family that interacts with the N-methyl D-aspartate (NMDA) receptor.[39] It has been reported that the LRFN2 can subvert hematopoietic differentiation to increase erythropoiesis and lead to erythroblastosis in cooperation with MYC.[40] NMDA receptors are glutamate receptors, consisting of

Table 2. Associations of rs2494938 at 6p21.1 and rs2285947 at 7p15.3 with the Risks of Lung Cancer, Noncardia Gastric Cancer, and Esophageal Squamous-Cell Carcinoma

Studies	6p21.1: rs2494938 (G/A)[a]				7p15.3: rs2285947 (G/A)[a]			
	N (cases/controls)	MAF[b] (cases/controls)	OR (95%CI)[c]	p[c]	N (cases/controls)	MAF[b] (cases/controls)	OR (95%CI)[c]	p[c]
Lung Cancer								
GWAS-Central	1,473/1,962	0.24/0.22	1.13(1.01–1.26)	3.70×10^{-2}	1,457/1,947	0.29/0.27	1.12(1.00–1.24)	4.69×10^{-2}
GWAS-Northern	858/2,044	0.25/0.22	1.18(1.03–1.35)	1.42×10^{-2}	856/2,044	0.31/0.26	1.24(1.09–1.41)	7.48×10^{-4}
Replication-Northern	1,534/2,905	0.25/0.23	1.13(1.02–1.25)	2.21×10^{-2}	1,526/2,986	0.32/0.28	1.19(1.08–1.31)	4.45×10^{-4}
Replication-Southern	1,114/1,971	0.27/0.23	1.18(1.05–1.33)	4.86×10^{-3}	1,118/1,976	0.25/0.22	1.14(1.01–1.29)	2.90×10^{-2}
Combined	**4,979/8,882**	**0.25/0.23**	**1.15(1.08–1.22)**	$\mathbf{1.95 \times 10^{-6}}$	**4,957/8,863**	**0.29/0.26**	**1.17(1.11–1.24)**	$\mathbf{1.57 \times 10^{-8}}$
NCGC								
GWAS-Central	550/1,962	0.26/0.22	1.25(1.07–1.46)	3.94×10^{-3}	546/1,947	0.30/0.27	1.19(1.03–1.38)	1.92×10^{-2}
GWAS-Northern	456/2,044	0.26/0.22	1.31(1.10–1.55)	2.34×10^{-3}	434/2,044	0.33/0.26	1.41(1.19–1.66)	5.64×10^{-5}
Replication-Central	1,882/6,488	0.26/0.23	1.17(1.07–1.27)	3.01×10^{-4}	1,876/6,452	0.29/0.27	1.11(1.02–1.20)	1.55×10^{-2}
Replication-Northern	1,434/2,905	0.26/0.23	1.16(1.03–1.30)	1.22×10^{-2}	1,431/2,896	0.30/0.28	1.10(0.99–1.23)	8.62×10^{-2}
Combined	**4,322/13,399**	**0.26/0.23**	**1.18(1.12-1.25)**	$\mathbf{4.91 \times 10^{-9}}$	**4,287/13,339**	**0.30/0.27**	**1.14(1.08–1.21)**	$\mathbf{1.36 \times 10^{-6}}$
ESCC								
GWAS-Northern	2,031/2,044	0.26/0.22	1.23(1.11–1.37)	8.82×10^{-5}	2,029/2,044	0.31/0.26	1.23(1.12–1.36)	2.67×10^{-5}
Replication-Central	2,990/6,488	0.25/0.24	1.09(1.01–1.18)	2.48×10^{-2}	2,985/6,452	0.29/0.27	1.10(1.02–1.18)	9.40×10^{-3}
Combined	**5,021/8,532**	**0.25/0.23**	**1.13(1.06–1.20)**	$\mathbf{5.58 \times 10^{-5}}$	**5,014/8,496**	**0.30/0.27**	**1.14(1.08–1.21)**	$\mathbf{3.24 \times 10^{-6}}$
All combined	**14,322/15,370**	**0.25/0.23**	**1.15(1.10–1.19)**	$\mathbf{1.20 \times 10^{-12}}$	**14,258/15,315**	**0.30/0.27**	**1.17(1.12–1.21)**	$\mathbf{1.26 \times 10^{-16}}$

[a]Major/minor alleles.
[b]MAF: minor allele frequency.
[c]Odds ratios (ORs), 95% confidence intervals (CIs), and p values were calculated in additive models with adjustment for age, sex, and smoking status.

NR1 and NR2 (2A to 2D) subunits.[41,42] NMDA receptor 2B (NR2B) is methylated in ESCC and non-small cell lung cancer and exhibit a tumor-suppressive activity.[43,44] Interestingly, it is recently revealed that NMDA channels may play an important proapoptotic function in gastric surface epithelial cells and regulate cell survival and death pathways during development of gastric cancers associated with *H. pylori* infection.[45] However, the exact mechanism of the locus at 6p21.1 is largely unknown though *LRFN2* might function as a susceptibility gene for multiple cancers through LRFN2-NMDA receptor pathway.

The locus of 7p15.3 was also annotated in Figure S4, and SNPs in strong LD with rs2285947 are located in the initial parts of both *SP4* (Specificity Protein 4 [MIM 600540]) and *DNAH11* (Dynein, axonemal, heavy chain 11 [MIM 603339]). Publicly available data of *cis*-expression quantitative trait loci (eQTLs) indicate that rs7788515, a SNP in strong LD with rs2285947 ($r^2 = 0.92$), is associated with the expression of *DNAH11* ($p = 5.4 \times 10^{-7}$).[46] Dyneins are microtubule-associated motor protein complexes. Functional link has been established between MAPK (mitogen-activated protein kinase) components and dynein motors, which are indispensable for activation of MAPK kinase3/6 and p38 in vivo.[47] The p38-MAPK pathway that is strongly activated by stress plays important roles in the immune and inflammatory responses[48,49] as well as in the regulation of cell survival, differentiation, and migration.[50,51] However, the effects of variants in this region could be on other genes or non-coding regulatory elements at a distance, and further functional studies are warranted to understand the potentially functional significance of cancer risk-related locus at 7p15.3.

In the current study, we identified two loci at 6p21.1 and 7p15.3 that may serve as susceptibility loci for multiple cancers. Although the approach searching consistent effects on all three cancer types used in this study may represent a cost-efficient manner to discover loci of pleiotropy, it may be too stringent and miss some real loci associated with multiple cancers even though some loci were inconsistent in one study. Therefore, further studies by removing each study per disease may introduce

more candidate loci for further replication and facilitate to discover additional pleiotropy loci. Moreover, these two loci were not investigated and reported in individual cancer study previously[31–33] due to relative high p values in GWAS stage ($p > 10^{-5}$). A genome-wide significance was observed after combining GWAS and replication stages for associations of rs2494938 at 6p21.1 with NCGC ($p = 4.91 \times 10^{-9}$) and rs2285947 at 7p15.3 with lung cancer ($p = 1.57 \times 10^{-8}$), suggesting that further comprehensive replication studies for individual cancer GWAS are required to indentify missing susceptibility loci.

In summary, our study indicates variants at 6p21.1 and 7p15.3 as candidate susceptibility loci for multiple types of human cancer, though the biological mechanism remains to be elucidated. Further investigations are warranted to extend these findings to other types of human cancers and to other ethnic populations.

Supplemental Data

Supplemental Data includes four figures, two tables, and Supplemental Experimental Procedures and can be found with this article online at http://www.cell.com/AJHG/.

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Web Resources

The URLs for data presented herein are as follows:

LocusZoom, https://statgen.sph.umich.edu/locuszoom/
Minimac, http://genome.sph.umich.edu/wiki/Minimac/
Online Mendelian Inheritance in Man (OMIM), http://www.omim.org/
Plink, http://pngu.mgh.harvard.edu/~purcell/plink/
UCSC genome browser, http://genome.ucsc.edu/

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