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Genetic variant in *TP63* on locus 3q28 is associated with risk of lung adenocarcinoma among never-smoking females in Asia

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Abstract

A recent genome-wide association study (GWAS) of subjects from Japan and South Korea reported a novel association between the *TP63* locus on chromosome 3q28 and risk of lung adenocarcinoma ($p = 7.3 \times 10^{-12}$); however, this association did not achieve genome-wide significance ($p < 10^{-7}$) among never-smoking males or females. To determine if this association

with lung cancer risk is independent of tobacco use, we genotyped the *TP63* SNPs reported by the previous GWAS (rs10937405 and rs4488809) in 3,467 never-smoking female lung cancer cases and 3,787 never-smoking female controls from 10 studies conducted in Taiwan, Mainland China, South Korea, and Singapore. Genetic variation in rs10937405 was associated with risk of lung adenocarcinoma [n = 2,529 cases; $p = 7.1 \times 10^{-8}$; allelic risk = 0.80, 95% confidence interval (CI) = 0.74–0.87]. There was also evidence of association with squamous cell carcinoma of the lung (n = 302 cases; p = 0.037; allelic risk = 0.82, 95% CI = 0.67–0.99). Our findings provide strong evidence that genetic variation in *TP63* is associated with the risk of lung adenocarcinoma among Asian females in the absence of tobacco smoking.

Introduction

In our initial genome-wide association study (GWAS) of lung cancer among never-smoking females from East Asia, we found that genetic variation in the *CLPTM1L-TERT* locus on 5pl5.33 was associated with risk of lung adenocarcinoma (Hsiung et al. 2010). Recently, a GWAS conducted among subjects from Japan and South Korea replicated the association between lung adenocarcinoma and the *CLPTM1L-TERT* locus in East Asians (Miki et al. 2010). This scan also identified a novel association between lung adenocarcinoma and the *TP63* locus on 3q28 (Miki et al. 2010); however, when restricted to never-smoking males [odds ratios (OR) = 1.22, 95% confidence intervals (95% CI) = 0.96–1.56; p = 0.012] and never-smoking females [OR = 1.38, 95% CI = 1.20–1.57; $p = 3.5 \times 10^{-6}$], the association was less clear as it did not achieve genome-wide significance ($p \leq 10^{-7}$). To further explore the strength of this association with lung cancer risk in the absence of tobacco use, we expanded our initial pool of lung cancer studies conducted in East Asia (Hsiung et al. 2010) to include 10 studies conducted in Mainland China, Taiwan, South Korea, and Singapore and genotyped the *TP63* SNPs (rsl0937405 and rs4488809) initially reported by Miki et al. (2010) in 3,467 never-smoking female cases and 3,787 never-smoking female controls.

Methods

Seven of the 10 lung cancer studies in East Asia pooled for this effort were described previously in our first lung cancer GWAS (Hsiung et al. 2010). These seven studies include the Genetic Epidemiological Study of Lung Adenocarcinoma (GELAC) (Jou et al. 2009), the Chinese Academy of Medical Sciences Cancer Hospital Study (CAMSCH) (Wu et al. 2009), the Seoul National University Study (SNU) (Kim et al. 2006), the Korea University Medical Center Study (KUMC) (Jung et al. 2008), the Kyungpook National University Hospital Study (KNUH) (Park et al. 2002), the Shanghai Women's Health Cohort Study (SWHS) (Zhang et al. 2007; Zheng et al. 2005), and the Genes and Environment in Lung Cancer, Singapore Study (GEL-S) (Tang et al. 2010). For this effort, we pooled an additional three studies from Mainland China, including the Shenyang Lung Cancer Study (SLCS) (Yin et al. 2009), the Fudan Lung Cancer Study (FLCS), and the Tianjin Lung Cancer Study (TLCS) (Qian et al. 2011). All studies were case–control by design, except the SWHS, which was a prospective cohort study. Each study was approved by the local institutional review board and all study participants provided informed consent.

In the aggregate, we included 3,787 never-smoking female controls and 3,467 never-smoking female lung cancer cases, of which 2,557 (74%) were adenocarcinomas and 309 (9%) were squamous cell carcinomas. All cases and controls were genotyped for rs10937405 and rs4488809 using TaqMan assays designed by the National Cancer Institute Core Genotyping Facility (CGF). The TaqMan assays (Applied Biosystems Inc., Foster City, CA) were optimized on the ABI 7900HT detection system with high concordance with the sequence analysis of 102 individuals as listed on the SNP500Cancer website (http://

www.snp500cancer.nci.nih.gov). SNU, KUMC, KNUH, and SWHS samples were all genotyped at the CGF. The GELAC and GEL-S studies were genotyped in Taiwan and Singapore, respectively. Genotyping for the CAMSCH, SLCS, TLCS and FLCS studies were conducted at their local institutions in Mainland China. All of the genotype frequencies showed fitness for Hardy–Weinberg proportion ($p > 0.05$) using a χ^2 test. Genotype completion rates were greater than 97% across all studies.

Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by logistic regression models using the homozygote of the common allele as the reference group and adjusting for study and age as a continuous variable. Tests for trend were conducted by assigning the ordinal values (0,1,2) to the most prevalent genotypes in rank order of wild type, heterozygous, and variant homozygous genotypes, respectively. All statistical analyses were performed using SAS (Cary, NC).

Results

Ten lung cancer studies in East Asia included a total of 3,467 cases and 3,787 controls (Table 1). All cases and controls were never-smoking females. Cases and controls in each study were similar in age.

Of the two *TP63* SNPs we genotyped, Table 2 shows that rs10937405 achieved genome-wide significance ($p = 7.2 \times 10^{-8}$; T allelic risk = 0.82, 95% CI = 0.76-0.88). The risk was predominately associated with the risk of lung adenocarcinoma ($p = 7.1 \times 10^{-8}$; allelic risk = 0.80, 95% CI = 0.74–0.87) (Table 2). The magnitude and direction of lung adenocarcinoma risk associated with rs10937405 were similar in most studies (heterogeneity $p = 0.43$) (Fig. 1; Supplemental Table 1). The T allele at rs10937405 was marginally associated with risk of squamous cell carcinoma ($p = 0.037$; allelic risk = 0.82, 95% CI = 0.67–0.99).

The associations between rs4488809 and lung cancer are provided for all lung cancer ($p = 0.0011$; allelic risk = 1.12, 95% CI = 1.05–1.19), adenocarcinoma ($p = 7.4 \times 10^{-5}$; allelic risk = 1.16, 95% CI = 1.08–1.24), and squamous cell carcinoma ($p = 0.65$; allelic risk = 0.96, 95% CI = 0.81–1.14) in Supplemental Table 2. Supplemental Table 3 presents the risk of rs4488809 associated with all lung cancers and lung adenocarcinomas by study. When both rsl0937405 ($p = 0.0001$; allelic risk = 0.82, 95% CI = 0.75–0.91) and rs4488809 ($p = 0.31$; allelic risk = 1.05, 95% CI = 0.96–1.14) were included in the same logistic regression model, only rs10937405 remained significant for adenocarcinoma.

Discussion

We have replicated the association between lung adeno-carcinoma and a SNP marker, rs10937405 that localizes to the *TP63* gene. This marker was previously reported by a GWAS conducted in Japan and South Korea (Miki et al. 2010). We have been able to expand the initial findings by evaluating this risk in women who have never smoked tobacco. Contrary to Miki et al. (2010), *TP63* rsl0937405 showed a stronger association with lung cancer in our population than did *TP63* rs4488809. A recent study among Han Chinese also found that genetic variation in the *TP63* region was associated with lung cancer risk, with the effects being more pronounced for rs4488809, although the results were not reported for never-smoking females (Hu et al. 2011).

The location of the SNP rs10937405 maps to the *TP63* gene, whose product, p63, is an important component of the p53 family of genes. The p53 pathway plays a critical role in cell-cycle regulation by functioning as a tumor suppressor in numerous cancers, and p53 mutations occur in about two-thirds of all human cancer (Hernandez-Boussard et al. 1999).

Further, p63 has been found to play an important role in cancer development and progression through its interaction with mutant p53 (Melino 2011). An isoform of *TP63* has been proposed to have oncogenic properties on the basis of its dominant negative effects on p53, and *TP63* genomic gains have been identified as potential indicators of pre-invasive lung lesions and early lung cancer diagnosis (Massion et al. 2009).

It is notable that lung cancer risk was not associated with *TP63* variants at the genome-wide significance level in previous GWAS conducted in subjects of European descent (Amos et al. 2008; Hung et al. 2008; McKay et al. 2008; Wang et al. 2008; Landi et al. 2009). A GWAS carried out in Europe reported a suggestive but weak association between lung cancer and *TP63* rs4488809 (Hung et al. 2008). Given that the allele frequencies are similar between the Asian and Caucasian HapMap populations for *TP63* rs10937405 (T allele: Asian = 30%, Caucasian = 36%) and *TP63* rs4488809 (T allele: Asian = 48%, Caucasian = 49%), and that the numbers of cases and controls in the Caucasian studies were larger than in the East Asian studies, these efforts had similar power to detect an association. The weaker association found in Caucasians compared with East Asians may be due to the different environmental exposures in North America and Europe compared to those in East Asia. In particular, the subjects in the European descent lung cancer GWAS were primarily tobacco smokers, whereas our Asian study populations were restricted to never-smokers. Alternatively, genomic coverage with the current platforms of the causal, functional variant in this region may be higher for Asian compared with Caucasian populations; therefore, the association between the tested SNPs and the causal variant may be lower in Caucasians as compared to Asians.

Globally, cigarette smoking is the primary risk factor for lung cancer, with 85% of tumors in men and 47% in women attributed to smoking tobacco (Parkin et al. 2005). Although only 10–15% of lung cancers occur in non-smokers, this still accounts for about 200,000 incident cancer cases worldwide per year. Extensive research has been conducted on the environmental and genetic determinants of nonsmoking lung cancer throughout Asia (Lan et al. 2000, 2002, 2004; Hosgood III et al. 2007, 2008; Yang et al. 2004; Xu et al. 1989; Lubin et al. 2005), where lung cancer rates among nonsmoking women in some regions are among the highest in the world (Mumford et al. 1987; Lam 2005). The relatively high rates of lung cancer among nonsmoking females in Asia are partially attributed to known environmental risk factors, such as exposure to combustion products of indoor heating and cooking solid fuel and cooking oil fumes (Lubin et al. 2005; Lan et al. 2002; Hosgood III et al. 2011). In-home coal used for heating and cooking has been classified as carcinogenic in humans (Straif et al. 2006), and genetic variation has been shown to influence this association (Hosgood III et al. 2007, 2008; Lan et al. 2000). North American and Western European populations do not typically experience these high levels of indoor air pollution exposures attributed to indoor heating and cooking.

In conclusion, our study of never-smoking lung cancer among Asian females has reported an association with genetic variants in the *TP63* region. Since it is unlikely that genetic variation alone will explain the lung cancer burden among never-smoking females in Asia, further research is needed to identify environmental exposures and gene–environment interactions in these populations. Further, the functional genetic variants and mechanisms underpinning this association will require additional studies including fine mapping and laboratory studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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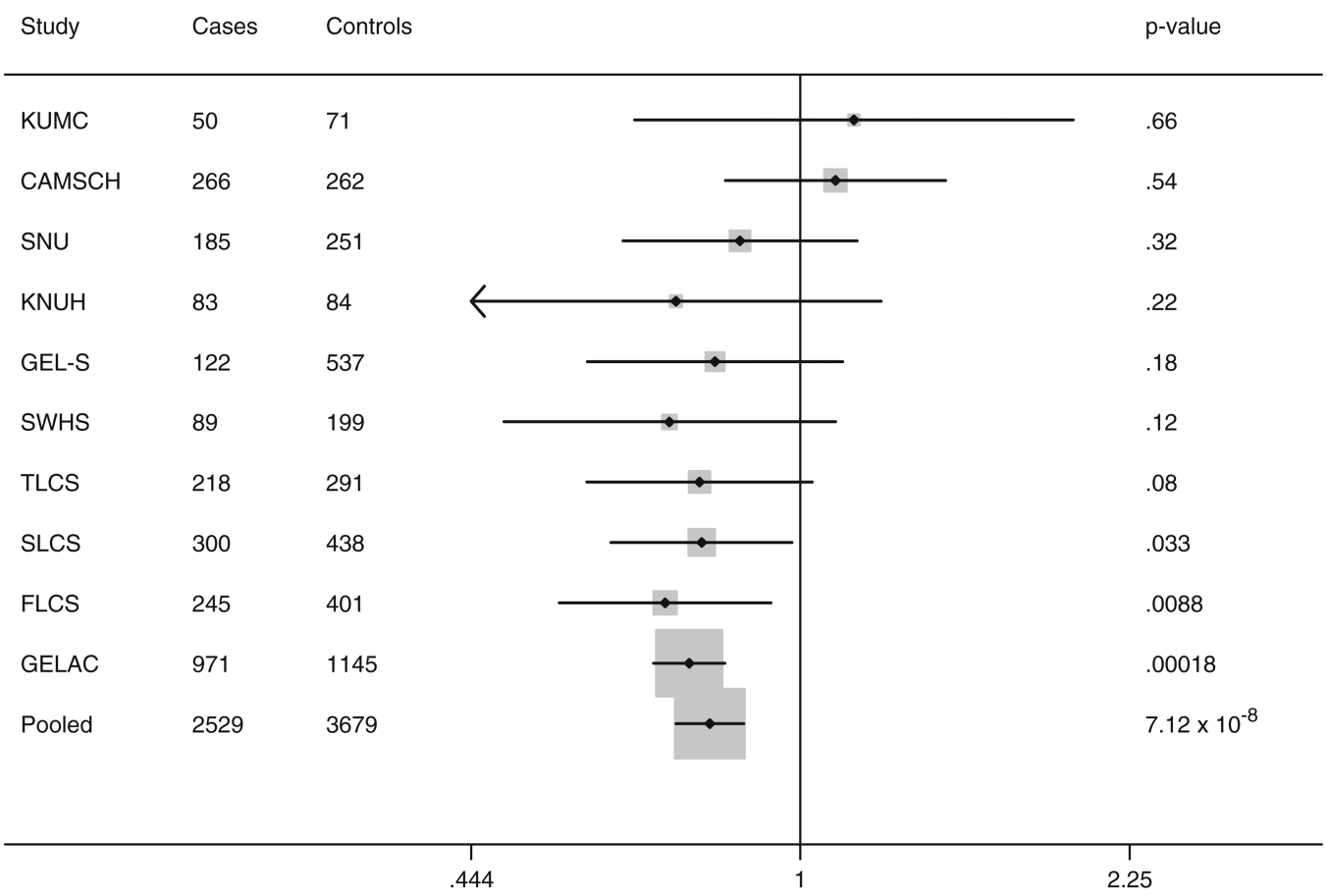

Fig. 1.

Lung adenocarcinoma risk associated with *TP63* rs 10937405 among never-smoking females from Asia, by study. Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age; *KUMC* Korea University Study, *KNUH* Kyungpook National University Study, *FLCS* Fudan Lung Cancer Study, *SLCS* Shenyang Lung Cancer Study, *SWHS* Shanghai Women's Health Cohort Study, *SNU* Seoul National University Study, *CAMSCH* Chinese Academy of Medical Sciences Cancer Hospital Study, *GELS* Genes and Environment in Lung Cancer, Singapore Study, *GELAC* Genetic Epidemiological Study of Lung Adenocarcinoma (in Taiwan), *TLCS* Tainjin Lung Cancer Study

Table 1

Region, study design, and number of cases and controls for each participating study

Study center	Region	Cases (*n* = 3,467)	Controls (*n* = 3,787)	Age [mean (std)]		Study design
				Cases	Controls	
GELAC	Taiwan	1,193	1,145	59.6 (11.5)	57.9 (12.6)	Case control
SLCS	Mainland China	450	450	56.6 (12.1)	56.4(11.4)	Case control
FLCS	Mainland China	424	404	59.2 (11.4)	59.9(11.3)	Case control
CAMSCH	Mainland China	321	321	56.9 (10.3)	48.5 (13.7)	Case control
TLCS	Mainland China	300	306	57.2 (9.8)	57.2 (9.9)	Case control
SNU	South Korea	225	258	61.6 (10.4)	60.7 (10.2)	Case control
GEL-S	Singapore	193	537	63.3 (12.0)	64.8 (11.5)	Case control
SWHS	Mainland China	193	200	59.0 (8.2)	58.6 (8.4)	Cohort
KNUH	South Korea	97	90	61.7 (9.3)	61.1 (6.9)	Case control
KUMC	South Korea	71	76	62.7 (10.8)	60.9 (6.5)	Case control

KUMC Korea University Study, *KNUH* Kyungpook National University Study, *FLCS* Fudan Lung Cancer Study, *SLCS* Shenyang Lung Cancer Study, *SWHS* Shanghai Women's Health Cohort Study, *SNU* Seoul National University Study, *CAMSCH* Chinese Academy of Medical Sciences Cancer Hospital Study, *GEL-S* Genes and Environment in Lung Cancer, Singapore Study, *GELAC* Genetic Epidemiological Study of Lung Adenocarcinoma (in Taiwan), *TLCS* Tainjin Lung Cancer Study

Table 2

Lung cancer risk associated with *TP63* rs 10937405 among never-smoking females from Asia, by histology

rs number	Genotype	Controls		Cases		OR[a]	95% CI[a]	*p* value
		n	%	*n*	%			
rsl0937405		*All lung cancers*						
	CC	1,791	48.7	1,872	54.8			
	CT	1,572	42.7	1,313	38.4	0.80	0.72–0.88	5.4×10^{-6}
	TT	316	8.6	230	6.7	0.69	0.58–0.83	7.2×10^{-5}
	Trend					0.82	0.76–0.88	7.2×10^{-8}
		Adenocarcinomas						
	CC	1,791	48.7	1,406	55.6			
	CT	1,572	42.7	953	37.7	0.77	0.69–0.86	2.0×10^{-6}
	TT	316	8.6	170	6.7	0.68	0.56–0.83	0.00015
	Trend					0.80	0.74–0.87	7.1×10^{-8}
		Squamous cell carcinomas						
	CC	1,791	48.7	163	54.0			
	CT	1,572	42.7	121	40.1	0.84	0.66–1.07	0.17
	TT	316	8.6	18	6.0	0.63	0.38–1.03	0.068
	Trend					0.82	0.67–0.99	0.037

[a]Odds ratios (OR) and 95% confidence intervals (CI) adjusted for study and age