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International Lung Cancer Consortium: Coordinated association study of 10 potential lung cancer susceptibility variants

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***Background*. Analysis of candidate genes in individual studies has had only limited success in identifying particular gene variants that are conclusively associated with lung cancer risk. In the International Lung Cancer Consortium (ILCCO), we conducted a coordinated genotyping study of 10 common variants selected because of their prior evidence of an association with lung cancer. These variants belonged to candidate genes from different cancer-related pathways including inflammation (*IL1B*), folate metabolism (*MTHFR*), regulatory function (*AKAP9* and *CAMKK1*), cell adhesion (*SEZL6*) and apoptosis (*FAS*, *FASL*, *TP53*, *TP53BP1* and *BAT3*). *Methods*. Genotype data from 15 ILCCO case–control studies were available for a total of 8431 lung cancer cases and 11 072 controls of European descent and Asian ethnic groups. Unconditional logistic regression was used to model the association between each variant and lung cancer risk. *Results*. Only the association between a non-synonymous variant of *TP53BP1* (rs560191) and lung cancer risk was significant (OR = 0.91, $P = 0.002$). This association was more striking for squamous cell carcinoma (OR = 0.86, $P = 6 \times 10^{-4}$). No heterogeneity by center, ethnicity, smoking status, age group or sex was observed. In order to confirm this association, we included results for this variant from a set of independent studies (9966 cases/11 722 controls) and we reported similar results. When combining all these studies together, we reported an overall OR = 0.93 (0.89–0.97) ($P = 0.001$). This association was significant only for squamous cell carcinoma [OR = 0.89 (0.85–0.95), $P = 1 \times 10^{-4}$]. *Conclusion*. This study suggests that rs560191 is associated to lung cancer risk and further highlights the value of consortia in replicating or refuting published genetic associations.**

Introduction

It has been long recognized that there is a genetic component for lung cancer based on familial studies and analysis of family cancer history in case–control studies (1–5). However, progress in identifying specific susceptibility loci and genes has been slow, mainly due to inadequate study designs, underpowered sample sizes and preferential reporting of false-positive findings. Recently, several genome-wide association studies (GWAS) reported lung cancer susceptibility loci at 15q25, 6p21 and 5p15.33, providing additional evidence of a genetic contribution to lung cancer (6–10).

Although replication of findings is fundamental to the GWAS approach, the replication of significant variants in studies based on the more traditional candidate gene approach may also be an important procedure. To confirm the role of candidate genetic variants that were found to be associated with lung cancer risk, we established a fast-track replication mechanism for testing genetic variants within the framework of the International Lung Cancer Consortium (ILCCO).

Abbreviations: GWAS, genome-wide association studies; ILCCO, International Lung Cancer Consortium; SNPs, single nucleotide polymorphisms.

†See Appendix for the complete list of co-authors of EPIC-lung and their affiliations.

ILCCO was established in 2004 with the aim of sharing comparable data from ongoing lung cancer case–control and cohort studies. The overall objectives are to increase statistical power, especially for subgroup analyses, reduce duplication of research efforts, replicate novel findings and afford substantial cost savings through large collaborative efforts. Details on the organization of the consortium have been published previously (11).

In order to prioritize genetic variants for this rapid replication within the consortium, a procedure was established to replicate genetic variants newly associated with risk in previous lung cancer studies. Two criteria were used to prioritize the genetic variants: (i) a similar significant main effect ($P < 0.05$) in at least two studies, both of which had sample sizes of at least 500 case–control pairs or (ii) a strongly significant main effect ($P < 0.001$) from a single study. Ten potential lung cancer susceptibility variants meeting the criteria were proposed by the consortium members for replication (Table I). These variants belonged to genes from various cancer-related pathways including inflammation (*IL1B*), folate metabolism (*MTHFR*), regulatory function (*AKAP9* and *CAMKK1*), cell adhesion (*SEZL6*) and apoptosis (*FAS*, *FASL*, *TP53*, *TP53BP1* and *BAT3*). The description of the selected variants is detailed in supplementary Table I (available at *Carcinogenesis* Online).

Materials and methods

Study population

In the current study, we conducted a coordinated genotyping of 10 potential lung cancer susceptibility variants in 15 studies. From these studies, six were conducted in the USA, six in Asia and three in Europe. Study designs are briefly outlined in Table II, and more detailed information for some of these studies has been published previously (6,20–31). Studies are referred to by study location or coordinating institute.

Eligibility criteria based on age were applied in two studies: ≤50 years for the German study and <65 years for the University of California, Los Angeles study. Eligibility criteria based on smoking status were applied in three studies: the Singapore study was restricted to never-smoking women, whereas the MD Anderson and Norway studies included only ever smokers. In all studies, cases were histologically or cytologically confirmed, except in the NCI-China study where the inclusion criteria comprise a positive histology or cytology, or clinically diagnosed cases that died within a 1 year period. Therefore, the NCI-China study did not have information on histology for all cases. The Norway study was restricted to non-small cell carcinomas cases. The control group in most of the studies was frequency matched to the cases on age and sex, whereas some also matched on ethnicity, residence area or smoking status, and two studies did not apply any matching factors (Kyushu University and Mayo clinic studies).

Written informed consent was obtained from all study subjects, and approval from the relevant ethics board was obtained at each study center. Genotype data were available for a total potential number of 8705 cases and 11 562 controls, of whom 68% where European descent, 28% were Asian and 4% were of different ethnic groups (African-American, Hispanic, Native Hawaiian and American Indian). Only European descent (5876 cases and 7874 controls) and Asian (2555 cases and 3198 controls) ethnic groups were included in the present study. The remaining ethnic groups were excluded due to small sample size.

Genotyping and quality control

Genomic DNA was extracted from blood samples in all centers, except in the Penn State College of Medicine and the NCI-China studies for which DNA was extracted from oral buccal mucosa cells. Several studies had independently genotyped some of the selected variants prior to this initiative using their own protocol and did not genotype additional variant (German, MD Anderson, NCI-China, Aichi and Nanjing-China studies). The genotyping procedures of these studies are described elsewhere (6,23,24,28,31). For all other centers, the genotyping was done locally using Taqman (Applied Biosystems, Forster City, CA). Three studies (Kyushu, Seoul and Singapore studies) genotyped a subset of the selected single nucleotide polymorphisms (SNPs) due to DNA availability. Procedures for inter-laboratory quality control were applied for the German study and all centers that used Taqman probes: each genotyped a generic series of common DNAs (either SNP500, HapMap CEU trios or International Agency for Research on Cancer generic series) using their local genotyping facility. The genotype concordance across studies was subsequently computed for each genotyping assay. Discrepancies rates for all assays were <5%. Studies with a call rate of <90% for a variant were excluded from analysis for that variant. Table III shows the number of cases and controls included in analysis and minor allele frequency among controls for each variant and each study by ethnic group. It should be noted that in this replication study, centers that have generated the hypothesis on a variant were excluded from analysis for the corresponding variant. As the number of participating studies differed for each variant, subjects included in analysis varied greatly from a variant to another especially in Asians.

We used a Chi-squared test with one degree of freedom to verify that allele distributions for each of the 10 SNPs were in Hardy–Weinberg equilibrium within each study and among European descent controls and Asian controls separately. A Bonferroni correction for multiple tests was applied for the Hardy–Weinberg equilibrium test giving an indicative P-value of 5×10^{-4} (based on ~100 tests carried out). All genotype distributions respected Hardy–Weinberg equilibrium.

Statistical analysis

Smoking status was categorized into three categories as never, former and current smokers. Former smokers were defined as smokers who stopped smoking for at least 2 years prior to the diagnosis (for cases) or interview (for controls). In the Norway and NCI-China studies, it was not possible to distinguish former from current smokers and ever smokers were considered as current smokers.

We used unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals. Pooled ORs were calculated using individual-level data from ILCCO studies. The heterozygous and homozygous carriers of the minor allele were each compared with the homozygous carriers of the major allele. OR per allele or P-values for trend were calculated assuming a log-additive genetic model with one degree of freedom. European descent and Asian subjects were analyzed as separate groups as well as together. Models were adjusted for study-matching variables and potential confounders

Table I. Evidence from genetic studies: summary of results that generated hypothesis on the 10 selected variants

Studies providing initial results	Study setting	Cases/controls	Variant	Level of evidence
Rudd *et al.* (12)	UK	1529/2707	*BAT3 S625P* (rs1052486)	OR = 0.84 (0.77–0.92), $P = 0.0002$
			CAMKK1 E375G (rs7214723)	OR = 1.18 (1.08–1.29), $P = 0.0003$
			TP53BP1 D353E (rs560191)	OR = 0.85 (0.77–0.92), $P = 0.0009$
			AKAP9 M463I (rs6964587)	OR = 1.32 (1.15–1.52), $P = 0.0001$[a]
Engels *et al.*, (13) (MD Anderson study)	TX, USA	1553/1730	*IL1B 3954C>T* (rs1143634)	OR = 1.27 (1.10–1.47), $P = 0.001$[a]
Gorlov *et al.*, (14)	TX, USA	289/291	*SEZ6L M430I* (rs663048)	Combined OR: wTT versus GG: 3.32 (1.81–7.21), $P = 0.0006$
	Liverpool, UK	248/233		
Zhang *et al.*, (15)	China	1000/1270	*FASL 844T>C* (rs763110)	OR = 1.79 (1.26–2.52), $P = 0.001$[b]
			FAS 1377G>A (rs2234767)	OR = 1.59 (1.21–2.10), $P = 0.001$[b]
Shen *et al.*, (16) (China study)	China	122/122	*MTHFR 677C>T* (rs1801133)	OR = 2.49 (1.41–4.42), $P = 0.002$[a]
Zhang *et al.*, (17)	China	505/500		TT versus CC: OR = 2.40 (1.61–3.59)
Hung *et al.*, (18) (IARC study)	Central Europe	2250/2899		OR = 1.37 (1.10–1.71), $P = 0.005$[b]
Wu *et al.*, (19) (MD Anderson study)	TX, USA	635/635	*TP53 intron3 16 bp duplication*	$P < 0.001$
Hung *et al.*, (20) (IARC study)	Central Europe	2238/2289		OR = 1.99 (1.27–3.13), $P = 0.003$[b]

IARC, International Agency for Research on Cancer.
[a]Dominant model.
[b]Recessive model, otherwise log-additive model.

Table II. Description of the participating studies

Coordinating institute	Study location	Study reference	Period of case recruitment	Control source	Control eligibility/recruitment	Number of cases[a]	Number of controls[a]
National Institute of Occupational Health, Oslo	Norway	(21)	1986–2005	Population	From the Oslo health screening 2000–2001, current smokers or quit smoking <5 years	332	412
Kyushu University	Japan	—	1994–1996	Population	Employees from Fukuoka prefectural government	462	379
University of California, Los Angeles	CA, USA	(22)	1999–2004	Population	18- to 65-year-old, Los Angeles resident at time of recruitment	545	940
Helmholtz Centers Heidelberg and Munich	Germany	(23)	1997–2004	Population	From KORA study: <50 years old	622	1205
MD Anderson Cancer Center	TX, USA	(6)	1992–2008	Hospital	Cancer-free patients, ever smokers	1154	1137
IARC	Central Europe	(20)	1998–2002	Hospital	Patients with non-tobacco related disease	2202	2834
National Cancer Institute	China	(24)	1995–1996	Population	Residence in Xuan Wei county	119	113
Seoul National University	Korea	(25)	2001–2008	Hospital	Cancer-free patients	579	636
National University of Singapore	Singapore	(26)	2005–2007	Hospital	Never smokers; no diagnosis or suspicion of malignancy or chronic respiratory disease	119	162
University of Hawaii	HI, USA	(27)	1992–1997	Population	26- to 79-year-old, Hawaii residents, with no history of lung cancer	325	449
Aichi Cancer Center	Japan	(28)	2000–2003	Hospital	Cancer-free patients	515	1030
Norris Cotton Cancer Center, Dartmouth Medical School	NH, USA	(29)	2005–2008	Population	Random sample from commercial database	228	162
Mayo Clinic	MN, USA	—	1997–2006	Hospital	Community residents	600	850
Penn State College of Medicine	FL, USA	(30)	1999–2003	Hospital	Subjects from screening clinics with no history of cancer	410	683
Nanjing Medical University School of Public Health	Nanjing, China	(31)	2002–2005	Population	Community residents with no history of cancer	603	655
					Total	8815	11 647

IARC, International Agency for Research on Cancer.
[a]Maximum number of cases and controls of all ethnic groups with DNA.

including age, sex, smoking status and center when appropriate. We conducted stratified analysis by smoking status and age of diagnosis to evaluate effect modification. We also analyzed the association of genetic variants and lung cancer risk by major histological subtypes (squamous cell carcinoma, adenocarcinoma and small cell carcinoma). Heterogeneity of ORs across the studies and across the stratification groups (age, sex and ethnicity) was assessed using the Cochran's *Q*-test. All analysis was conducted with SAS 9.1.

Additional replication analysis

In order to confirm the association we found between rs560191 (*TP53BP1*) and lung cancer risk in the ILCCO sample, we have genotyped additionally 1996 cases and 3487 controls from two further case–control studies (Poland and EPIC-lung) using Taqman. We have also incorporated results from several GWAS on lung cancer (National Cancer Institute, Texas, Canada, Tromso, CARET) including a total of 7970 cases and 8235 controls, as this variant is tagged on the Illumina panel by the proxy rs2602141 ($R^2 = 1.00$, $D' = 1.00$).

The Polish study is a hospital-based case–control study conducted in Szczecin between 2004 and 2007 (32). No data on smoking status were available for this study. EPIC-lung study is a case–control study nested in the EPIC cohort (European Prospective Investigation into Cancer and Nutrition) that was conducted in 10 European countries (Sweden, Denmark, The Netherlands, UK, France, Germany, Spain, Italy, Greece and Norway). This study was described in detail previously (7,33).

The NCI, Texas, Canada, HUNT2/Tromso and CARET GWAS studies were part of a meta-analysis that was conducted previously (34). Briefly, the NCI GWAS (National Cancer Institute) was drawn from four different studies: the Environment and Genetics in Lung Cancer Etiology, a population-based case–control study conducted in Italy in 2002–2005 (35); the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (36), a cohort study including male smokers enrolled in Finland in 1985–1993; the Prostate, Lung, Colon, Ovary Screening Trial, a randomized trial conducted in 10 US centers between 1992 and 2001 (37) and the Cancer Prevention Study II Nutrition Cohort, a cohort study conducted across all US in 1992–2001(38). The Texas study is a hospital-based case–control study including only smokers; cases with non-small cell lung cancer were diagnosed at the University of Texas MD Anderson Cancer Center since 1991 (6). The CARET cohort study (Carotene and Retinol Efficacy Trial) was conducted in six US centers between 1983 and 1994 and included only smokers with a smoking history of at least 20 pack-years (39). The HUNT2/Tromso study included cases and controls from two large population-based studies: the North Trondelag Health Study (HUNT2) conducted in 1995–1997 and the Tromso IV study conducted in 1994–1995. The Canada study is a hospital-based case–control study conducted at the University of Toronto and the Samuel Lunenfeld Research Institute in 1997–2002 (7).

All these cases and controls were of European descents. As no heterogeneity was detected across studies, we used a fixed-effects model to calculate ORs and 95% confidence intervals for all studies combined.

Results

Table IV shows the ORs of lung cancer for the 10 selected variants, for all subjects and stratified by ethnicity. No significant heterogeneity across ethnic groups was reported. We did not observe an association between any of the variants and risk of lung cancer, except rs560191 (*TP53BP1*), which was significantly associated with lung cancer risk in European descents and Asians [overall OR per rare allele = 0.91 (0.86–0.97), *P*-value = 0.002]. When considering both ethnic groups, no significant heterogeneity by study, histology, smoking status, age group or sex was observed (supplementary Figure 1 is available at *Carcinogenesis* Online). However, even if the heterogeneity by histology was non-significant ($P = 0.15$), the association was more striking for squamous cell carcinoma [OR = 0.86 (0.79–0.94), $P = 6 \times 10^{-4}$] than for adenocarcinoma [OR = 0.97 (0.89–1.04), $P = 0.39$] or small cell carcinoma [OR = 0.91 (0.80–1.03), $P = 0.14$].

In order to confirm the findings on rs560191, we have genotyped this variant in two additional studies (EPIC-Lung and Poland) and we have also incorporated results from several GWAS studies on rs2602141 (a proxy of rs560191). The results of this meta-analysis are reported in Table V. The associations found are similar to those of the ILCCO study. Overall, we reported an OR of 0.95 (0.91–0.99) ($P = 0.02$). The association was significant for squamous cell carcinoma [OR = 0.92 (0.86–0.99), $P = 0.03$] but not for adenocarcinoma [OR = 0.95 (0.89–1.02)] and small cell carcinoma [OR = 0.98 (0.88–1.09)] (*P*-heterogeneity by histology = 0.60).

Table III. Number of cases and controls included in analysis and minor allele frequency among controls

	BAT3 rs1052486		*CAMKK1* rs7214723		*TP53BP1* rs560191		*IL1B* rs1143634		*SEZ6L* rs663048		*FASL* rs763110		*FAS* rs2234767		*MTHFR* rs1801133		*AKAP9* rs6964587		*TP53intr* N/a	
	Ca/Co	*MAF*	Ca/Co	*MAF*	Ca/Co	*MAF*	Ca/Co	*MAF*	Ca/Co	*MAF*	Ca/Co	*MAF*	Ca/Co	*MAF*	Ca/Co	*MAF*	Ca/Co	*MAF*	Ca/Co	*MAF*
European descent																				
Norway	321/412	*0.45*	325/402	*0.43*	306/400	*0.29*	326/404	*0.23*	326/394	*0.21*	303/377	*0.35*	323/402	*0.13*	321/397	*0.31*	308/399	*0.41*	330/411	*0.13*
UCLA	315/575	*0.48*	312/568	*0.44*	315/575	*0.32*	315/569	*0.25*	313/569	*0.24*	310/566	*0.38*	314/572	*0.13*	314/574	*0.36*	312/573	*0.41*	—	—
Germany	—	—	—	—	619/1195	*0.31*	618/1108	*0.24*	—	—	618/1194	*0.36*	621/1201	*0.11*	617/1198	*0.33*	620/1184	*0.38*	—	—
MD Anderson	1066/1065	*0.50*	—	—	—	—	O	—	1154/1136	*0.23*	—	—	—	—	1153/1137	*0.34*	—	—	O	—
IARC	2070/2657	*0.47*	2071/2655	*0.41*	2039/2647	*0.29*	2041/2673	*0.25*	2041/2696	*0.28*	2021/2695	*0.33*	2044/2685	*0.10*	O	—	2024/2664	*0.36*	O	
Hawaii	135/174	*0.47*	136/171	*0.47*	135/172	*0.29*	137/174	*0.20*	137/174	*0.26*	137/174	*0.39*	134/174	*0.10*	135/170	*0.33*	133/171	*0.41*	—	—
NELCS	193/144	*0.54*	192/144	*0.46*	199/148	*0.29*	196/143	*0.28*	176/141	*0.24*	195/142	*0.37*	196/146	*0.14*	—	—	197/144	*0.46*	—	—
Mayo	588/833	*0.48*	596/843	*0.44*	594/846	*0.33*	599/842	*0.22*	599/844	*0.25*	594/840	*0.36*	600/834	*0.11*	592/841	*0.33*	596/828	*0.39*	—	—
Penn State	368/548	*0.50*	354/539	*0.43*	357/528	*0.32*	356/540	*0.23*	363/563	*0.24*	346/529	*0.35*	367/555	*0.10*	X	—	333/522	*0.41*	—	—
Total	**5056/6398**		**3986/5322**		**4564/6511**		**4588/6453**		**5109/6517**		**4524/6517**		**4599/6569**		**3132/4317**		**4523/6485**		**330/411**	
P-heterogeneity		***0.30***		***0.29***		***0.25***		***0.44***		***0.01***		***0.19***		***0.27***		***0.72***		***0.08***		
Asian																				
Kyushu	—	—	—	—	462/379	*0.46*	462/379	*0.06*	—	—	—	—	—	—	462/379	*0.36*	—	—	—	—
UCLA	58/52	*0.55*	58/53	*0.37*	56/53	*0.37*	57/50	*0.04*	58/53	*0.09*	55/52	*0.35*	57/53	*0.48*	58/53	*0.31*	57/51	*0.18*	—	—
NCI-China	—	—	—	—	—	—	119/110	*0.01*	—	—	—	—	—	—	116/111	*0.33*	—	—	—	—
Seoul	—	—	—	—	—	—	—	—	—	—	275/292	*0.29*	356/350	*0.39*	577/634	*0.43*	—	—	465/460	*0.05*
Singapore	—	—	—	—	—	—	113/160	*0.01*	118/162	*0.05*	—	—	—	—	119/161	*0.25*	—	—	—	—
Hawaii	100/170	*0.46*	97/169	*0.49*	99/170	*0.38*	99/170	*0.05*	99/170	*0.06*	99/168	*0.28*	100/170	*0.37*	98/166	*0.40*	98/169	*0.19*	—	—
Aichi	—	—	—	—	—	—	—	—	—	—	—	—	—	—	515/1030	*0.40*	—	—	—	—
China	—	—	—	—	603/655	*0.42*	—	—	—	—	—	—	—	—	O	—	—	—	—	—
Total	**158/222**		**155/222**		**1220/1257**		**850/869**		**275/385**		**429/512**		**513/573**		**1945/2534**		**155/220**		**465/460**	
P-heterogeneity		***0.28***		***0.12***		***0.24***		***0.03***		***0.63***		***0.67***		***0.37***		***0.0008***		***0.84***		

—, Not genotyped; Ca, number of cases; Co, number of controls; IARC, International Agency for Research on Cancer; MAF, minor allele frequency; *P-heterogeneity*, heterogeneity test across MAF; O, study that generated the hypothesis; UCLA, University of California, Los Angeles; x, excluded because of QC failure.

Table IV. Association between the 10 selected variants and lung cancer risk in European descent and Asian

		All				European descents				Asian				*P*-heterogeneity across ethnic groups
		Ca	Co	OR	95% CI	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI	
***BAT3* (rs1052486)**	AA	1443	1799	**1.00**	Ref	1406	1737	**1.00**	Ref	37	62	**1.00**	Ref	
	AG	2559	3305	**0.96**	(0.87–1.05)	2482	3199	**0.95**	(0.87–1.05)	77	106	**1.06**	(0.62–1.80)	
	GG	1212	1516	**0.99**	(0.89–1.11)	1168	1462	**1.00**	(0.90–1.12)	44	54	**1.11**	(0.60–2.04)	
				P-trend = 0.86				*P-trend = 0.97*				*P-trend = 0.74*		*P = 0.28*
Number of studies		***8***				***8***				***2***				
***CAMKK1* (rs7214723)**	TT	1357	1802	**1.00**	Ref	1310	1740	**1.00**	Ref	47	62	**1.00**	Ref	
	TC	2079	2778	**1.00**	(0.91–1.11)	1997	2663	**1.01**	(0.91–1.12)	82	115	**0.95**	(0.57–1.57)	
	CC	705	964	**1.00**	(0.88–1.14)	679	919	**0.99**	(0.86–1.13)	26	45	**0.92**	(0.48–1.77)	
				P-trend = 0.98				*P-trend = 0.89*				*P-trend = 0.80*		*P = 0.69*
Number of studies		***7***				***7***				***2***				
***TP53BP1* (rs560191)**	CC	2763	3554	**1.00**	Ref	2340	3135	**1.00**	Ref	423	419	**1.00**	Ref	
	CG	2465	3408	**0.91**	(0.84–0.98)	1844	2800	**0.89**	(0.81–0.97)	621	608	**0.98**	(0.82–1.18)	
	GG	556	806	**0.84**	(0.74–0.96)	380	576	**0.91**	(0.78–1.06)	176	230	**0.75**	(0.58–0.96)	
				P-trend = 0.002				*P-trend = 0.02*				*P-trend = 0.05*		*P = 0.54*
Number of studies		***10***				***8***				***4***				
***IL1B* (rs1143634)**	GG	3375	4548	**1.00**	Ref	2622	3750	**1.00**	Ref	753	798	**1.00**	Ref	
	GA	1744	2407	**1.02**	(0.94–1.11)	1656	2339	**1.00**	(0.91–1.09)	88	68	**1.19**	(0.84–1.70)	
	AA	319	367	**1.19**	(1.00–1.41)	310	364	**1.16**	(0.97–1.38)	9	3	**2.96**	(0.76–11.52)	
				P-trend = 0.11				*P-trend = 0.33*				*P-trend = 0.10*		*P = 0.17*
Number of studies		***11***				***8***				***5***				
***SEZ6L* (rs663048)**	CC	3101	3990	**1.00**	Ref	2870	3648	**1.00**	Ref	231	342	**1.00**	Ref	
	CA	1967	2478	**1.01**	(0.93–1.10)	1926	2438	**1.00**	(0.92–1.09)	41	40	**1.47**	(0.90–2.39)	
	AA	316	434	**0.98**	(0.83–1.15)	313	431	**0.97**	(0.82–1.14)	3	3	**1.63**	(0.31–8.53)	
				P-trend = 0.99				*P-trend = 0.80*				*P-trend = 0.11*		*P = 0.12*
Number of studies		***9***				***8***				***3***				
***FASL* (rs763110)**	GG	2198	3055	**1.00**	Ref	1970	2804	**1.00**	Ref	228	251	**1.00**	Ref	
	GA	2165	3102	**0.97**	(0.89–1.05)	2005	2881	**0.96**	(0.88–1.05)	160	221	**0.80**	(0.50–1.07)	
	AA	590	872	**0.97**	(0.85–1.10)	549	832	**0.95**	(0.83–1.09)	41	40	**1.00**	(0.61–1.64)	
				P-trend = 0.45				*P-trend = 0.35*				*P-trend = 0.41*		*P = 0.62*
Number of studies		***9***				***8***				***3***				
***FAS* (rs2234767)**	GG	3786	5426	**1.00**	Ref	3613	5218	**1.00**	Ref	173	208	**1.00**	Ref	
	GA	1183	1552	**1.06**	(0.96–1.16)	931	1274	**1.06**	(0.96–1.18)	252	278	**1.08**	(0.82–1.43)	
	AA	143	164	**1.09**	(0.84–1.41)	55	77	**0.97**	(0.66–1.42)	88	87	**1.16**	(0.80–1.69)	
				P-trend = 0.23				*P-trend = 0.34*				*P-trend = 0.42*		*P = 0.84*
Number of studies		***9***				***8***				***3***				
***MTHFR* (rs1801133)**	GG	2081	2904	**1.00**	Ref	1389	1928	**1.00**	Ref	629	976	**1.00**	Ref	
	GA	2283	3031	**1.05**	(0.96–1.14)	1367	1882	**1.01**	(0.91–1.12)	916	1149	**1.14**	(0.99–1.30)	
	AA	713	916	**1.08**	(0.96–1.21)	376	507	**1.06**	(0.91–1.25)	337	409	**1.13**	(0.94–1.36)	
				P-trend = 0.16				*P-trend = 0.52*				*P-trend = 0.10*		*P = 0.29*
Number of studies		***11***				***6***				***7***				
***AKAP9* (rs6964587)**	CC	1831	2567	**1.00**	Ref	1732	2426	**1.00**	Ref	99	141	**1.00**	Ref	
	CA	2183	3227	**0.96**	(0.88–1.05)	2130	3151	**0.95**	(0.87–1.04)	53	76	**0.96**	(0.60–1.53)	
	AA	664	911	**1.00**	(0.88–1.14)	661	908	**0.99**	(0.87–1.13)	3	3	**0.84**	(0.14–5.03)	
				P-trend = 0.63				*P-trend = 0.66*				*P-trend = 0.82*		*P = 0.89*
Number of studies		***8***				***8***				***2***				
TP53 intron 3	Ins/ins	685	724	**1.00**	Ref	258	303	**1.00**	Ref	427	421	**1.00**	ref	
	Ins/del	98	139	**0.76**	(0.57–1.01)	60	103	**0.68**	(0.48–0.98)	38	36	**0.97**	(0.59–1.60)	
	Del/del	12	8	**1.72**	(0.69–4.26)	12	5	**2.80**	(0.97–8.07)	0	3	—	—	
				P-trend = 0.33				*P-trend = 0.56*						*P = 0.42*
Number of studies		**2**				**1**				**1**				

OR adjusted for sex, age, center and smoking status. Ca, number of cases; Co, number of control.

The result of the combined analysis of the ILCCO study and the additional studies is shown in Figure 1. We reported an overall OR of 0.93 (0.89–0.97) ($P = 0.001$), and we found that this association concerned mostly squamous cell carcinoma [OR = 0.89 (0.85–0.95), $P = 1 \times 10^{-4}$]. When combined with the initial association that generated the hypothesis reported by Rudd *et al.* [OR = 0.85 (0.77–0.92)], $P = 9 \times 10^{-4}$, Table II), the allelic OR was 0.91 (0.88–0.95), $P = 6 \times 10^{-6}$.

Stratified analyses were also performed for the other variants considered, and the results showed no consistent patterns (results not shown).

Discussion

This replication study was based on common variants that were previously found associated with lung cancer risk in a candidate gene approach. We evaluated the effect of 10 variants proposed by the ILCCO members on lung cancer risk in a pooled analysis of 15 studies. The large sample size collected in European descent and Asian groups permitted us to analyze potential effect modification in subgroups of interest (by smoking status, age of onset and histological subtypes). We found that rs560191 (*TP53BP1)* was associated with a decreased risk of lung cancer. This association was more striking for squamous cell carcinoma. This result was replicated in a meta-analysis of eight independent studies based on an additional 9966 cases and 11 722 controls.

We did not find an association between lung cancer risk and any of the other variants. With the exception of *MTHFR* C677T, none of these variants had been previously analyzed in the context of a pooled or a meta-analysis of lung cancer studies (40,41).

Table V. Meta-analysis of the association between rs560191/rs2602141and lung cancer risks in additional studies independent from ILCCO

	All histology			Adenocarcinomas			Squamous cell carcinomas			Small cell carcinomas		
	Ca/Co	OR (95% CI)	*p*	Ca/Co	OR (95% CI)	*P*	Ca/Co	OR (95% CI)	*P*	Ca/Co	OR (95% CI)	*P*
GWAS												
NCI	5739/5848	0.94 (0.88–1.00)	*0.07*	1578/5848	0.97 (0.88–1.06)	*0.50*	1315/5848	0.95 (0.85–1.05)	*0.33*	618/5848	0.94 (0.82–1.09)	*0.45*
Texas	1154/1137	0.88 (0.77–1.00)	*0.05*	628/1137	0.90 (0.76–1.05)	*0.18*	309/1137	0.77 (0.62–0.95)	*0.02*	—	—	
Canada	291/475	1.10 (0.87–1.39)	*0.44*	90/475	1.11 (0.78–1.57)	*0.58*	50/475	1.01 (0.62–1.64)	*0.97*	22/475	0.85 (0.44–1.64)	*0.62*
HUNT2/ Tromso	389/382	1.02 (0.78–1.33)	*0.87*	75/382	1.19 (0.79–1.78)	*0.41*	78/382	0.79 (0.50–1.26)	*0.32*	50/382	0.58 (0.32–1.07)	*0.08*
CARET	397/393	1.06 (0.86–1.31)	*0.61*	90/393	1.10 (0.78–1.55)	*0.59*	72/393	1.27 (0.87–1.85)	*0.21*	50/185	1.55 (0.85–2.85)	*0.15*
Additional studies												
EPIC-Lung	1141/2466	1.03 (0.92–1.17)	*0.52*	333/2466	0.91 (0.76–1.10)	*0.33*	256/2466	1.04 (0.85–1.28)	*0.70*	156/2466	1.14 (0.88–1.48)	*0.33*
Poland	855/1021	0.84 (0.73–0.98)	*0.02*	180/1021	0.80 (0.62–1.04)	*0.10*	318/1021	0.79 (0.64–0.97)	*0.02*	91/1021	0.99 (0.71–1.39)	*0.98*
Overall	**9966/11 722**	**0.95 (0.91–0.99)**	***0.02***	**2974/11 722**	**0.95 (0.89–1.02)**	***0.13***	**2398/11 722**	**0.92 (0.86–0.99)**	***0.03***	**987/10 377**	**0.98 (0.88–1.09)**	***0.73***
		P-heterogeneity = 0.20			***P-heterogeneity = 0.52***			***P-heterogeneity = 0.13***			***P-heterogeneity = 0.23***	

All OR are adjusted for age, sex and smoking status, except for Poland study for which smoking status was not available. Ca, number of cases; CARET, Carotene and Retinol Efficacy Trial; Co, number of controls; GWAS, genome-wide association studies; NCI, National Cancer Institute.

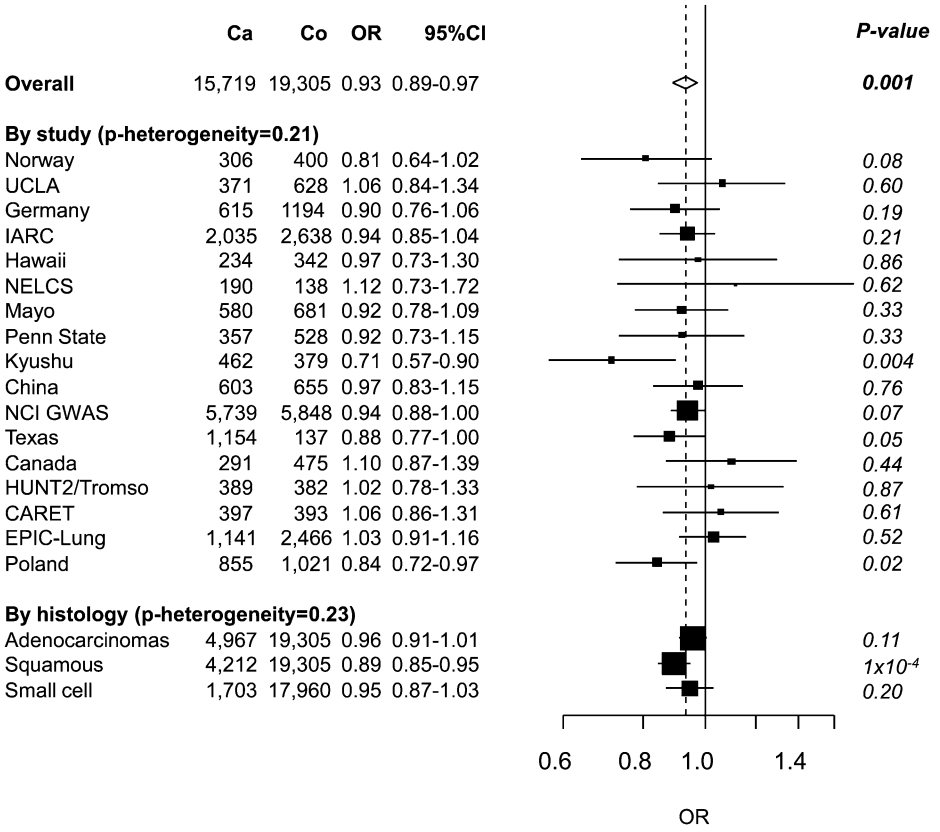

Fig. 1. Forest plot representing association between rs560191/rs2602141 (*TP53BP1*) and lung cancer risk by study and by histology. Ca, number of cases; Co, number of controls; Overall OR and ORs by histology are derived from a fixed effect model OR by study are adjusted for age, sex and smoking status, except the Polish study that was adjusted for age and sex only (as smoking status was not available).

To our knowledge, only one study has investigated the role of *TP53BP1* variants in lung cancer susceptibility (12). This study analyzed the association between lung cancer and 1476 non-synonymous variants from 871 candidate cancer genes in a large case–control study conducted in UK (1529 cases and 2797 controls) and reported a decreased risk of lung cancer among rare allele carriers of rs560191 [OR per allele = 0.85 (0.77–0.93)]. This result was replicated in the present study [OR = 0.93 (0.89–0.97), $P = 0.001$]. This association remains significant after a Bonferroni correction for multiple tests based on 10 independent tests carried out (corresponding to the number of variants analyzed) and then considering a threshold *P*-value of 0.005. No heterogeneity across studies and ethnic groups was observed in the overall analysis. However, even if the test for heterogeneity was non-significant across histology groups ($P = 0.23$), we reported a stronger

association between squamous cell carcinoma and rs560191 [OR = 0.89 (0.85–0.95), $P = 1 \times 10^{-4}$].

rs560191 is a non-synonymous variant of *TP53BP1*, although no report on any functional relevance of this variant was published so far. *TP53BP1* is one of the *TP53*-regulated genes and it is known to be involved in DNA damage–signaling pathways, in checkpoint signaling and in DNA repair activities (42,43). It is also known to interact with the DNA-binding domain of *TP53* to enhance TP53-mediated transcriptional activation (44). One study suggested that *TP53BP1* may have protective effects on squamous cell carcinoma of the head and neck risk but such effects were confined to *TP53* variant allele/haplotype carriers (45). In the present pooled analysis, only one study had data for both *TP53BP1* and *TP53* intron 3, and we did not observe any interaction between these two variants in lung cancer risk (data not shown).

Several case–control studies have reported previously on the association between the *MTHFR* C677T variant and lung cancer risk, including predominantly European (18,46–48) and Asian studies (16,17,49,50). Some of these studies (16,18,28,46) also analyzed possible effect modification by folate intake, as the MTHFR enzyme is involved in folate metabolism. A recent meta-analysis of these studies (41) suggested no evidence for a major role of the *MTHFR* C677T polymorphisms in carcinogenesis of lung cancer. Another recent meta-analysis (40), including stratified analysis by folate intake levels, observed a non-significant increased risk of lung cancer among *MTHFR* 677 TT individuals with low folate intake. In the present study, no association between *MTHFR* C677T and lung cancer risk was observed; however, information on folate intake was not available.

Few studies have investigated the association between the other variants considered and lung cancer risk. *AKAP9* M463I, *CAMKK1* E375G *and BAT3* S625P were detected as candidate variants in the same study mentioned above that highlighted *TP53BP1* D353E (12). Interestingly, a variant in BAT3 was recently found strongly associated with lung cancer risk (10), although $D' = 1.0$ and $r^2 < 0.08$ with BAT3 S625P. Association between *IL1B* C3954T and lung cancer risk was reported in a study from US that evaluated a panel of 59 variants in 37 inflammation-related genes (13). Another study also found such an association with this variant, but only among former smokers and men (51). Conversely, a study conducted in Norway found no association between *IL1B* C3954T and lung cancer risk but reported significant associations with other variants in this gene (52,53). *SEZ6L M430I* was detected as a candidate variant affecting lung cancer risk in a pilot study testing 83 715 SNPs and this association was confirmed in two replication studies (14). *FAS* G1377A and *FASL* C844T were investigated in a case–control study conducted in China (15). This study reported an increase risk of lung cancer among wild allele carriers for both SNPs and a multiplicative gene–gene interaction. These results were not replicated in two other independent studies, one conducted in Korea (54) and the other conducted in US (51). Association between the *TP53* intron 3 polymorphism and lung cancer risk was examined by three studies. Two studies conducted, respectively, in US and Central Europe (19,20) reported that carrying 16 bp duplications in *TP53* intron 3 increased the risk of lung cancer, whereas another study conducted in Sweden (55) did not detect any association.

The present study shows the importance of consortia in replicating potential significant results from candidate gene studies. Only for 1 of 10 variants was the association replicated, suggesting that initial positive results for the other SNPs may be false.

In conclusion, among the 10 variants selected for replication based on prior evidence of a potential association with lung cancer risk, we reported significant results only for rs560191 (*TP53BP1)*. Rare allele carriers of this variant were found to have a modest decreased risk of lung cancer. This association concerned mainly squamous cell carcinomas. Subsequent studies from ILCCO will focus on replication of lung cancer susceptibility variants identified by GWAs.

Supplementary material

Supplementary Table 1 and Figure 1 can be found at http://carcin.oxfordjournals.org/

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