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Table I. Characteristics of study subjects

Category	Group	No.	Age (Mean±SD)	Sex (% male)	Smoking habit (%)		Pack-years of smokers (Mean±SD)
					Non-smoker	Smoker	
NCCH set	Case	2,343	59±9	65	34	66	51±30
	Adenocarcinoma	1,656	58±9	56	46	54	43±27
	Squamous cell carcinoma	390	62±7	91	3	97	61±29
	Small cell carcinoma	297	62±9	80	5	95	62±32
	Control	1,173	48±14	58	63	37	27±21
NNGH set	Case	136	68±10	74	27	73	55±29
	Adenocarcinoma	84	67±10	64	39	61	48±25
	Squamous cell carcinoma	52	70±9	90	6	94	62±32
	Control	145	64±14	71	33	67	45±35

Table II. GWAS and validation studies to identify loci associated with lung adenocarcinoma risk

Stage	Subject (No.)		Polymorphic loci analyzed	Genotyping method	Loci/Allele	Result			
	Case	Control				Crude OR (95% CI)	P value	Adjusted OR ^a (95% CI)	P value
GWAS 1st ^b	Patients of NCCH (200)	Volunteers enrolled in Tokai University (200)	23,010 microsatellites	Pooled DNA typing	1,328 loci	ND	$P_{2xm} < 0.05$	ND	ND
2nd ^c	Patients of NCCH (200)	Volunteers enrolled in Keio University (200)	431 microsatellites	Pooled DNA typing	17 loci	ND	$P_{2xm} < 0.05$	ND	ND
3rd ^d	Patients of NCCH (576) consisting of 192 1st set, 192 2nd set and 192 another subjects	Tokai and Keio volunteers and non-cancer NCCH patients (576) consisting of 192 1st and 192 2nd set volunteers; and 192 non-cancer NCCH patients	17 microsatellites	Individual DNA typing	D6S00671 and other 5 loci	ND	$P_{2xm} = 2.4 \times 10^{-7}$ at D6S00671 $P_{2xm} = 0.012-0.0011$ at 5 other loci	ND	ND
SNP analysis ^e	Randomly selected 3rd stage GWAS subjects (525)	Randomly selected 3rd stage GWAS subjects (525)	56 SNPs	24 SNPs by sequencing 32 SNPs by Taqman PCR	rs17426593 DQA1*03 DQA1*01	1.51 (1.27-1.80) 1.50 (1.26-1.79) 0.69 (0.58-0.82)	4.2×10^{-6} 6.6×10^{-6} 2.8×10^{-5}	ND	ND
	Same as above	Same as above	rs17426593 and rs34843907	-	DQA1*03 DQA1*01	1.52 (1.27-1.81) 0.69 (0.58-0.82)	3.4×10^{-6} 2.3×10^{-5}	ND	ND
Validation	Other patients of NCCH (1,131)	Other subjects (648) consisting of 9 Tokai and 478 Keio volunteers; and 161 non-cancer NCCH patients	Same as above	Taqman PCR	DQA1*03 DQA1*01	1.27 (1.11-1.45) 0.86 (0.75-0.99)	5.6×10^{-3} 0.030	ND	ND
(Combined analysis)	Patients of NCCH (1,656)	Subjects (1,173) consisting of 200 Tokai and 635 Keio volunteers and 338 non-cancer NCCH patients	Same as above	-	DQA1*03 DQA1*01	1.35 (1.21-1.51) 0.78 (0.70-0.87)	5.6×10^{-6} 6.0×10^{-6}	1.36 (1.20-1.54) 0.77 (0.68-0.87)	5.3×10^{-7} 1.4×10^{-5}
Validation in another set	Patients of NINGH (84)	Non-cancer patients of NINGH (145)	Same as above	Taqman PCR	DQA1*03 DQA1*01	1.57 (1.07-2.30) 0.77 (0.52-1.13)	0.022 0.18	1.70 (1.14-2.53) 0.68 (0.49-1.09)	0.0087 0.12

ND: not determined.

^aadjusted for sex, age, and smoking.

^b23,010 microsatellite loci containing repeat units of 2-6-bp were examined, and 1,328 loci showed significant differences in allele distribution.

^cAmong 1,328 loci selected in the 1st GWAS stage, 431 loci that contained repeat units of 3-6-bp were examined, and 17 loci showed significant differences in allele distribution.

^d17 loci selected in the 2nd GWAS stage were examined, and 6 loci showed significant differences in allele distribution. Only the D6S00671 locus was identified as being significantly different, after Bonferroni correction (i.e., $P < 0.05/23,010 = 2.2 \times 10^{-7}$). In this stage, 576 subjects consisted of two sets of 192 subjects which were chosen from two sets of 200 subjects examined in the 1st and 2nd GWAS stages, respectively, and another 192 subjects were examined.

^eIn this stage, 525 cases and 525 controls, which were randomly chosen from the 576 cases and 576 controls examined in the 3rd GWAS stage, were examined for 56 SNPs.

Table III. Differences in the allele distribution of 56 SNPs in the 450-kb region surrounding the D6S0067i locus between 525 lung adenocarcinoma cases and 525 controls

SNP	Genome location	Gene	Position	Allele	Minor allele frequency		P value	OR	95%CI	Deviation from HWE (P)		LD block
					Control	Case				Control	Case	
First 32 SNPs												
rs7773756	32,510,442			T/C	0.375	0.443	0.0016	1.33	1.11 - 1.58	0.66	0.83	1
rs16822586	32,515,751	<i>HLA-DRA</i>	exon 1	G/C	0.076	0.074	0.86	0.97	0.70 - 1.34	0.20	0.001	1
rs2239806	32,519,285	<i>HLA-DRA</i>	intron 3	G/A	0.208	0.179	0.089	0.83	0.67 - 1.03	0.09	0.31	1
rs7192*	32,519,624	<i>HLA-DRA</i>	exon 4	G/T	0.444	0.376	0.0016	0.76	0.63 - 0.90	1.00	0.19	1
rs3129763 ^a	32,698,903			G/A	0.064	0.070	0.60	1.10	0.78 - 1.55	0.91	0.44	1
rs9272346	32,712,350			G/A	0.469	0.564	1.5x10 ⁻⁵	1.46	1.23 - 1.74	0.11	0.95	1
rs2187668 ^a	32,713,862	<i>HLA-DQA1</i>	intron 1	G/A	0.033	0.040	0.42	1.21	0.77 - 1.91	0.54	0.09	1
rs17426593	32,716,055	<i>HLA-DQA1</i>	intron 1	T/C	0.344	0.442	4.2x10 ⁻⁶	1.51	1.27 - 1.80	0.55	0.18	1
rs34843907	32,718,037	<i>HLA-DQA1</i>	intron 3	A/C	0.470	0.563	1.3x10 ⁻⁵	1.45	1.22 - 1.72	0.11	0.91	1
rs28584179	32,734,097			C/T	0.106	0.063	4.1x10 ⁻⁴	0.57	0.41 - 0.78	0.68	0.50	1
rs17205373	32,734,188			C/G	0.054	0.046	0.42	0.85	0.57 - 1.26	0.66	0.92	1
rs6906021	32,734,289			T/C	0.377	0.358	0.39	0.92	0.77 - 1.10	0.82	0.28	1
rs28672722	32,734,515			G/T	0.416	0.353	0.0032	0.77	0.64 - 0.91	0.59	0.86	1
rs28746825	32,741,450	<i>HLA-DQB1</i>	intron 1	A/G	0.365	0.463	5.4x10 ⁻⁶	1.50	1.26 - 1.79	0.22	0.26	1
rs34692792	32,741,519	<i>HLA-DQB1</i>	intron 1	T/C	0.218	0.205	0.47	0.93	0.75 - 1.14	0.47	0.29	1
rs2647012 ^a	32,772,436			G/A	0.214	0.143	2.3x10 ⁻⁵	0.61	0.49 - 0.77	0.37	0.22	1
rs1794282 ^a	32,774,504			G/A	0.000	0.000	-	-	-	-	-	-
rs2856717	32,778,286			C/T	0.219	0.147	1.7x10 ⁻⁵	0.61	0.49 - 0.77	0.19	0.33	1
rs2051600	32,817,287	<i>HLA-DQA2</i>	intron 1	C/T	0.188	0.153	0.030	0.78	0.62 - 0.98	0.62	0.33	2
rs2239800 ^a	32,821,245	<i>HLA-DQA2</i>	intron 2	T/C	0.289	0.292	0.88	1.01	0.84 - 1.23	0.92	0.47	2
rs2071798	32,822,570	<i>HLA-DQA2</i>	3'UTR	T/C	0.360	0.302	0.0048	0.77	0.64 - 0.92	0.33	0.92	2
rs9276558	32,832,039			G/A	0.358	0.301	0.0051	0.77	0.64 - 0.92	0.28	0.94	2
rs1573649 ^a	32,839,236			T/C	0.426	0.377	0.021	0.81	0.68 - 0.97	0.11	0.77	2
rs2071475	32,890,365	<i>HLA-DOB</i>	intron 2	C/T	0.238	0.261	0.21	1.14	0.93 - 1.38	0.53	0.24	2
rs2071469 ^a	32,892,761	<i>HLA-DOB</i>	5'UTR	G/A	0.424	0.469	0.037	1.20	1.01 - 1.43	0.13	0.66	2
rs241455	32,903,997	<i>TAP2</i>	3'UTR	G/T	0.314	0.339	0.21	1.12	0.94 - 1.35	0.35	0.17	2
rs1800454	32,908,390	<i>TAP2</i>	exon 6	G/A	0.126	0.150	0.12	1.22	0.95 - 1.56	0.51	0.20	2/3
rs2071552	32,914,439	<i>TAP2</i>	5'UTR	T/C	0.418	0.406	0.56	0.95	0.80 - 1.13	0.53	0.22	3
rs2071463	32,920,506	<i>PSMB8</i>	5'UTR	G/A	0.380	0.404	0.25	1.11	0.93 - 1.32	0.74	0.18	3
rs1057373 ^a	32,921,257	<i>TAP1</i>	3'UTR	G/T	0.105	0.121	0.23	1.18	0.90 - 1.55	0.72	0.18	3
rs2071480	32,929,837			G/T	0.339	0.341	0.95	1.01	0.84 - 1.20	0.16	0.23	3
rs17587 ^a	32,933,068	<i>PSMB9</i>	exon 3	G/A	0.243	0.225	0.33	0.90	0.74 - 1.11	0.47	0.71	3
Additional 24 SNPs for HLA allele discrimination												
DRB1_2_244	32,659,890	<i>HLA-DRB1</i>	exon 2	G/T	0.269	0.271	0.88	1.01	0.84 - 1.23	0.49	0.88	1
DRB1_2_160	32,659,974	<i>HLA-DRB1</i>	exon 2	C/A	0.029	0.023	0.69	0.79	0.47 - 1.33	0.52	0.56	1
DRB1_2_156	32,659,978	<i>HLA-DRB1</i>	exon 2	G/A	0.204	0.259	0.0055	1.37	1.12 - 1.66	0.83	1.00	1
DRB1_2_127	32,660,007	<i>HLA-DRB1</i>	exon 2	A/T	0.418	0.325	1.1x10 ⁻⁵	0.67	0.56 - 0.80	0.16	0.28	1
DRB1_2_106	32,660,028	<i>HLA-DRB1</i>	exon 2	T/A	0.003	0.004	0.70	1.35	0.30 - 6.03	0.95	0.93	1
DRB1_2_84	32,660,050	<i>HLA-DRB1</i>	exon 2	A/C	0.191	0.266	1.2x10 ⁻⁴	1.53	1.26 - 1.87	0.86	0.57	1
DRB1_2_81	32,660,053	<i>HLA-DRB1</i>	exon 2	T/C	0.224	0.207	0.30	0.90	0.74 - 1.10	0.47	0.66	1
DRB1_2_64	32,660,070	<i>HLA-DRB1</i>	exon 2	T/A	0.130	0.154	0.047	1.22	0.97 - 1.55	0.60	0.79	1
DRB1_2_61	32,660,073	<i>HLA-DRB1</i>	exon 2	G/A	0.002	0.000	0.16	0.00	-	0.96	1.00	1
DRB1_2_33	32,660,101	<i>HLA-DRB1</i>	exon 2	C/T	0.172	0.174	0.91	1.01	0.82 - 1.26	0.10	0.47	1
DQA1_2_136	32,717,200	<i>HLA-DQA1</i>	exon 2	A/T	0.464	0.568	8.4x10 ⁻⁶	1.52	1.28 - 1.79	0.16	0.84	1
DQA1_2_141	32,717,205	<i>HLA-DQA1</i>	exon 2	A/C	0.348	0.450	9.7x10 ⁻⁶	1.54	1.30 - 1.83	0.91	0.27	1
DQA1_2_145	32,717,209	<i>HLA-DQA1</i>	exon 2	A/G	0.348	0.444	6.7x10 ⁻⁶	1.50	1.26 - 1.79	0.51	0.26	1
DQA1_2_150	32,717,304	<i>HLA-DQA1</i>	exon 2	G/A	0.470	0.562	2.8x10 ⁻⁵	1.44	1.22 - 1.71	0.11	0.83	1
DQB1_2_156	32,740,667	<i>HLA-DQB1</i>	exon 2	G/A	0.029	0.031	0.90	1.07	0.65 - 1.76	0.49	0.47	1
DQB1_2_145	32,740,678	<i>HLA-DQB1</i>	exon 2	A/T	0.471	0.560	1.8x10 ⁻⁵	1.43	1.21 - 1.69	0.04	0.87	1
DQB1_2_134	32,740,689	<i>HLA-DQB1</i>	exon 2	G/A	0.065	0.059	0.72	0.90	0.64 - 1.27	0.53	0.39	1
DQB1_2_131	32,740,692	<i>HLA-DQB1</i>	exon 2	G/C	0.092	0.058	0.0029	0.61	0.44 - 0.84	0.19	0.86	1
DQB1_2_121	32,740,702	<i>HLA-DQB1</i>	exon 2	G/A	0.097	0.099	0.81	1.03	0.77 - 1.36	0.73	0.15	1
DQB1_2_101	32,740,722	<i>HLA-DQB1</i>	exon 2	G/A	0.315	0.355	0.034	1.20	1.00 - 1.43	0.71	0.96	1
DQB1_2_100	32,740,723	<i>HLA-DQB1</i>	exon 2	C/T	0.335	0.323	0.55	0.95	0.79 - 1.13	0.43	0.51	1
DQB1_2_68	32,740,755	<i>HLA-DQB1</i>	exon 2	G/A	0.114	0.065	3.2x10 ⁻⁵	0.54	0.40 - 0.73	0.42	0.50	1
DQB1_2_55	32,740,768	<i>HLA-DQB1</i>	exon 2	G/T	0.103	0.153	7.3x10 ⁻³	1.57	1.22 - 2.03	0.72	0.61	1
DQB1_2_27	32,740,796	<i>HLA-DQB1</i>	exon 2	A/C	0.121	0.116	0.80	0.96	0.74 - 1.24	0.57	0.64	1

*SNPs examined in other GWASs^{4,5,6}.

Table IV. Differences in the distribution of the HLA class II alleles between 525 lung adenocarcinoma cases and 525 controls

Gene	No.	Allele ^a	Frequency		OR	(95% CI)	P value by χ^2 test
			Control	Case			
DRB1	1	DRB1*1502	0.148	0.125	0.82	(0.64 - 1.05)	0.12
	2	<u>DRB1*0901</u>	0.117	0.157	1.40	(1.09 - 1.81)	0.0079
	3	<u>DRB1*0405</u>	0.106	0.154	1.53	(1.18 - 1.98)	0.0012
	4	<u>DRB1*1302</u>	0.097	0.058	0.58	(0.42 - 0.81)	0.0011
	5	<u>DRB1*1501</u>	0.091	0.055	0.58	(0.41 - 0.81)	0.0013
	6	DRB1*0803	0.073	0.075	1.02	(0.74 - 1.42)	0.90
	7	DRB1*0101	0.057	0.033	0.56	(0.37 - 0.86)	0.0077
	8	DRB1*1401/1405/1406/1412/1429	0.057	0.069	1.24	(0.87 - 1.77)	0.23
	9	DRB1*0802	0.052	0.037	0.70	(0.46 - 1.07)	0.10
	10	DRB1*0403/0404/0406	0.044	0.073	1.73	(1.19 - 2.52)	0.0040
	11	DRB1*1201/1202	0.040	0.050	1.25	(0.82 - 1.89)	0.30
	12	DRB1*1101	0.026	0.022	0.81	(0.46 - 1.42)	0.47
	13	DRB1*0410	0.021	0.016	0.78	(0.41 - 1.48)	0.44
	Total		0.929	0.924			
DQA1	1	DQA1*01	0.530	0.438	0.69	(0.58 - 0.82)	2.8x10 ⁻⁵
	2	DQA1*03	0.348	0.444	1.50	(1.26 - 1.79)	6.6x10 ⁻⁶
	3	DQA1*04/05/06	0.122	0.118	0.88	(0.68 - 1.14)	0.43
	Total		1.000	1.000			
DQB1	1	DQB1*0601	0.218	0.205	0.92	(0.75 - 1.14)	0.46
	2	DQB1*0303	0.139	0.164	1.22	(0.96 - 1.54)	0.11
	3	<u>DQB1*0401</u>	0.104	0.153	1.54	(1.19 - 2.00)	0.0010
	4	<u>DQB1*0604</u>	0.097	0.058	0.57	(0.41 - 0.79)	7.4x10 ⁻⁴
	5	DQB1*0301	0.093	0.093	1.01	(0.75 - 1.35)	0.97
	6	<u>DQB1*0602</u>	0.086	0.053	0.59	(0.42 - 0.84)	0.0028
	7	DQB1*0302	0.081	0.092	1.15	(0.85 - 1.57)	0.35
	8	DQB1*0501	0.061	0.059	0.96	(0.67 - 1.37)	0.82
	9	DQB1*0402	0.042	0.051	1.21	(0.80 - 1.82)	0.36
	10	DQB1*0502	0.030	0.027	0.90	(0.54 - 1.51)	0.70
	11	DQB1*0503	0.028	0.028	1.03	(0.61 - 1.72)	0.93
	Total		0.979	0.983			
DR-DQ	1	DRB1*1502-DQA1*01-DQB1*0601	0.150	0.130	0.85	(0.66 - 1.09)	0.19
	2	<u>DRB1*0901-DQA1*03-DQB1*0303</u>	0.119	0.153	1.34	(1.05 - 1.73)	0.021
	3	<u>DRB1*0405-DQA1*03-DQB1*0401</u>	0.101	0.144	1.51	(1.16 - 1.96)	0.0022
	4	<u>DRB1*1302-DQA1*01-DQB1*0604</u>	0.094	0.057	0.58	(0.42 - 0.81)	0.0013
	5	<u>DRB1*1501-DQA1*01-DQB1*0602</u>	0.082	0.051	0.60	(0.42 - 0.85)	0.0042
	6	DRB1*0803-DQA1*01-DQB1*0601	0.070	0.072	1.02	(0.73 - 1.43)	0.89
	7	DRB1*0101-DQA1*01-DQB1*0501	0.047	0.034	0.72	(0.46 - 1.12)	0.14
	8	<u>DRB1*0403/0404/0406-DQA1*03-DQB1*0302</u>	0.040	0.068	1.72	(1.17 - 2.54)	0.0058
	9	DRB1*1201/1202-DQA1*04/05/06-DQB1*0301	0.032	0.032	0.99	(0.61 - 1.61)	0.97
	10	DRB1*1401/1405/1406/1412/1429-DQA1*01-DQB1*0503	0.028	0.031	1.13	(0.68 - 1.88)	0.64
	11	DRB1*1101-DQA1*04/05/06-DQB1*0301	0.025	0.017	0.68	(0.37 - 1.25)	0.21
	12	DRB1*0802-DQA1*04/05/06-DQB1*0402	0.024	0.026	1.10	(0.64 - 1.91)	0.73
	Total		0.812	0.815			

^aDRB1 and DQB1 alleles linked to the DQA1*03 or DQA1*01 alleles and DR-DQ alleles containing the DQA1*03 or DQA1*01 alleles, which were significantly associated with lung ADC risk, are underlined.

Figure 1

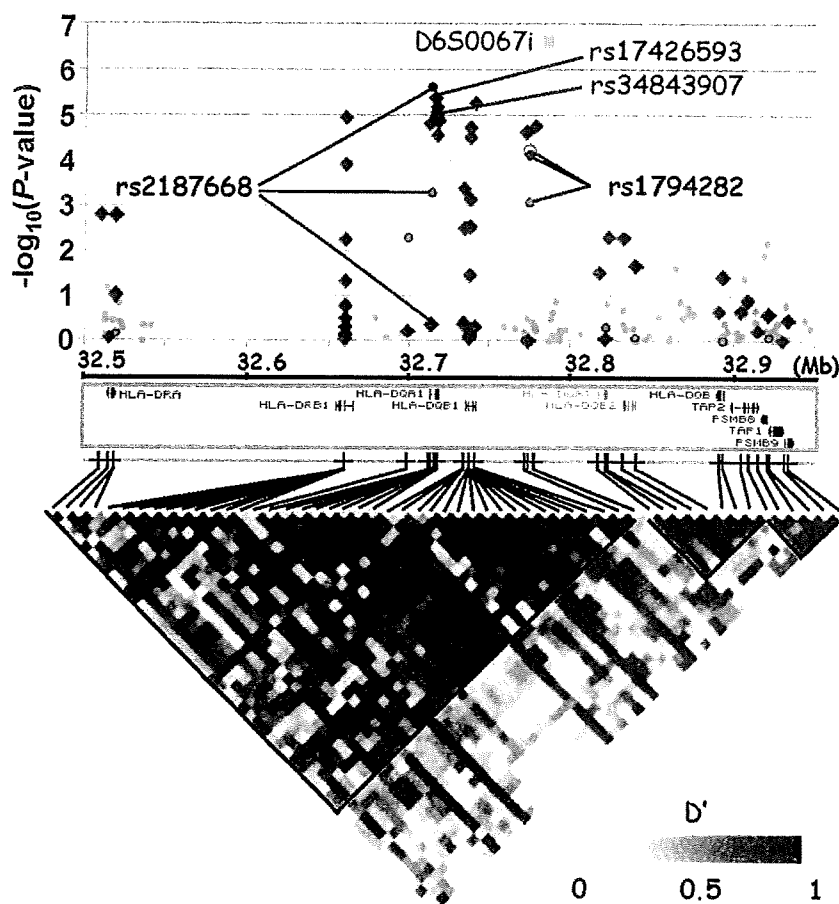


Figure 2a

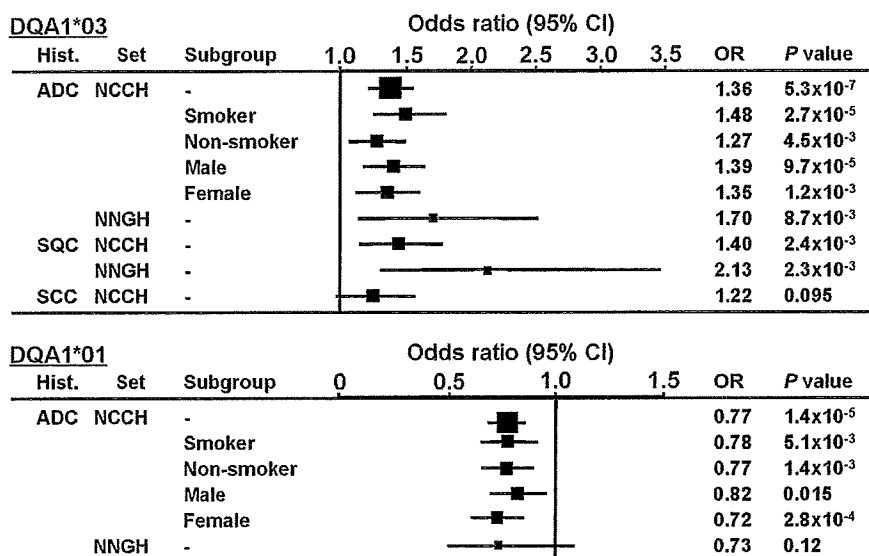


Figure 2b

No. of Risk allele	Genotype		Freq ^a	Odds ratio (95%CI)					OR	P value
	DQA1	TERT		0	1	2	3	4		
0	other/other	-	0.40						1.0	
1	other/*03	-	0.47		■				1.49	2.5x10 ⁻⁵
2	*03/*03	-	0.13		■	■			1.90	1.8x10 ⁻⁶

0	-	T/T	0.38						1.0	
1	-	T/G	0.48		■				1.32	3.5x10 ⁻³
2	-	G/G	0.14		■	■			2.21	4.8x10 ⁻¹⁰

0	other/other	T/T	0.15						1.0	
1	other/other	T/G	0.19		■				1.27	0.13
1	*03/other	T/T	0.06		■				1.44	0.027
2	*03/*03	T/T	0.18		■	■			1.97	3.1x10 ⁻³
2	*03/other	T/G	0.22		■	■			1.99	6.3x10 ⁻⁶
2	other/other	G/G	0.07		■	■			2.23	2.3x10 ⁻⁴
3	*03/*03	T/G	0.05		■	■			2.42	1.9x10 ⁻⁵
3	*03/ other	G/G	0.06		■	■			3.06	2.2x10 ⁻⁹
4	*03/*03	G/G	0.02		■	■	■		4.76	4.2x10 ⁻⁷
Per risk-allele					◇				1.43	7.8x10 ⁻¹⁶
P value for interaction										0.88

^aFrequency in controls.

Supplementary Table I. Inflation factors for the 1st and 2nd stages of GWAS

Repeat unit	1st stage		2nd stage	
	No. of markers	Inflation factor ^a	No. of markers	Inflation factor ^a
All	23,010	0.639	1,328	-
2-bp	16,545	0.520	897	-
3-bp	1,295	0.919	86	0.812
4-bp	4,502	0.958	303	1.026
5-bp	648	1.022	41	1.265
6-bp	20	0.947	1	-
3~6-bp	6,465	0.955	431	1.010

^aThe mean of the lower 90% of the test statistics (-log P values by Fisher's exact test) divided by the mean of the lower 90% of the expected values.

Supplementary Table II. Linkage disequilibrium between the D6S0067i polymorphisms and SNPs/alleles in the 6p21.31 locus

SNP/Allele	Controls		ADC cases	
	D'	R ²	D'	R ²
rs17426593	0.516	0.225	0.603	0.349
rs34843907	0.531	0.152	0.688	0.280
DQA1_2_145	0.514	0.223	0.607	0.352
DQA1_2_150	0.531	0.152	0.689	0.283
DQA1*01	0.531	0.152	0.689	0.283
DQA1*03	0.516	0.225	0.607	0.352

Supplementary Table III. Linkage disequilibrium between exonic and intronic HLA-DQA1 SNPs among case and control populations

Population	DQA1_2_145 and rs17426593		DQA1_2_150 and rs34843907	
	D'	R ²	D'	R ²
Controls	1.000	0.983	1.000	0.996
ADC cases	1.000	0.996	0.996	0.992

Supplementary Table IV. Correlation coefficients of HLA-DQA1 alleles determined by exonic SNPs and intronic SNPs

Population	R ²	
	DQA1*01	DQA1*03
Controls	1.000	0.983
ADC cases	0.996	0.996

Supplementary Table V. ORs of the DQA1*03 and DQA1*01 alleles for lung cancer risk

Allele	Category	Histological type	Subgroup	No.		Crude			Adjusted		
				Case	Control ^a	OR	(95% CI)	P value	OR	(95% CI)	P value
DQA1*03	NCCH	ADC		1,656	1,173	1.35	(1.21 - 1.51)	5.6x10 ⁻⁸	1.36 ^b	(1.20 - 1.54)	5.3x10 ⁻⁷
			Smoker	896	363	1.46	(1.22 - 1.75)	2.9x10 ⁻⁵	1.48 ^c	(1.23 - 1.77)	2.7x10 ⁻⁵
			Non-smoker	760	610	1.27	(1.09 - 1.48)	0.0022	1.27 ^c	(1.08 - 1.50)	0.0045
			Male	924	675	1.35	(1.16 - 1.57)	1.4x10 ⁻⁴	1.39 ^d	(1.18 - 1.65)	9.7x10 ⁻⁵
		Female	732	498	1.27	(1.09 - 1.49)	0.0021	1.35 ^d	(1.12 - 1.61)	0.0012	
		SQC	390	1,173	1.27	(1.08 - 1.50)	0.0047	1.40 ^b	(1.13 - 1.74)	0.0024	
		SCC	297	1,173	1.17	(0.98 - 1.41)	0.089	1.22 ^b	(0.97 - 1.54)	0.095	
	NNGH	ADC	84	145	1.57	(1.07 - 2.30)	0.022	1.70 ^b	(1.14 - 2.53)	0.0087	
		SQC	52	145	2.07	(1.32 - 3.27)	0.0016	2.13 ^b	(1.31 - 3.49)	0.0023	
DQA1*01	NCCH	ADC		1,656	1,173	0.78	(0.70 - 0.87)	6.0x10 ⁻⁶	0.77 ^b	(0.68 - 0.87)	1.4x10 ⁻⁵
			Smoker	896	363	0.78	(0.65 - 0.92)	0.0040	0.78 ^c	(0.65 - 0.93)	0.0051
			Non-smoker	760	610	0.78	(0.67 - 0.91)	0.0016	0.77 ^c	(0.65 - 0.90)	0.0014
			Male	924	675	0.83	(0.72 - 0.96)	0.0150	0.82 ^d	(0.69 - 0.96)	0.0150
		Female	732	498	0.74	(0.62 - 0.87)	4.6x10 ⁻⁴	0.72 ^d	(0.60 - 0.86)	2.8x10 ⁻⁴	
	NNGH	ADC	84	145	0.77	(0.52 - 1.13)	0.18	0.73 ^b	(0.49 - 1.09)	0.12	

^aInformation on smoking was not available for 200 subjects.

^bAdjusted for age, sex and smoking.

^cAdjusted for age and sex.

^dAdjusted for sex and smoking.

Supplementary Table VI. Differences in the allele distribution of SNPs in lung cancer susceptibility loci identified by GWASs

Allele	Chromosomal location	Position	Gene	Category	Minor allele frequency		OR (95% CI, P)
					Control	Case	
rs2736100-G	5p15.33	1339516	TERT (intron 2)	All	0.377	0.444	1.38 (1.23 - 1.56, 6.3×10^{-8}) ^a
				ADC		0.465	1.46 (1.30 - 1.65, 6.6×10^{-10}) ^a
				SQC		0.382	0.95 (0.77 - 1.19, 0.68) ^a
				SCC		0.407	1.07 (0.85 - 1.35, 0.58) ^a
rs401681-T	5p15.33	1375087	CLPTM1L (intron 13)	Non-smoker	0.380	0.470	1.47 (1.25 - 1.73, 4.1×10^{-6}) ^b
				Smoker	0.372	0.431	1.29 (1.08 - 1.53, 4.2×10^{-3}) ^b
				All	0.334	0.312	0.88 (0.78 - 0.99, 0.044) ^a
				ADC		0.314	0.89 (0.79 - 1.01, 0.077) ^a
rs1051730-T	15q25.1	76681394	CHRNA3 (Y215Y)	SQC		0.300	0.88 (0.70 - 1.10, 0.27) ^a
				SCC		0.315	0.87 (0.68 - 1.11, 0.27) ^a
				Non-smoker	0.333	0.297	0.81 (0.68 - 0.96, 0.014) ^b
				Smoker	0.336	0.319	0.96 (0.80 - 1.15, 0.65) ^b
rs1051730-T	15q25.1	76681394	CHRNA3 (Y215Y)	All	0.015	0.032	1.79 (1.19 - 2.78, 9.5×10^{-3}) ^a
				ADC		0.030	1.72 (1.14 - 2.69, 9.5×10^{-3}) ^a
				SQC		0.033	2.29 (1.14 - 4.72, 0.020) ^a
				SCC		0.037	2.22 (1.09 - 4.58, 0.027) ^a
rs1051730-T	15q25.1	76681394	CHRNA3 (Y215Y)	Non-smoker	0.015	0.030	1.65 (0.94 - 3.02, 0.083) ^b
				Smoker	0.017	0.033	1.94 (1.09 - 3.79, 0.023) ^b

^aAdjusted for sex, age and smoking.

^bAdjusted for sex and age.

Supplementary Table VII. ORs for genotypes of the HLA-DQA1, TERT and CHRNA3 loci

Locus	Number of risk allele	Genotype	Control (%)	Case (%)	OR* (95% CI)	P
HLA-DQA1	0	other/other	389 (40.2)	509 (30.7)	Reference	
	1	*03/other	455 (47.0)	859 (51.9)	1.49 (1.24 - 1.79)	2.5×10^{-5}
	2	*03/*03	124 (12.8)	288 (17.4)	1.90 (1.45 - 2.48)	1.8×10^{-6}
rs2736100 (TERT)	0	T/T	373 (38.5)	488 (29.5)	Reference	
	1	T/G	460 (47.5)	796 (48.0)	1.32 (1.10 - 1.60)	3.5×10^{-3}
	2	G/G	135 (14.0)	372 (22.5)	2.21 (1.72 - 2.86)	4.8×10^{-10}
rs1051730 (CHRNA3)	0	G/G	939 (97.0)	1,558 (94.1)	Reference	
	1	G/A	28 (2.9)	95 (5.7)	1.82 (1.18 - 2.89)	6.4×10^{-3}
	2	A/A	1 (0.1)	3 (0.2)	0.94 (0.11 - 19.0)	0.960

^a Adjusted for sex, age and smoking.

Supplementary Table VIII. Risk of combined *HLA-DQA1*, *TERT* and *CHRNA3* genotypes for lung adenocarcinoma

Gene	Number Risk allele	Genotype	Control (%)	Case (%)	OR ^a (95% CI)	P	
2		rs2736100 (<i>TERT</i>) *03 (<i>HLA-DQA1</i>)					
	0	T/T	other/other	148 (15.3)	149 (9.0)	Reference	
	1	T/G	other/other	188 (19.4)	249 (15.0)	1.27 (0.93 -1.74)	0.13
	1	T/T	*03/other	176 (18.2)	243 (14.7)	1.44 (1.04 -1.99)	0.027
	2	T/T	*03/*03	49 (5.1)	96 (5.8)	1.97 (1.25 -3.13)	3.1 × 10 ⁻³
	2	T/G	*03/other	212 (21.9)	415 (25.1)	1.99 (1.47 -2.70)	6.3 × 10 ⁻⁶
	2	G/G	other/other	53 (5.5)	111 (6.7)	2.23 (1.45 -3.45)	2.3 × 10 ⁻⁴
	3	T/G	*03/*03	60 (6.2)	132 (8.0)	2.42 (1.61 -3.68)	1.9 × 10 ⁻⁵
	3	G/G	*03/other	67 (6.9)	201 (12.1)	3.06 (2.11 -4.48)	2.2 × 10 ⁻⁹
	4	G/G	*03/*03	15 (1.5)	60 (3.6)	4.76 (2.53 -9.47)	4.2 × 10 ⁻⁷
Per risk-allele					1.43 (1.31 -1.56)	7.8 × 10 ⁻¹⁶	
P value for interaction						0.88	
2		rs2736100 (<i>TERT</i>) rs1051730 (<i>CHRNA3</i>)					
	0	T/T	G/G	362 (37.4)	457 (39.7)	Reference	
	1 or 2		G/A + A/A	11 (1.1)	31 (2.7)	1.73 (0.84 -3.80)	0.14
	1	T/G	G/G	445 (46.0)	749 (65.0)	1.32 (1.09 -1.60)	4.5 × 10 ⁻³
	2 or 3		G/A + A/A	15 (1.5)	47 (4.1)	2.40 (1.30 -4.69)	4.9 × 10 ⁻³
	2	G/G	G/G	132 (13.6)	352 (30.6)	2.22 (1.71 -2.88)	9.3 × 10 ⁻¹⁰
3 or 4					4.27 (1.38 -18.8)	9.9 × 10 ⁻³	
Per risk-allele					1.48 (1.33 -1.66)	3.9 × 10 ⁻¹¹	
P value for interaction						0.73	
2		*03 (<i>HLA-DQA1</i>) rs1051730 (<i>CHRNA3</i>)					
	0	other/other	G/G	380 (39.3)	470 (40.8)	Reference	
	1	*03/other	G/G	440 (45.5)	809 (70.2)	1.53 (1.26 -1.84)	1.1 × 10 ⁻⁵
	2 or 3		G/A + A/A	15 (1.5)	50 (4.3)	2.47 (1.36 -4.74)	2.5 × 10 ⁻³
	2	*03/*03	G/G	119 (12.3)	279 (24.2)	2.01 (1.54 -2.65)	2.9 × 10 ⁻⁷
3 or 4					1.37 (0.44 -4.77)	0.59	
Per risk-allele					1.35 (1.21 -1.50)	5.1 × 10 ⁻⁷	
P value for interaction						0.083	
3	0			144 (14.9)	132 (8.0)	Reference	
	1			356 (36.8)	479 (28.9)	1.45 (1.08 -1.94)	0.013
	2			319 (33.0)	619 (37.4)	2.15 (1.60 -2.88)	3.0 × 10 ⁻⁷
	3			127 (13.1)	349 (21.1)	3.11 (2.24 -4.35)	9.3 × 10 ⁻¹²
	4			22 (2.3)	73 (4.4)	4.16 (2.39 -7.50)	2.0 × 10 ⁻⁷
	5			0 (0)	4 (0.2)	- (- - -)	-
	6			0 (0)	0 (0)	- (- - -)	-
Per risk-allele					1.45 (1.40 -1.50)	2.5 × 10 ⁻¹⁷	

^aAdjusted for sex, age and smoking.

Supplementary Table IX. Association of 10 SNPs commonly analyzed in the present and other GWASs with lung cancer risk

SNP	Genome location	Gene	Position	Allele	Minor allele frequency		Allele OR		P value	
					Japanese*	Others	Japanese ^a	Others	Japanese*	Others
rs7192	32,519,624	HLA-DRA	exon 4	G/T	0.444	0.370	0.76	0.98 ^b	0.0016	0.65
rs3129763	32,698,903			G/A	0.064	0.270	1.10	1.14 ^b	0.60	0.0048
rs2187668	32,713,862	HLA-DQA1	intron 1	G/A	0.033	0.100	1.21	1.11 ^e	0.42	3.6x10 ⁻⁷
rs2647012	32,772,436			G/A	0.214	0.330	0.61	1.27 ^b	2.3x10 ⁻⁵	0.95
rs1794282	32,774,504			G/A	0.000	0.080	-	1.22 ^c	-	8.0x10 ⁻⁴
rs2239800	32,821,245	HLA-DQA2	intron 2	T/C	0.289	0.130	1.01	1.18 ^e	0.88	7.2x10 ⁻⁵
rs1573649	32,839,236			T/C	0.426	0.420	0.81	1.20 ^c	0.021	0.82
rs2071469	32,892,761	HLA-DOB	5'UTR	G/A	0.424	0.430	1.20	1.26 ^d	0.037	0.95
rs1057373	32,921,257	TAP1	3'UTR	G/T	0.105	0.080	1.18	1.20 ^e	0.23	0.78
rs17587	32,933,068	PSMB9	exon 3	G/T	0.243	0.280	0.90	0.95 ^b	0.33	0.33

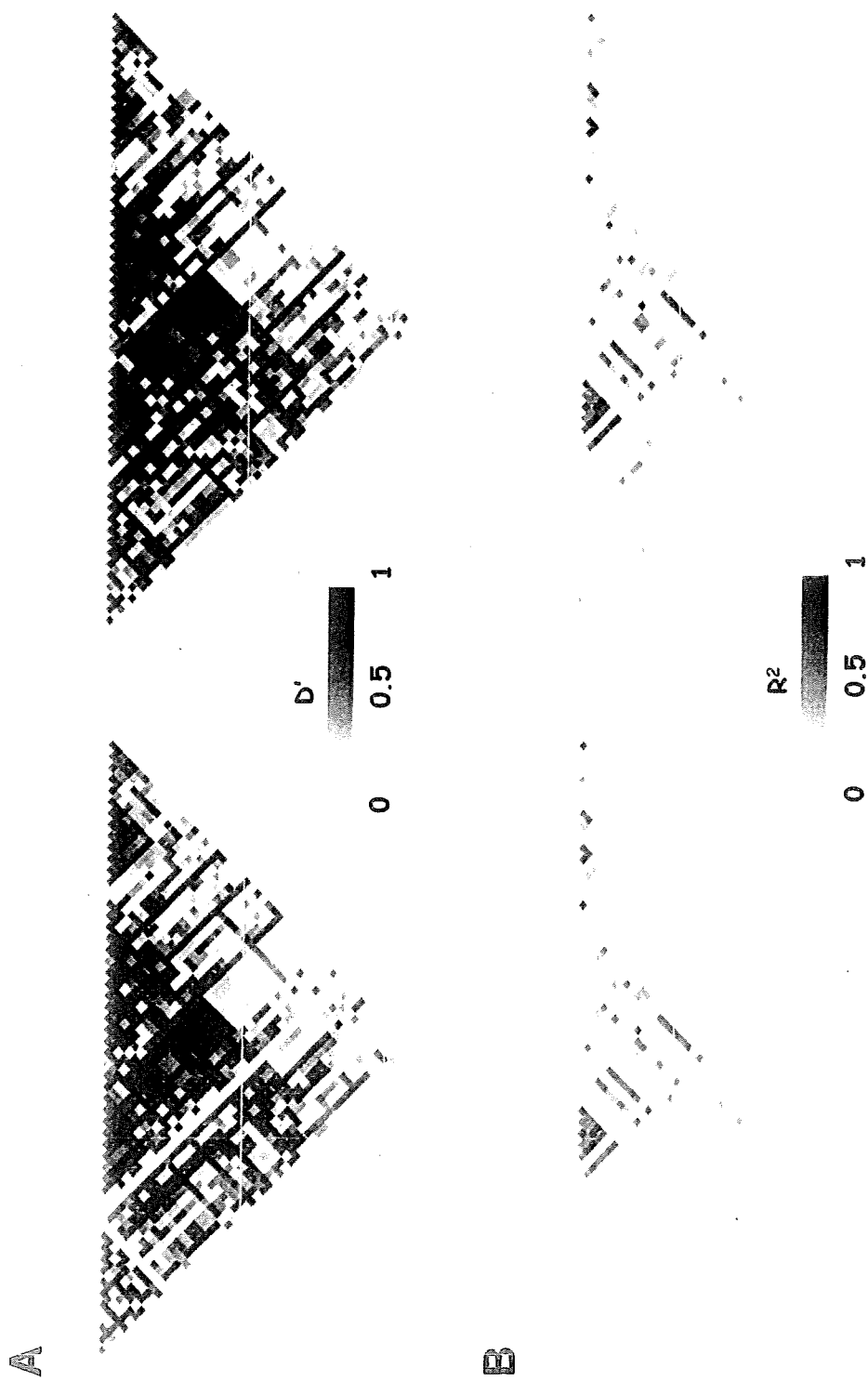
^a Association with lung adenocarcinoma risk on 525 cases and 525 controls.

^b Association with lung cancer risk on 1,989 cases and 2,625 controls in European countries⁸.

^c Association with lung cancer risk on 5,095 cases and 5,200 controls in European countries and USA⁴.

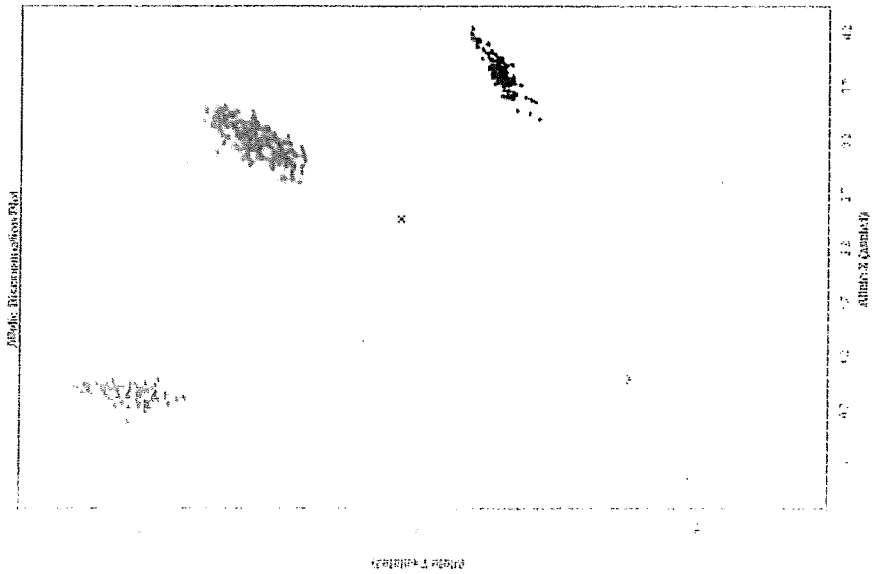
^d Association with lung cancer risk on 2,971 cases and 3,746 controls in European countries, Canada and USA⁵.

^e Association with lung cancer risk on 13,300 cases and 19,666 controls in European countries and USA¹¹.

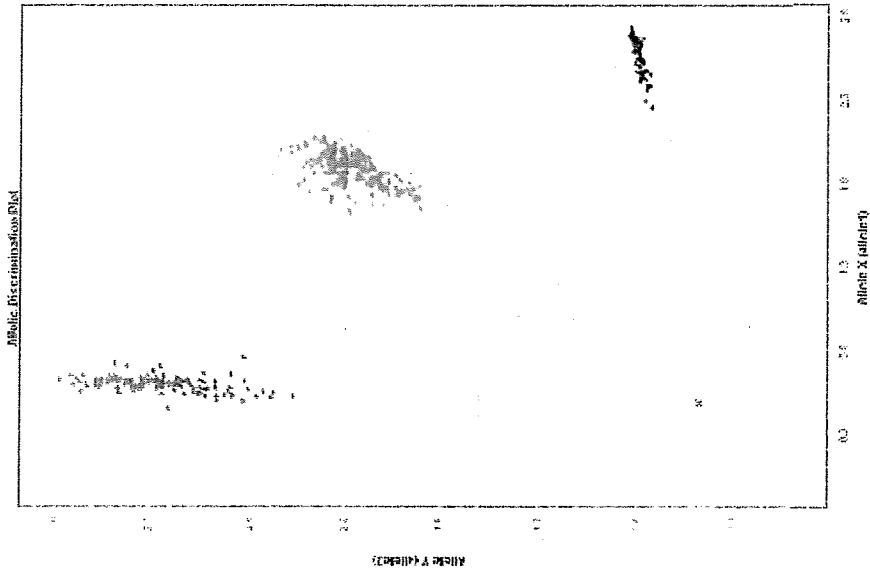


Supplementary Fig. 1. Linkage disequilibrium among 55 SNPs in the 6p21.31 locus. (A) D' value. (B) R^2 value. Results in 525 cases (left) and 525 controls (right) are shown. Boxes are shaded according to the pair-wise D' or R^2 values. A SNP, DRB1_2_61, was monomorphic in the cases, therefore, D' and R^2 values were not plotted in the cases.

rs34843907



rs17426593



Supplementary Fig. 2. The Taqman cluster plots for the rs34843907 and rs17426593 SNPs. Left: rs34843907. Red: homozygotes for the A allele; Green: heterozygotes; Blue: homozygotes for the C allele. Right: rs17426593. Red: homozygotes for the C allele; Green: heterozygotes; Blue: homozygotes for the T allele. Undetermined genotypes are labeled X.