Supporting Online Material

Supplemental Tables 1–5

Supplemental Table 1. Number of SNPs in the 16 genes evaluated for association with gene methylation.

Gene	No. of SNPs*
ATM	8
ATR	10
Artemis	19
CHEK1	14
CHEK2	12
Ku70	6
Ku80	25
LIG4	11
MRE11	14
NBN†	42
PRKDC	12
RAD50	10
TP53	8
XRCC2	18
XRCC3	16
XRCC4	27
total	252

* Tag SNPs were selected by pairwise r^2 method by using Phase I HapMap data for whites and Latino and White data from USC.

† SNPs were selected for NBN using dbSNPs based on the haplotype block structures and the validation status, Illumina design score, and functional potential of SNPs.

Supplemental Table 2. Prevalence of gene promoter methylation in sputum from 824 cohort members.

Gene	% Positive
p16	17.0
MGMT	22.9
RASSF1A	1.2
DAPK	16.3
GATA 4	31.2
GATA 5	19.9
PAX5 α	18.7
PAX5 β	10.8
Number of Genes Methylated	
0	32.5
1	28.6
2	19.8
3	10.3
4	5.7
5	2.2
6	0.8

Supplemental Table 3. Chromatid break per cell induced by bleomycin between cases and controls stratified by covariates.

Variables	Case subjects		Control subjects		*P*-value*
	n	Mean ± SD	n	Mean ± SD	
Total	77	0.473 ± 0.110	78	0.318 ± 0.098	< 0.0001
Age at sputum collection, yr					
< 51	17	0.434 ± 0.061	30	0.293 ± 0.098	< 0.0001
51–63	26	0.465 ± 0.103	32	0.335 ± 0.095	< 0.0001
≥ 63	34	0.499 ± 0.129	16	0.329 ± 0.099	< 0.0001
P-value†		0.0351		0.0270	
Gender					
Female	48	0.482 ± 0.125	48	0.318 ± 0.088	< 0.0001
Male	29	0.460 ± 0.081	30	0.316 ± 0.114	< 0.0001
P-value†		0.3690		0.8484	
Race					
Non-Hispanic White	57	0.480 ± 0.119	57	0.311 ± 0.097	< 0.0001
Hispanic	13	0.447 ± 0.040	17	0.349 ± 0.104	0.0017
Others	7	0.473 ± 0.125	4	0.274 ± 0.062	0.0167
P-value†		0.6700		0.4187	
Current smoker					
Yes	36	0.474 ± 0.115	49	0.316 ± 0.093	< 0.0001
No	41	0.473 ± 0.107	29	0.320 ± 0.107	< 0.0001
P-value†		0.3526		0.0694	
Pack years					
< 33.2	38	0.468 ± 0.126	37	0.315 ± 0.081	< 0.0001
≥ 33.2	39	0.478 ± 0.094	41	0.320 ± 0.112	< 0.0001
P-value†		0.9862		0.7088	
Smoking duration, yr					
< 34	38	0.465 ± 0.106	40	0.306 ± 0.089	< 0.0001
≥ 34	39	0.482 ± 0.117	38	0.330 ± 0.106	< 0.0001
P-value†		0.8654		0.3242	
Chronic airway obstruction					
Yes	28	0.489 ± 0.099	20	0.323 ± 0.089	< 0.0001
No	49	0.464 ± 0.116	56	0.319 ± 0.102	< 0.0001
P-value†		0.4465		0.7346	

* Two-sided two sample *t* test between cases and controls.

† Multivariate analysis of covariance with adjustment for age at sputum collection, sex, race, current smoking status, pack years, seeding number of lymphocytes, cryopreservation time, and log-transformed spontaneous chromatid breaks/cell.

Supplemental Table 4. Individual SNPs associated with risk for promoter methylation at p values ≤ 0.15 for the 16 genes evaluated in this study.

rs_num*	Chr	Gene†	Allele	MAF	*P*-value	ORs	low	high
rs7913426	chr10	Artemis	G	0.13	0.044	0.56	0.31	0.97
rs7476111	chr10	Artemis	T	0.33	0.138	1.32	0.92	1.91
rs584531	chr11	MRE11	C	0.39	0.058	0.70	0.48	1.01
rs2508678	chr11	MRE11	T	0.32	0.131	1.34	0.92	1.97
rs7117042	chr11	MRE11	T	0.05	0.002	3.00	1.51	6.28
rs604845	chr11	MRE11	T	0.39	0.038	0.68	0.47	0.98
rs533984	chr11	MRE11	A	0.34	0.092	1.37	0.95	1.98
rs540199	chr11	MRE11	G	0.37	0.144	0.76	0.53	1.10
rs1801516	chr11	ATM	A	0.09	0.062	1.74	0.98	3.16
rs373759	chr11	ATM	T	0.41	0.110	0.73	0.50	1.07
rs540723	chr11	CHEK1	A	0.10	0.082	1.62	0.95	2.82
rs537046	chr11	CHEK1	G	0.16	0.075	0.64	0.39	1.04
rs9514825	chr13	LIG4	T	0.36	0.075	1.38	0.97	1.98
rs4635191	chr13	LIG4	G	0.25	0.107	1.37	0.94	2.01
rs1151402	chr13	LIG4	T	0.45	0.045	0.67	0.45	0.99
rs2273175	chr14	XRCC3	C	0.41	0.089	0.73	0.51	1.05
rs2295148	chr14	XRCC3	T	0.47	0.061	0.70	0.49	1.01
rs2295146	chr14	XRCC3	T	0.47	0.015	0.63	0.43	0.91
rs8548	chr14	XRCC3	C	0.40	0.097	0.73	0.51	1.06
rs3825550	chr14	XRCC3	T	0.03	0.096	2.25	0.89	6.19
rs828910	chr2	Ku80	G	0.46	0.108	1.35	0.94	1.96
rs828911	chr2	Ku80	A	0.41	0.093	1.37	0.95	1.98
rs828701	chr2	Ku80	T	0.45	0.066	1.40	0.98	2.02
rs2303400	chr2	Ku80	C	0.46	0.113	0.74	0.50	1.07
rs207908	chr2	Ku80	T	0.43	0.105	1.37	0.94	2.01
rs5752776	chr22	CHEK2	A	0.34	0.099	0.73	0.49	1.06
rs9620817	chr22	CHEK2	T	0.13	0.067	0.56	0.29	1.03
rs5762763	chr22	CHEK2	C	0.30	0.023	1.58	1.07	2.36
rs2236141	chr22	CHEK2	T	0.12	0.032	1.76	1.06	2.99
rs6519265	chr22	Ku70	A	0.20	0.114	1.39	0.93	2.12
rs132793	chr22	Ku70	A	0.20	0.091	1.43	0.95	2.17
rs10804682	chr3	ATR	A	0.22	0.094	0.67	0.41	1.07
rs2244012	chr5	RAD50	G	0.18	0.135	1.43	0.90	2.29
rs6596087	chr5	RAD50	A	0.18	0.112	1.46	0.92	2.34
rs6871536	chr5	RAD50	C	0.18	0.138	1.42	0.90	2.27
rs3218400	chr7	XRCC2	T	0.12	0.123	0.62	0.33	1.13
rs7830743	chr8	DNA-PKc	G	0.11	0.071	0.54	0.27	1.04
rs4873737	chr8	DNA-PKc	G	0.12	0.080	0.57	0.30	1.06
rs4873772	chr8	DNA-PKc	A	0.31	0.128	1.34	0.92	1.97
rs10091017	chr8	DNA-PKc	A	0.10	0.062	0.52	0.26	1.02
rs14448	chr8	NBN	G	0.06	0.064	1.91	0.98	3.87
rs9995	chr8	NBN	G	0.36	0.102	0.73	0.49	1.06
SB_rs1063054	chr8	NBN	G	0.36	0.130	0.74	0.50	1.09
SB_rs2735383	chr8	NBN	G	0.36	0.141	0.75	0.51	1.10
rs6998169	chr8	NBN	A	0.13	0.014	0.45	0.23	0.84

* The underlined SNPs were selected from each gene ($p < 0.15$) to represent the allelic status for those genes.

† XRCC2 and XRCC4 were not listed in this table because of no SNPs showing association with methylation at p value less than 0.15.

Supplemental Table 5. Common haplotypes of the MRE11A gene.

Haplotype †	Tag SNPs*														Prevalence (%)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Hap1	C	C	C	C	T	T	G	A	G	T	T	A	G	T	33.8
Hap2	T	T	G	C	C	C	T	G	A	C	C	G	C	C	21.7
Hap3	T	C	C	C	C	T	G	A	G	T	T	A	G	T	21.2
Hap4	T	T	C	**T**	C	T	G	A	A	C	C	A	C	C	7.5
Hap5	T	C	C	C	C	C	G	G	G	C	C	G	C	C	6.0

* SNP1 to SNP14 correspond to rs584531, rs2508678, rs1271079, rs7117042, rs604845, rs654718, rs529126, rs641936, rs533984, rs1270146, rs659349, rs540199, rs2509943, and rs610899. These SNPs are sorted by their position on chromosome 11. The bolded **T** allele identifies the risk haplotype associated with high methylation index.
† Haplotypes were generated by HaploView.