

SUPPLEMENTARY MATERIALS

Associations between 25 lung cancer risk-related SNPs and polycyclic aromatic hydrocarbon-induced genetic damage in coke oven workers

Xiayun Dai¹, Siyun Deng¹, Tian Wang¹, Gaokun Qiu¹, Jun Li¹, Binyao Yang¹, Wei Feng¹, Xiaosheng He¹, Qifei Deng¹, Jian Ye¹, Wangzhen Zhang², Meian He¹, Xiaomin Zhang¹, Huan Guo¹, and Tangchun Wu^{1*}

Table S1. The relationships of age groups, gender, and smoking status to the levels of PAH metabolites, BPDE-Alb Adducts and genetic damage

Variables	Age groups ^b		P-value ^a	Gender		P-value ^a	Smoke status			P-value ^a
	≤41 years	>41 years		male	female		smoking	quit	never	
Sample size	777	777		1333	224		882	64	609	
PAH metabolites (µg/mmol creatinine, median (5%, 95%))										
1-hydroxynaphthalene	1.51 (0.43, 7.19)	1.73 (0.51, 7.05)	0.249	1.67 (0.47, 7.18)	1.31 (0.35, 6.65)	0.856	1.91 (0.62, 7.45)	1.27 (0.44, 4.80)	1.20 (0.34, 6.26)	<0.001
2-hydroxynaphthalene	1.42 (0.31, 6.01)	1.76 (0.41, 5.92)	0.302	1.69 (0.38, 6.28)	1.17 (0.30, 3.95)	0.732	2.12 (0.63, 7.02)	0.94 (0.25, 4.38)	0.92 (0.25, 3.93)	<0.001
2-hydroxyfluorene	0.88 (0.29, 4.08)	0.87 (0.31, 3.10)	0.002	0.88 (0.31, 3.68)	0.80 (0.28, 3.04)	0.169	0.92 (0.31, 3.78)	0.83 (0.29, 2.25)	0.82 (0.30, 3.52)	0.128
9-hydroxyfluorene	0.55 (0.01, 4.55)	0.58 (0.01, 4.08)	0.861	0.56 (0.01, 3.93)	0.61 (0.01, 6.64)	0.644	0.56 (0.01, 3.76)	0.54 (0.004, 3.2)	0.57 (0.01, 5.21)	0.599
1-hydroxyphenanthrene	0.84 (0.10, 3.90)	0.92 (0.10, 4.33)	0.080	0.86 (0.10, 4.01)	0.98 (0.09, 5.05)	0.097	0.87 (0.10, 3.95)	0.92 (0.09, 3.02)	0.91 (0.10, 4.80)	0.626
2-hydroxyphenanthrene	0.30 (0.05, 1.47)	0.30 (0.04, 1.30)	0.054	0.29 (0.05, 1.35)	0.33 (0.04, 1.74)	0.347	0.29 (0.05, 1.24)	0.28 (0.06, 1.07)	0.32 (0.05, 1.61)	0.205
3-hydroxyphenanthrene	0.38 (0.05, 1.74)	0.36 (0.03, 1.38)	0.001	0.36 (0.04, 1.58)	0.37 (0.02, 1.52)	0.657	0.37 (0.04, 1.60)	0.38 (0.03, 1.06)	0.36 (0.03, 1.58)	0.591
4-hydroxyphenanthrene	0.33 (0.004, 2.05)	0.33 (0.003, 2.21)	0.552	0.32 (0.003, 1.81)	0.44 (0.004, 3.28)	0.148	0.30 (0.003, 1.68)	0.34 (0.004, 2.15)	0.36 (0.004, 2.63)	0.992
9-hydroxyphenanthrene	0.69 (0.16, 3.89)	0.80 (0.17, 3.86)	0.842	0.73 (0.16, 3.70)	0.85 (0.18, 4.77)	0.029	0.74 (0.16, 3.54)	0.71 (0.26, 3.15)	0.75 (0.15, 4.39)	0.670
1-hydroxypyrene	3.32 (0.88, 15.67)	3.31 (0.85, 13.58)	0.773	3.18 (0.85, 13.1)	4.60 (0.95, 19.0)	0.002	3.22 (0.86, 12.53)	3.16 (0.77, 14.64)	3.52 (0.87, 16.68)	0.502
ΣOH-PAHs	11.47 (4.21, 50.95)	12.04 (4.71, 41.2)	0.365	11.7 (4.39, 42.8)	12.43 (3.96, 49.2)	0.107	12.4 (4.89, 41.66)	11.01 (4.23, 34.1)	10.97 (3.73, 49.9)	0.075
BPDE-Alb adducts (ng/mg albumin)	4.25 (1.75, 7.46)	4.28 (1.75, 8.58)	0.084	4.25 (1.75, 7.93)	4.31 (3.13, 8.33)	0.415	4.25 (1.75, 8.22)	4.20 (1.75, 6.01)	4.30 (3.05, 7.55)	0.075
Genetic damage (mean ± SD)										
8-OHdG (nmol/mmol creatinine) ^c	4.68 ± 1.13	4.58 ± 1.19	0.481	4.55 ± 1.14	5.11 ± 1.15	<0.001	4.51 ± 1.16	4.64 ± 0.98	4.80 ± 1.16	0.254
MN frequency (%)	3.54 ± 2.55	4.09 ± 3.00	<0.001	3.61 ± 2.65	5.02 ± 3.33	<0.001	3.61 ± 2.53	3.54 ± 3.13	4.15 ± 3.10	0.205

^aA poisson loglinear model and a general linear model were used for MN frequency (%) and other biomarkers, respectively, properly adjusting for age, gender, smoking status, alcohol use, and BMI;

^bThe population was classified into two subgroups according to the median value of age;

^cThe levels of 8-OHdG were ln-transformed.

Table S2. Levels of genetic damage in coke oven workers according to lung cancer risk-related SNPs

SNPs (Major (A)/ Minor alleles(a))	8-OHdG (LSM ± SE)			MN frequency (LSM ± SE)		
	AA	Aa	aa	AA	Aa	aa
rs10937405 (C/T)	4.91 ± 0.09	4.83 ± 0.09	4.79 ± 0.13	4.13 ± 0.22	4.09 ± 0.23	3.75 ± 0.31
rs11080466 (A/G)	4.91 ± 0.09	4.88 ± 0.10	4.69 ± 0.16	3.99 ± 0.22	4.14 ± 0.24	3.94 ± 0.39
rs1333040 (T/C)	4.85 ± 0.09	4.84 ± 0.09	4.98 ± 0.12	4.23 ± 0.22	3.89 ± 0.23	4.28 ± 0.30
rs1663689 (A/G)	4.87 ± 0.10	4.87 ± 0.09	4.83 ± 0.11	4.23 ± 0.23	4.1 ± 0.22	3.71 ± 0.27
rs2131877 (T/C)	4.90 ± 0.10	4.89 ± 0.09	4.74 ± 0.10	3.94 ± 0.24	4.11 ± 0.22	4.25 ± 0.25
rs247008 (C/T)	4.98 ± 0.10	4.80 ± 0.09	4.86 ± 0.10	3.96 ± 0.24	4.20 ± 0.22	4.02 ± 0.24
rs2736100 (T/G)	4.92 ± 0.10	4.84 ± 0.09	4.83 ± 0.11	4.10 ± 0.24	4.08 ± 0.22	4.14 ± 0.26
rs2853677 (T/C)	4.91 ± 0.10	4.83 ± 0.09	4.87 ± 0.11	4.14 ± 0.23	4.02 ± 0.22	4.27 ± 0.28
rs2895680 (T/C)	4.87 ± 0.09	4.86 ± 0.10	4.83 ± 0.13	4.15 ± 0.22	3.96 ± 0.23	4.18 ± 0.30
rs36600 (C/T)	4.89 ± 0.09	4.75 ± 0.11	4.68 ± 0.28	4.06 ± 0.21	4.22 ± 0.26	4.44 ± 0.70
rs3813572 (A/G)	4.89 ± 0.09	4.78 ± 0.10	4.74 ± 0.18	4.20 ± 0.22	3.9 ± 0.24	3.66 ± 0.43
rs3817963 (A/G)	4.90 ± 0.09	4.81 ± 0.09	4.90 ± 0.16	4.09 ± 0.22	4.07 ± 0.23	4.18 ± 0.38
rs401681 (C/T)	4.88 ± 0.09	4.87 ± 0.09	4.80 ± 0.12	4.15 ± 0.22	4.05 ± 0.23	4.02 ± 0.29
rs4488809 (C/T)	4.84 ± 0.10	4.86 ± 0.09	4.91 ± 0.10	4.10 ± 0.24	4.20 ± 0.22	3.87 ± 0.24
rs465498 (T/C)	4.88 ± 0.09	4.82 ± 0.10	4.73 ± 0.18	4.07 ± 0.21	4.2 ± 0.24	3.80 ± 0.43
rs4677662 (T/C)	4.87 ± 0.09	4.87 ± 0.09	4.73 ± 0.13	4.00 ± 0.22	4.16 ± 0.22	4.28 ± 0.32
rs4809957 (G/A)	4.85 ± 0.09	4.88 ± 0.09	4.85 ± 0.11	4.24 ± 0.23	3.99 ± 0.22	4.04 ± 0.26
rs6495309 (C/T)	4.80 ± 0.10	4.87 ± 0.09	4.94 ± 0.11	4.07 ± 0.24	4.12 ± 0.22	4.06 ± 0.26
rs667282 (T/C)	4.77 ± 0.10	4.86 ± 0.09	4.92 ± 0.11	4.08 ± 0.24	4.09 ± 0.22	4.18 ± 0.25
rs7086803 (G/A)	4.86 ± 0.09	4.87 ± 0.09	4.81 ± 0.13	4.08 ± 0.22	4.08 ± 0.23	4.19 ± 0.32
rs7216064 (A/G)	4.85 ± 0.09	4.87 ± 0.09	4.92 ± 0.11	4.13 ± 0.22	3.99 ± 0.23	4.21 ± 0.27
rs753955 (T/C)	4.81 ± 0.09	4.87 ± 0.09	5.11 ± 0.12	4.09 ± 0.22	4.17 ± 0.23	3.71 ± 0.30
rs9387478 (C/A)	4.87 ± 0.10	4.86 ± 0.09	4.84 ± 0.10	4.13 ± 0.24	4.00 ± 0.23	4.21 ± 0.25
rs9439519 (T/C)	4.88 ± 0.09	4.85 ± 0.09	4.84 ± 0.13	4.04 ± 0.22	4.13 ± 0.23	4.16 ± 0.31
rs16988393 (T/C)	4.86 ± 0.09	4.85 ± 0.10	5.14 ± 0.31	4.12 ± 0.21	4.09 ± 0.25	2.96 ± 0.72

LSM: least square mean;

SE: standard error.

Table S3. Spearman correlations between genetic damage and potentially influential variables in coke oven workers

Variables	Correlation (r)/P-value	Gender	Age	Worked years	Smoking	Pack-years	BMI	Drinking	BPDE-Alb adducts	ΣOH-PAHs
Gender	r	1.000	-0.126	-0.107	0.482	-0.437	-0.220	0.279	0.018	0.063
	P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.487	0.013
Age	r	-0.126	1.000	0.816	-0.181	0.391	0.089	-0.194	-0.001	0.041
	P-value	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	0.974	0.106
Working year	r	-0.107	0.816	1.000	-0.191	0.365	0.086	-0.185	0.003	0.021
	P-value	<0.001	<0.001		<0.001	<0.001	0.001	<0.001	0.918	0.399
Smoking	r	0.482	-0.181	-0.191	1.000	0.852	-0.110	0.326	0.009	-0.073
	P-value	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	0.735	0.004
Pack-years	r	-0.437	0.391	0.365	0.852	1.000	0.129	-0.335	-0.038	0.075
	P-value	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	0.140	0.003
BMI	r	-0.220	0.089	0.086	-0.110	0.129	1.000	-0.020	-0.065	-0.058
	P-value	<0.001	<0.001	0.001	<0.001	<0.001		0.429	0.011	0.024
Drinking	r	0.279	-0.194	-0.185	0.326	-0.335	-0.020	1.000	0.047	-0.020
	P-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.429		0.067	0.429
BPDE-Alb adducts	r	0.018	-0.001	0.003	0.009	-0.038	-0.065	0.047	1.000	0.189
	P-value	0.487	0.974	0.918	0.735	0.140	0.011	0.067		0.000
ΣOH-PAHs	r	0.063	0.041	0.021	-0.073	0.075	-0.058	-0.020	0.189	1.000
	P-value	0.013	0.106	0.399	0.004	0.003	0.024	0.429	0.000	
8-OHdG	r	0.181	-0.043	-0.068	0.134	-0.120	-0.126	0.076	0.154	0.494
	P-value	<0.001	0.109	0.012	<0.001	<0.001	<0.001	0.005	<0.001	<0.001
MN frequency (%)	r	0.159	0.112	0.092	0.070	-0.045	-0.112	-0.021	0.297	0.097
	P-value	<0.001	<0.001	<0.001	0.006	0.075	<0.001	0.411	<0.001	<0.001

Tables S4. Relationships of internal exposure to PAHs and lung cancer risk-related SNPs to genetic damage of coke oven workers

SNPs	Genotypes ^a	N	8-OHdG				MN frequency (%)			
			β (95% CI) ^b	<i>P</i> -value ^b	<i>P</i> _{interaction} ^d	FDR	β (95% CI) ^c	<i>P</i> -value ^c	<i>P</i> _{interaction} ^d	FDR
rs10937405	CC	768	0.029 (0.024, 0.034)	<0.001	0.327	0.509	0.009 (0.003, 0.015)	0.004	0.453	0.566
	CT+TT	749	0.025 (0.021, 0.03)	<0.001			0.011 (0.006, 0.017)	<0.001		
rs11080466	AA	923	0.025 (0.021, 0.03)	<0.001	0.176	0.345	0.009 (0.003, 0.014)	0.001	0.397	0.522
	AG+GG	569	0.03 (0.024, 0.035)	<0.001			0.012 (0.006, 0.018)	<0.001		
rs1333040	TT	738	0.024 (0.02, 0.028)	<0.001	0.021	0.075	0.011 (0.004, 0.018)	0.001	0.844	0.898
	TC+CC	779	0.032 (0.027, 0.038)	<0.001			0.010 (0.005, 0.015)	<0.001		
rs1663689	AA	544	0.037 (0.031, 0.044)	<0.001	0.002	0.042	0.010 (0.004, 0.016)	0.002	0.862	0.898
	AG	710	0.024 (0.02, 0.029)	<0.001			0.009 (0.001, 0.016)	0.021		
	GG	260	0.023 (0.015, 0.03)	<0.001			0.013 (0.005, 0.021)	0.001		
rs2131877	TT	458	0.022 (0.017, 0.027)	<0.001	0.011	0.075	0.040 (0.021, 0.059)	<0.001	0.034	0.135
	TC	754	0.033 (0.028, 0.038)	<0.001			0.016 (0.010, 0.022)	<0.001		
	CC	306	0.026 (0.017, 0.035)	<0.001			0.013 (0.003, 0.023)	0.011		
rs247008	CC	397	0.029 (0.022, 0.036)	<0.001	0.689	0.758	0.010 (0.003, 0.016)	0.003	0.056	0.142
	CT	750	0.026 (0.021, 0.03)	<0.001			0.008 (0.002, 0.014)	0.006		
	TT	370	0.028 (0.021, 0.035)	<0.001			0.028 (0.011, 0.044)	0.001		
rs2736100	TT	515	0.031 (0.024, 0.038)	<0.001	0.436	0.573	0.013 (0.004, 0.021)	0.004	<0.001	0.001
	TG	757	0.028 (0.023, 0.032)	<0.001			0.008 (0.003, 0.013)	0.003		
	GG	244	0.024 (0.016, 0.031)	<0.001			0.045 (0.026, 0.063)	<0.001		
rs2853677	TT	569	0.032 (0.026, 0.039)	<0.001	0.132	0.329	0.005 (-0.001, 0.012)	0.123	0.060	0.142
	TC	741	0.025 (0.02, 0.029)	<0.001			0.017 (0.01, 0.024)	<0.001		
	CC	207	0.03 (0.021, 0.040)	<0.001			0.007 (0, 0.015)	0.061		
rs2895680	TT	743	0.027 (0.022, 0.032)	<0.001	0.637	0.758	0.014 (0.008, 0.02)	<0.001	0.139	0.242
	TC+CC	774	0.026 (0.022, 0.031)	<0.001			0.008 (0.003, 0.013)	0.003		
rs36600	CC	1246	0.027 (0.024, 0.031)	<0.001	0.741	0.771	0.013 (0.008, 0.017)	<0.001	0.056	0.142
	CT+TT	272	0.026 (0.019, 0.034)	<0.001			0 (-0.012, 0.011)	0.960		
rs3813572	AA	998	0.028 (0.024, 0.032)	<0.001	0.698	0.758	0.014 (0.008, 0.019)	<0.001	0.038	0.135
	AG+GG	511	0.026 (0.019, 0.032)	<0.001			0.026 (0.017, 0.035)	<0.001		
rs3817963	AA	926	0.026 (0.022, 0.03)	<0.001	0.271	0.451	0.013 (0.007, 0.019)	<0.001	0.172	0.269
	AG +GG	589	0.03 (0.024, 0.036)	<0.001			0.007 (0.001, 0.013)	0.020		
rs401681	CC	668	0.031 (0.025, 0.036)	<0.001	0.116	0.321	0.006 (0.001, 0.012)	0.022	0.068	0.142
	CT+TT	849	0.025 (0.021, 0.03)	<0.001			0.015 (0.009, 0.021)	<0.001		
rs4488809	CC	395	0.021 (0.016, 0.026)	<0.001	0.021	0.075	0.011 (0.002, 0.021)	0.022	0.190	0.279
	CT	747	0.028 (0.023, 0.034)	<0.001			0.013 (0.008, 0.019)	<0.001		
	TT	372	0.034 (0.026, 0.041)	<0.001			0.005 (-0.002, 0.012)	0.178		
rs465498	TT	1044	0.025 (0.021, 0.029)	<0.001	0.017	0.075	0.008 (0.003, 0.013)	0.002	0.135	0.242
	TC+CC	475	0.034 (0.027, 0.041)	<0.001			0.014 (0.007, 0.022)	<0.001		
rs4677662	TT	757	0.029 (0.024, 0.034)	<0.001	0.361	0.509	0.016 (0.009, 0.022)	<0.001	0.024	0.121
	TC+CC	759	0.026 (0.021, 0.03)	<0.001			0.007 (0.001, 0.012)	0.017		
rs4809957	GG	560	0.025 (0.02, 0.03)	<0.001	0.506	0.633	0.006 (0.001, 0.011)	0.028	0.076	0.142
	GA	704	0.028 (0.023, 0.033)	<0.001			0.002 (-0.001, 0.006)	0.183		

	AA	253	0.031 (0.022, 0.04)	<0.001			0.011 (0.001, 0.022)	0.035		
rs6495309	CC	476	0.025 (0.019, 0.031)	<0.001	0.176	0.345	0.012 (0.005, 0.019)	0.001	0.145	0.242
	CT	745	0.031 (0.026, 0.036)	<0.001			0.008 (0.002, 0.013)	0.005		
	TT	291	0.023 (0.016, 0.031)	<0.001			0.021 (0.006, 0.035)	0.004		
rs667282	TT	477	0.024 (0.018, 0.03)	<0.001	0.012	0.075	0.015 (0.006, 0.024)	0.001	0.238	0.331
	TC	730	0.033 (0.028, 0.038)	<0.001			0.008 (0.003, 0.013)	0.001		
	CC	309	0.021 (0.014, 0.028)	<0.001			0.016 (0.002, 0.03)	0.026		
rs7086803	GG	762	0.025 (0.021, 0.03)	<0.001	0.184	0.345	0.007 (0.002, 0.011)	0.005	<0.001	<0.001
	GA+AA	754	0.030 (0.025, 0.035)	<0.001			0.047 (0.034, 0.06)	<0.001		
rs7216064	AA	633	0.027 (0.022, 0.033)	<0.001	0.367	0.509	0.051 (0.035, 0.068)	<0.001	<0.001	<0.001
	AG+GG	882	0.029 (0.024, 0.035)	<0.001			0.006 (0.002, 0.011)	0.006		
rs753955	TT	755	0.022 (0.014, 0.029)	<0.001	0.193	0.345	0.072 (0.040, 0.103)	<0.001	0.940	0.940
	TC+CC	763	0.030 (0.024, 0.035)	<0.001			0.010 (0.003, 0.016)	0.003		
rs9387478	CC	390	0.025 (0.021, 0.03)	<0.001	0.030	0.095	0.011 (0.006, 0.016)	<0.001	0.548	0.632
	CA	734	0.025 (0.018, 0.032)	<0.001			0.015 (0.003, 0.027)	0.017		
	AA	358	0.024 (0.02, 0.029)	<0.001			0.011 (0.006, 0.016)	<0.001		
rs9439519	TT	792	0.038 (0.029, 0.047)	<0.001	0.874	0.873	0.006 (-0.002, 0.013)	0.126	0.064	0.142
	TC+CC	727	0.027 (0.022, 0.031)	<0.001			0.015 (0.009, 0.022)	<0.001		
rs16988393	TT	1223	0.028 (0.023, 0.033)	<0.001	0.015	0.747	0.007 (0.002, 0.012)	0.008	0.557	0.632
	TC+CC	295	0.030 (0.026, 0.034)	<0.001			0.009 (0.005, 0.014)	<0.001		

^aThe heterozygotes and wild homozygotes were pooled because of a low number of individuals with wild homozygotes (≤ 200);

^bA general linear model was used to calculate the β (95%CI) and P values of Σ OH-PAHs on urinary 8-OHdG;

^cA poisson loglinear model was used to calculate the β (95%CI) and P values of plasma BPDE-Alb adducts on MN frequency (%);

^d $P_{\text{interaction}}$ was for the interaction term which was the product between internal exposure (BPDE-Alb adducts or Σ OH-PAHs, continuous variables) and the genotypes of SNPs (categorical variables) in the model.