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Association of Matrix Metalloproteinase-1 Polymorphisms with Risk of COPD and Lung Cancer and Survival in Lung Cancer

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Abstract

Background—The primary risk factor for chronic obstructive pulmonary disease (COPD) and non-small cell lung cancer (NSCLC) is cigarette smoking but shared susceptibility factors, such as variations in the matrix metalloproteinase-1 (MMP1) gene, may also underlie both diseases.

Materials and Methods—Cases with prevalent COPD (n=167), incident NSCLC (n=242), or prevalent COPD plus incident NSCLC (n=128) were compared to disease-free controls (n=338) to assess six MMP1 polymorphisms. The association between these polymorphisms and survival in NSCLC was also evaluated.

Results—Rs11292517 among African-Americans [odds ratio (OR)=5.48, 95% confidence interval (CI)=1.17–25.72] and rs2071230 among Caucasians (OR=2.51, 95% CI=1.09–5.77) appeared to be associated with NSCLC risk in the presence of COPD. Rs470558 appeared to be associated with survival in NSCLC among African-Americans (hazard ratio=3.94; 95%CI=1.14–13.63). No associations remained after adjusting for multiple comparisons.

Conclusion—Polymorphisms in MMP1 were not consistently associated with prevalent COPD or incident NSCLC nor with survival in NSCLC.

Keywords

Lung cancer; case–control; survival; chronic bronchitis; emphysema; matrix metalloproteinase-1; gene polymorphism; rs11292517

Chronic obstructive pulmonary disease (COPD) is a recognized clinical risk indicator for lung cancer (1). However, the fact that cigarette smoking is such an overwhelmingly strong risk factor for both diseases makes it difficult to determine whether there are also shared

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Conflicts of Interest
The Authors have no conflicts of interest to disclose.

susceptibility factors. Only 10–20% of smokers develop COPD or lung cancer (2, 3), strongly suggesting that genetic susceptibility is an important factor.

Tissue degradation is one possible pathway that could underlie both diseases. Matrix metalloproteinase-1 (MMP1) is capable of degrading collagens (4) and an insertion of a guanine (G) at nucleotide −1607 (rs11292517) in the gene's promoter region results in significantly higher transcription (5, 6). Having two sequential guanines due to this insertion polymorphism ("2G allele") has been associated with increased susceptibility to and invasiveness of multiple types of cancer, including lung cancer (7–12). Overexpression of MMP1 has also been associated with COPD in the absence of lung cancer in animal models (13, 14) and found in bronchoalveolar lavage fluid of smokers with COPD (9, 15, 16).

This study was carried out to characterize the potential contribution of variation in the gene that encodes this protein to the susceptibility to COPD and lung cancer, and survival in lung cancer. Additionally, we compared the associations between African-Americans and Caucasians to determine if genetic variation could explain racial differences in the incidence of these two diseases (17).

Materials and Methods

Lung cancer and COPD case–control study

Histologically-confirmed non-small cell lung cancer (NSCLC) cases and two sets of controls (hospital and population) were enrolled, as previously described (18). For the current analyses, participants were further stratified according to self-reported COPD diagnosis, which was ascertained during a structured detailed interview that all participants underwent after providing informed consent, to form four study groups: i) controls without either disease (the referent category) and cases with ii) COPD-only, iii) NSCLC-only, and iv) COPD plus NSCLC.

At the time of study enrollment, the COPD cases had prevalent disease. Thereby, among the COPD cases, time-dependent characteristics (age and pack-years smoked) were truncated to the time of COPD diagnosis. Time-dependent variables for the disease-free controls were also truncated to maintain case–control comparability; a truncation age was randomly assigned based on the distribution of age at COPD diagnosis among cases within the same birth year (± 5 years) group.

Cohort study of survival in lung cancer

The NSCLC participants were followed for mortality *via* the National Death Index (NDI) (http://www.cdc.gov/nchs/ndi.htm). For this study, death from lung cancer as the immediate or underlying cause of death was the primary outcome. In the statistical analysis, individuals were censored at the time of death if they died of other causes, or at the end of the study period if they were still alive. Survival data are reported until December 31, 2005.

Genotyping

DNA from lymphocytes was extracted using Flexigene DNA extraction kits (Qiagen, Valencia, CA, U.S.A.). One functional *MMP1* polymorphism (rs1799750 (9) or rs11292517 (15)), which has been shown to affect transcription levels, was genotyped by BioServe Biotechnologies, Ltd. (Laurel, MD, USA) using a MassARRAY iPLEXTM platform (http://www.bioserve.com/preclinical-molecular-services/maldi-tof-massarray-iplex.cfm). The other five polymorphisms (rs10488, rs470558, rs5031036, rs5854, and rs2071230) were chosen because the National Cancer Institute's Core Genotyping Facility (Gaithersburg, MD, USA) had readily available and validated Sequencing or TaqMan assays and because

variant alleles were not rare (>5%) in the SNP500 population (http://snp500cancer.nci.nih.gov). The assay details for rs1799750 are provided (Table I) and those for the other five polymorphisms are available on the Core Genotyping Facility's website (http://variantgps.nci.nih.gov/cgfseq/pages/home.do). All genotype completion rates were at least 93% and there was 100% genotype concordance between duplicates for each test among a 10% random, blinded sample. All polymorphisms were in Hardy-Weinberg equilibrium.

Statistical analysis

All analyses were performed separately for Caucasians and African-Americans. Odds ratios (ORs) of COPD and NSCLC and 95% confidence intervals (CIs) were calculated using logistic regression adjusting for age, sex, smoking status and pack-years smoked. Hazard ratios (HRs) of lung cancer death and 95% CIs were calculated using Cox proportional hazards regression, adjusting for tumor stage at diagnosis, COPD, tumor histology (*e.g.*, adenocarcinoma, squamous cell), age, sex, smoking status and pack-years smoked. The time at risk began at enrollment. The proportional hazards assumption was checked for each polymorphism by including time interaction terms in the models. Analyses were performed using the SAS statistical software (version 8; Statistical Analysis Systems, Cary, NC, USA). The Bonferroni correction was applied to account for the multiple comparisons.

Results

Demographic characteristics of study participants are summarized in Table II.

The functional rs11292517 was not associated with risk of prevalent COPD among African-Americans or Caucasians (Table III). Among African-Americans, having at least one 2G allele for rs11292517 appeared to be associated with the risk of NSCLC but only in the presence of COPD (1G/2G or 2G/2G *vs.* 1G/1G: OR=5.48, 95% CI=1.17–25.72) and not after accounting for multiple comparisons. Among Caucasians, variations in rs11292517 were not associated with lung cancer risk neither in the absence nor presence of COPD. Among Caucasians, the C allele for rs2071230 appeared to be associated with increased risk of lung cancer in the presence of COPD (CT or CC *vs.* TT: OR= 2.51, 95% CI=1.09–5.77), but this association was no longer significant after adjusting for multiple comparisons. No other associations were observed.

Out of the 370 lung cancer cases, 352 (95%) had staging information and were included in the survival analysis. The functional rs11292517 was not associated with NSCLC death in either race (Table IV). Among African-Americans, there was indication that the A allele for rs470558 was associated with a higher risk of NSCLC death (AG or AA *vs.* GG: HR=3.94, 95% CI=1.14–13.63) but only before adjusting for multiple comparisons. No other associations were observed.

Discussion

In this study, the known functional rs11292517 was not associated with prevalent COPD risk, and was suggestively associated with lung cancer risk, but only in the presence of COPD and only among African-Americans, prior to adjusting for multiple comparisons. This null finding for COPD risk is in agreement with another study that found no difference in the allelic frequency between cases and controls participating in the National Emphysema Treatment Trial (19). However, these results are inconsistent with findings from the Lung Health Study where the 2G/2G genotype was inversely associated with COPD (20). Our finding of no association between the 2G/2G genotype and lung cancer risk among Caucasians and African-Americans without COPD is consistent with two previous studies

(10, 21). In contrast, two other studies found an overall significant increased risk of lung cancer of 1.7-fold among individuals with the 2G/2G genotype (11, 12). These inconsistencies may be partially due to variation in COPD prevalence between the study populations and/or to COPD definition. In agreement with Schabath *et al.* (11), we observed an increased risk of lung cancer in the presence of COPD, albeit only among African-Americans. A poorer prognosis for stage I lung cancer cases with the 2G/2G genotype was previously reported (10); but we did not find similar evidence among either race group when all stages were analyzed (Table IV) nor among those with only stage I tumors (data not shown).

To our knowledge, the results for the other five polymorphisms are novel with respect to risk of COPD, lung cancer and survival in lung cancer. The functionality of these other polymorphisms is unclear. Although rs5854 has been reported to be located in the promoter region of the gene, the effect of this polymorphism on *MMP1* expression is unknown (22). In this population rs5854 was not in linkage disequilibrium (LD) with the functional rs11292517. The unclear functionality and the inconsistent results by race interfere with making inferences about rs5854.

The differences in the magnitude of the associations by race observed may reflect true risk differences. However, racial differences in allelic frequencies could have influenced the precision of the estimates resulting in the observed associations, occurring due to chance alone. Additionally, because most of the polymorphisms studied were not known to be functional, racial variation in LD in this region could result in a polymorphism being associated with a disease outcome in one racial group but not another only because it is in LD with a functional polymorphism in one racial group but not the other.

This study had limitations that warrant discussion. Firstly, as a result of racial stratification this study had reduced statistical precision. Secondly, a potential survival bias may have been introduced by including prevalent COPD cases. We sought to minimize this potential bias by truncating all time-dependent variables for both the COPD cases and controls to make them as comparable as possible. Nonetheless, these findings should be interpreted with caution. Thirdly, inconsistent findings both within our study by race and with previous studies may be at least partially due to our classification of COPD. If the distribution of subcategory, COPD differed by race or between studies and if any of the studied polymorphisms were specifically associated with a subcategory of COPD then these associations are unlikely to have been detected. Additionally, with the exception of rs11292517, the polymorphisms evaluated in the study were not known to be functional and were not selected as tagging polymorphisms. However, in a post-hoc analysis of the HapMap data (http://hapmap.ncbi.nlm.nih.gov/) using the Tagger software program (http://www.broad.mit.edu/mpg/tagger/; r^2=0.8; minor allele frequency=0.05), three were tagging polymorphisms in Nigerians (rs10488, rs2071230 and rs5854), and two were tagging polymorphisms in Caucasians with ancestry from northern and western Europe (rs5031036 and rs5854). Finally, information on lung cancer treatment (*e.g.*, surgery, chemotherapy, radiotherapy) was incomplete and not adjusted for in the survival analysis. However, analyses were adjusted for stage at diagnosis, which is highly correlated with treatment.

This study had also notable strengths in that it examined variations in a candidate gene with the risk of both COPD and lung cancer and lung cancer prognosis stratified by race. The association between COPD and lung cancer has been investigated repeatedly over the past four decades (12), mainly using lung cancer case–control studies (22). Only recently have studies investigated variations in genes that may mechanistically underlie both diseases. Additionally, even though the current findings indicated that the *MMP1* polymorphisms did not account for the racial disparities in COPD and lung cancer incidence, this insight was

only possible because, unlike most previous studies, both Caucasian and African-American participants were included in this study. In conclusion, the observed pattern of associations was not consistent or strong enough to support the hypothesis that genetic variation in *MMP1* is associated with susceptibility to COPD, lung cancer or lung cancer survival.

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Table I

Primers and methods for genotyping rs1799750[**]

PCR Primer 1	ACGTTGGATGCTGCGTCAAGACTGATATCT
PCR Primer 2	ACGTTGGATGGTTATGCCACTTAGATGAGG
Extension Primer	GATTGATTTGAGATAAGTCATATC

Methods: 10 ng of sample DNA are used to do a MassARRAY iPLEX™ platform (http://www.bioserve.com/preclinical-molecular-services/maldi-tof-massarray-iplex.cfm) at BioServe Biotechnologies, Ltd. (Laurel, MD, USA). Reactions are set up using the above listed primers. The cycling parameters are as follows for polymerase chain reaction (PCR): 95°C for 15 min (activation of Taq enzyme); 45 cycles of 95°C for 20 sec (denaturation); 56°C for 30 sec (annealing); 72°C for 1 min (extension); a final extension temperature of 72°C for 3 min before cooling at 4°C. This is followed by a Shrimp Alkaline Phosphatase (SAP) Treatment as follows: SAP is added to the PCR product at 37°C for 20 min, followed by a hold at 85°C for 5 min and a final cooling step of 4°C. This process helps remove the unincorporated nucleotides. The single base extension protocol used was as follows: 94°C for a 30 sec hold; 40 cycles of 94°C for 5 sec; 52°C for 5 sec; 80°C for 5 sec; followed by a nested 5 cycles from 52°C for 5 sec, and 80°C for 5 sec in each of the 40 cycles; a final extension is performed at 72°C for 3 min and then cooled to 4°C.

[**] Also referred to in the literature as rs11292517.

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Table II

Demographic information by chronic obstructive pulmonary disease (COPD) and non-small cell lung cancer (NSCLC) status and race, Maryland Lung Cancer Study, 1998–2004.

Race	Characteristic	Controls	COPD cases	*p*[1]	NSCLC cases	*p*[1]	COPD plus NSCLC cases	*p*[1]	*p*[2]
African-American, n		n=147 (%)	n=44 (%)		n=71 (%)		n=26 (%)		
	Mean age±s.d. (years)	64.9±10.3	66.3±9.8	0.42	62.2±10.1	0.07	66.7±7.5	0.40	0.87
	Gender, %								
	Male	80 (54)	16 (36)		34 (48)		5 (19)		
	Female	67 (46)	28 (64)	0.04	37 (52)	0.37	21 (81)	<0.01	0.13
	Smoking status, %[3]								
	Never	49 (33)	14 (32)		9 (13)		0 (0)		
	Former	69 (47)	24 (54)		23 (32)		15 (58)		
	Current	29 (20)	6 (14)	0.57	39 (55)	<0.01	11 (42)	<0.01	<0.01
	Mean pack-years±s.d.[4]	23.5±18.6	32.3±24.3	0.04	36.0±23.3	<0.01	47.5±28.8	<0.01	0.04
	Mean age at first COPD diagnosis±s.d. (years)[§]	47.3±20.1	48.2±21.4	0.80			48.2±21.4		0.43
	Mean years since first COPD diagnosis±s.d.[§]	17.5±17.2	18.1±17.5	0.86			22.6±23.1		0.36
	Smoking Status at first COPD diagnosis, %[§]								
	Never	59 (40)	16 (36)				2 (8)		
	Former	40 (27)	10 (23)				4 (16)		
	Current	48 (33)	18 (41)	0.59			19 (76)		0.01
	Mean pack-years at first COPD diagnosis±s.d.[§4]	19.0±16.5	30.0±23.9	0.03			28.6±25.8		0.84
Caucasian, n		n=191 (%)	n=123 (%)		n=171 (%)		n=102 (%)		
	Mean age±s.d. (years)	66.1±10.3	66.9±9.7	0.47	66.7±10.9	0.57	66.5±8.9	0.73	0.73
	Gender, %								
	Male	105 (55)	68 (55)		100 (58)		44 (43)		
	Female	86 (45)	55 (45)	0.96	71 (42)	0.50	58 (57)	0.05	0.07
	Smoking status, %[3]								
	Never	77 (40)	4 (3)		13 (8)		4 (4)		
	Former	92 (48)	72 (59)		87 (51)		39 (38)		

Race	Characteristic	Controls	COPD cases	p^1	NSCLC cases	p^1	COPD plus NSCLC cases	p^1	p^2
	Current	22 (12)	47 (38)	<0.01	71 (42)	<0.01	59 (58)	<0.01	<0.01 [+]
	Mean pack-years±s.d.[4]	27.6±21.7	53.5±30.2	<0.01	42.7±24.9	<0.01	52.6±25.6	<0.01	0.81
	Mean age at first COPD diagnosis±s.d. (years)[§]	50.3±18.6	52.1±18.2	0.41			50.7±18.5		0.59
	Mean years since first COPD diagnosis±s.d.[§]	15.7±15.5	14.8±14.4	0.60			15.8±16.1		0.65
	Smoking Status at first COPD diagnosis, %[§]								
	Never	86 (45)	8 (7)				9 (9)		
	Former	47 (25)	27 (22)				18 (19)		
	Current	58 (30)	88 (72)	<0.01			69 (72)		0.75
	Mean pack-years at first COPD diagnosis±s.d.[§4]	23.6±19.4	43.1±30.4	<0.01			37.9±25.4		0.20

[1] Compared to controls using the *t*-test for continuous variables and the chi-square test for categorical variables.

[2] Compared to COPD cases using the *t*-test for continuous variables and the chi-square test for categorical variables.

[3] At the time of lung cancer diagnosis or study enrollment for those without lung cancer.

[4] Among ever smokers at that time.

[§] Values among the controls group were imputed in order to be comparable to the prevalent COPD cases.

[+] Fisher's exact test, s.d.: standard deviation.

Table III

Association between MMP1 polymorphisms with chronic obstructive pulmonary disease (COPD) and/or non-small cell lung cancer (NSCLC), Maryland Lung Cancer Study, 1998–2004.

				COPD cases		NSCLC cases		COPD plus NSCLC cases	
Race	**Polymorphism**	**Exposed/Unexposed**	**Controls N**	**N**	**OR (95% CI)[1,3]**	**N**	**OR (95% CI)[1,4]**	**N**	**OR (95% CI)[1,4]**	**OR (95% CI)[2,4]**
African-American										
	rs1799750**	1G-2G/1G-1G	77/44	24/12	1.18 (0.53, 2.63)	31/23	0.91 (0.45, 1.86)	12/5	3.42 (0.83, 14.14)	1.16 (0.23, 5.74)
		2G-2G/1G-1G	26/44	8/12	1.22 (0.43, 3.45)	17/23	1.24 (0.53, 2.91)	9/5	5.48 (1.17, 25.72)	3.03 (0.50, 18.29)
	rs10488	AG+AA/GG	29/118	10/34	1.52 (0.65, 3.56)	19/52	1.78 (0.85, 3.71)	8/18	2.48 (0.82, 7.44)	2.46 (0.63, 9.65)
	rs470558	AG+AA/GG	3/144	4/40	4.52 (0.94, 21.84)	4/67	2.11 (0.43, 10.36)	0/26	--	--
	rs5031036	AG+GG/AA	36/111	12/32	1.42 (0.64, 3.14)	22/49	1.67 (0.84, 3.35)	8/18	1.90 (0.65, 5.57)	1.70 (0.46, 6.33)
	rs2071230	CT+CC/TT	63/84	15/29	0.67 (0.33, 1.38)	33/38	1.13 (0.61, 2.09)	13/13	1.31 (0.49, 3.47)	1.37 (0.43, 4.39)
	rs5854	CT+TT/CC	67/80	18/26	0.81 (0.40, 1.63)	25/46	0.68 (0.36, 1.27)	12/14	1.10 (0.42, 2.90)	1.87 (0.57, 6.15)
Caucasian	rs1799750**	1G-2G/1G-1G	91/48	51/39	0.71 (0.37, 1.36)	86/52	0.84 (0.48, 1.47)	48/30	1.23 (0.58, 2.63)	1.26 (0.67, 2.38)
		2G-2G/1G-1G	52/48	33/39	0.69 (0.33, 1.41)	33/52	0.70 (0.36, 1.36)	24/30	1.15 (0.49, 2.68)	0.89 (0.43, 1.86)
	rs10488	AG+AA/GG	18/173	16/107	1.71 (0.72, 4.08)	17/154	1.16 (0.52, 2.61)	7/95	0.92 (0.28, 3.03)	0.49 (0.19, 1.26)
	rs470558	AG+AA/GG	24/167	14/109	0.99 (0.43, 2.27)	20/151	0.73 (0.36, 1.49)	13/89	1.38 (0.55, 3.44)	1.34 (0.58, 3.10)
	rs5031036	AG+GG/AA	18/173	16/107	1.37 (0.58, 3.20)	17/154	1.08 (0.49, 2.40)	9/93	1.11 (0.38, 3.28)	0.64 (0.27, 1.56)
	rs2071230	CT+CC/TT	23/168	22/100	1.40 (0.67, 2.92)	30/141	1.72 (0.88, 3.37)	22/80	2.51 (1.09, 5.77)	1.26 (0.64, 2.47)
	rs5854	CT/CC	88/75	47/58	0.59 (0.33, 1.07)	84/62	0.98 (0.58, 1.64)	46/42	0.57 (0.29, 1.13)	1.15 (0.63, 2.08)
		TT/CC	28/75	18/58	0.74 (0.33, 1.68)	25/62	1.10 (0.53, 2.28)	14/42	0.50 (0.18, 1.35)	1.04 (0.45, 2.38)

[1] Compared to controls or

[2] COPD-only cases

[3] adjusted for smoking status (never, former, current) and pack-years (continuous) truncated at COPD diagnosis or

[4] adjusted for smoking status (never, former, current) and pack-years (continuous) at enrollment, all MMP1 variables were included in the same model.

** Also referred to in the literature as rs11292517.

Table IV

Association between the MMP1 polymorphisms and lung cancer survival among all lung cancer cases combined.

			Censored n (%)	Died n (%)	HR[1] (95% CI)
African-American	rs1799750**	1G/1G+1G/2G	32 (48)	34 (52)	
		2G/2G	7 (30)	16 (70)	1.09 (0.56, 2.10)
	rs10488	GG	29 (45)	36 (55)	
		AG+AA	10 (42)	14 (58)	1.19 (0.60, 2.37)
	rs470558	GG	39 (46)	46 (54)	
		AG+AA	0 (0)	4 (100)	3.94 (1.14, 13.63)
	rs5031036	AA	28 (45)	34 (55)	
		AG+GG	11 (41)	16 (59)	1.09 (0.56, 2.10)
	rs2071230	TT	23 (50)	23 (50)	
		CT+CC	16 (37)	27 (63)	1.81 (0.89, 3.66)
	rs5854	CC	22 (39)	34 (61)	
		CT+TT	17 (52)	16 (48)	0.68 (0.37, 1.27)
Caucasian	rs1799750**	1G/1G+1G/2G	123 (59)	84 (41)	
		2G/2G	29 (52)	27 (48)	1.49 (0.95, 2.35)
	rs10488	GG	141 (59)	100 (41)	
		AG+AA	11 (50)	11 (50)	1.09 (0.56, 2.14)
	rs470558	GG	130 (57)	100 (43)	
		AG+AA	22 (67)	11 (33)	0.96 (0.50, 1.83)
	rs5031036	AA	141 (59)	98 (41)	
		AG+GG	11 (46)	13 (54)	1.27 (0.68, 2.36)
	rs2071230	TT	121 (57)	90 (43)	
		CT+CC	31 (60)	21 (40)	0.91 (0.56, 1.49)
	rs5854	CC	56 (56)	44 (44)	
		CT+TT	96 (59)	67 (41)	1.07 (0.72, 1.60)

HR: Hazards Ratio. CI: Confidence Interval.

[1]Adjusted for stage (I, II, III, IV), COPD, histology, age at entry (continuous), gender, smoking status (never, former, current), pack-years (continuous).

**Also referred to in the literature as rs11292517.

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