Association of Matrix Metalloproteinase-1 (-1607 1G/2G) Polymorphism with Increased Risk for Oral Squamous Cell Carcinoma

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Abstract. *Background: The purpose of this study was to investigate the possible relation of matrix metalloproteinase-1 (MMP-1) to increased risk for oral cancer, in light of recently found contribution of angiogenesis and thrombosis-related factors to the development of malignancies. Materials and Methods: The 1G/2G polymorphism in the MMP-1 gene, which influences its expression, was examined in 156 patients with oral squamous cell carcinoma and 141 healthy controls of comparable ethnicity (Greeks and Germans), gender and age. Results: In comparison to controls, the detected 2G allele frequency was significantly lower in the patient group and in subgroups with early cancer stages, with positive family history of thrombophilia, with tobacco abuse and without alcohol abuse ($p<0.05$). These findings were mainly due to a significant decrease in 2G/2G homozygotes despite a small increase in 1G/2G heterozygotes in the above groups. Conclusion: These findings suggest a significant involvement of the MMP-1 -1607 1G/2G polymorphism in the increasing risk for oral cancer in the 1G allele European carriers.*

Oral squamous cell carcinoma is a complex, multistage process, in which environmental factors (such as smoking and alcohol abuse), as well as genetic changes in oncogenes and tumor suppressor genes are implicated (1). Recent studies have also implicated factors associated with angiogenesis and thrombosis in increased risk for oncogenesis in the oral cavity (2-6). Furthermore, some proteases which degrade the basement membrane and extracellular matrix proteins (such as cathepsins, urokinase plasminogen activator and matrix metalloproteinases) have been correlated with the development of cancer, since they facilitate invasion of the surrounding connective tissue by neoplastic cells (7, 8). Among these proteases the most abundant is the membrane-type matrix metalloproteinase-1 (MMP-1), which has been strongly associated with angiogenesis, tumor development, invasion, metastasis and thrombosis (9-11).

MMP-1 is a zinc- and calcium-dependent protease that degrades fibrilar collagen and gelatin, and alters cellular signals by influencing the surrounding microenvironment (12-15). Overexpression of MMP-1 has been observed in malignant tissues and has been associated with tumor invasion and metastasis (16-17). Consequently, overexpression of MMP-1 has been correlated with a poor prognosis in oral, esophageal and colorectal cancer (18-22). The production of MMP-1 protease is regulated at the gene expression level by several factors (7).

Besides trans-acting transcription regulators, a single nucleotide polymorphism at -1607 1G/2G locus in the promoter region of the *MMP-1* gene influences its expression and, as a consequence, the degree of degradation of extracellular matrix and connective tissue (23). The additional guanine in the 2G allele creates the 5'-GGAT-3' sequence, which is the consensus binding site for the Ets

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family of transcription factors (23). The "mutant" 2G allele has been shown to considerably increase transcription of *MMP-1* in comparison to the 1G allele of this polymorphism (23, 24). The presence of the 2G allele has been associated with the development of lung, breast and ovarian cancer, as well as the invasiveness of colorectal cancer (24-27). The 2G allele frequencies range between 40-55% in Caucasians and 39-68% in Eastern Asian populations (23, 27-32).

Two studies of *MMP-1* -1607 1G/2G polymorphism in Chinese patients with squamous cell carcinoma in the oral region reported conflicting results. One suggested association of this polymorphism with oral cancer, while the other failed to detect any association with esophageal cancer (30, 31). On the other hand, a French study of patients with head and neck squamous cell carcinoma found that 1G/1G homozygotes had a significantly increased risk for cancer than 2G/2G homozygotes in comparison to controls (32). In order to examine if there is indeed any association of the -1607 1G/2G polymorphism with increased susceptibility for oral cancer, we studied this polymorphism in Greek and German patients and healthy controls.

Materials and Methods

The population under study included 297 Greek and German individuals, consisting of 156 patients with oral squamous cell carcinoma and 141 healthy blood donors (controls) of similar age, ethnicity and gender. The patients were mostly men (N=126) and their age ranged between 40-76 years (mean 57.1±9.4 years). The sex ratio and the age of the controls (N=105 men) (range 38-81 years; mean 56.8±10.3 years) were comparable to those of the patients.

Patients who had developed oral cancer and had been operated recently or up to a decade ago were included in this study. In addition to clinical presentation, biopsy with pathological diagnosis of tumor stages I-IV and family history regarding cancer and thrombophilia were available. Fifty-four patients (34.6%) had one or two first degree relatives with any type of cancer and their age range (mean=57.5 years) did not differ significantly from the whole group of patients. Furthermore, thirty-two patients (20.5%) had one or two first degree relatives with idiopathic thrombosis and an earlier age range (mean=58 years), but again with no statistical difference compared to the whole group. Sixteen patients (10.3%) had a positive family history for both cancer and thrombophilia (mean age=56.3 years).

Nearly all patients (93.6%) were smokers and about a third of them were alcohol abusers (32.05%). Two thirds of the controls (94%) reported abuse of tobacco and about one third abuse of alcohol (47%). The two groups had similar dietary habits and almost all worked in a low-risk environment (with the exception of one patient and three controls who worked in chemical factories).

Patients and controls were informed about the possible results of the study and willingly donated blood samples. DNA was isolated with the use of a NucleoSpin™ kit (Macherey-Nagel GmbH & Co, Düren, Germany). Molecular detection of the -1607 1G/2G polymorphism in the *MMP-1* gene was performed using restriction fragment length polymorphism typing and gel electrophoretic analysis, according to a previous study (31). The primers used were: 5'-TCGTGAGAATGTCTTCCCATT-3' (forward) and: 5'-TCTTGGATTGATTTGAGATAAGTGAAATC-3' (reverse). The generated PCR product of 118 bp was cleaved by the restriction enzyme Xmn I into two fragments of 89 bp and 29 bp only if the 1G allele was present. Where necessary samples were studied twice for verification of obtained results.

Table I. *Overall demographic characteristics of the studied population.*

	Controls (N=141)	Patients (N=156)
Age range (years)	31-81	40-84
Mean age (years)	55.9	58.1
Sex ratio (Males/Total)	0.81	0.75
Males total	105	126
Males <59 years old	72	80
Males >59 years old	33	46
Females total	36	30
Females <59 years old	21	15
Females >59 years old	15	15

The statistical analyses were performed using SAS® software (version 9.0; SAS Worldwide Headquarters SAS Institute Inc., Cary, NC, USA). The frequencies of alleles and genotypes of the whole group or subgroups of patients were compared to the respective frequencies of the control group using the Chi-square or Fisher's exact test and odds ratios, while all genotype distributions were according to Hardy-Weinberg estimates. In all statistical analyses concerning the number of relatives with a history of cancer, number of relatives with a history of thrombosis, nicotine use, alcohol use, it was assumed that all controls had nil values for the above variables (*i.e.* all controls had not a family history of cancer, all controls had not a family history of thrombosis, all controls did not use tobacco, and all controls did not drink alcohol). Thus, odds ratios were most likely expected to overestimate the true likelihood of *MMP-1* genotypes and these variables. The Maentel - Haenzel method was used for the calculation of all odds ratios with a 95% confidence interval (CI). A *p*-value less than 0.05 was considered statistically significant.

Results

Demographic characteristics of healthy controls (representing the general population) and patients, as well as the prevalence of MMP-1 genotypes are shown in Tables I-IV. The data for the Greek and German controls were analyzed together, since there were no significant differences of genotype and allele frequencies among the two studied populations. In the control group, the 2G allele frequency observed was 62.8% and the carrier frequency was 83%. All -1607 1G/2G genotype distributions were as expected in Hardy-Weinberg equilibrium in the control group, as well as in the whole group and subgroups of patients.

Table II. *Prevalence of MMP-1 -1607 1G/2G polymorphism in healthy controls and patients with oral cancer (total group of patients and subgroups with regard to cancer stage).*

Genotype	Controls	Patients			Patients with cancer stages I/II			Patients with cancer stages III&IV		
	(%)	(%)	*P*	OR(CI)	(%)	*P*	OR(CI)	(%)	*P*	OR(CI)
2G/2G	60 (42.6%)	52 (33.3%)	0.03	0.56 (0.29-1.09)	24 (27.3%)	0.014	0.38 (0.17-0.86)	28 (41.2%)	N.S	0.79 (0.35-1.78)
1G/1G	24 (17.0%)	36 (23.1%)			22 (25.0%)			14 (20.6%)		
1G/2G	57 (40.4%)	68 (43.6%)	N.S.	0.81 (0.42-1.56)	42 (47.7%)	N.S.	0.0 (0.38-1.70)	26 (38.2%)	N.S.	0.78 (0.34-1.78)
Total	141 (100%)	156 (100%)			88 (100%)			68 (100%)		
Prevalence of 2G allele										
2G allele frequency	62.8%	55.1%	0.01		51.1%	0.004		60.3%	N.S.	
Carrier frequency of 2G allele	83%	76.9%	N.S.		75.0%	0.046		79.4%	N.S.	

Fischer's *p*-value corresponds to genotype comparisons; χ^2 *p*-value corresponds to allele frequency comparisons; odds ratios (OR) are age-adjusted; N.S. not significant.

Table III. *Prevalence of MMP-1 -1607 1G/2G polymorphism in healthy controls and patients with oral cancer with regard to family history of either cancer or thrombophilia.*

Genotype	Controls	Patients with family history of cancer			Patients without family history of cancer			Patients with family history of thrombophilia			Patients without family history of thrombophilia		
	(%)	(%)	*P*	OR(CI)	(%)	*P*	OR(CI)	(%)	*P*	OR(CI)	(%)	*P*	OR(CI)
2G/2G	60 (42.6%)	22 (40.7%)	N.S.	0.66 (0.27-1.60)	30 (29.4%)	0.024	0.50 (0.24-1.07)	10 (31.3%)	0.016	0.25 (0.08-0.71)	42 (33.9%)	N.S.	0.68 (0.33-1.38)
1G/1G	24 (17.0%)	12 (22.2%)			24 (23.5%)			12 (37.5%)			24 (19.4%)		
1G/2G	57 (40.4%)	20 (37.0%)	N.S.	0.81 (0.34-1.94)	48 (47.1%)	N.S.	0.78 (0.37-1.63)	10 (31.3%)	0.02	0.61 (0.21-1.78)	58 (46.8%)	N.S.	0.94 (0.47-1.91)
Total	141 (100%)	54 (100%)			102 (100%)			32 (100%)			124 (100%)		
Prevalence of 2G allele													
2G allele frequency	62.8%	59.3%	N.S.		52.9%	0.007		46.9%	0.008		57.3%	0.031	
Carrier frequency of 2G allele	83%	77.8%	N.S.		76.5%	N.S.		62.5%	0.009		80.6%	N.S.	

Fischer's *p*-value is for genotype comparisons; χ^2 *p*-value is for allele frequency comparisons; odds ratios (OR) are age-adjusted; N.S. not significant.

Table IV. *Prevalence of MMP-1 -1607 1G/2G polymorphism in healthy controls and patients with oral cancer with regard to either alcohol consumption or smoking habits.*

Genotype	Controls	Patients with tobacco abuse			Patients without tobacco abuse			Patients with alcohol abuse			Patients without alcohol abuse		
	(%)	(%)	*P*	OR(CI)	(%)	*P*	OR(CI)	(%)	*P*	OR(CI)	(%)	*P*	OR(CI)
2G/2G	60 (42.6%)	46 (31.5%)	0.023	0.52 (0.26-1.02)	6 (60.0%)	N.S.	0.41 (0.06-3.00)	22 (44.0%)	N.S.	0.99 (0.37-2.64)	30 (28.3%)	0.008	0.43 (0.20-0.89)
1G/1G	24 (17.0%)	34 (23.3%)			2 (20.0%)			8 (16.0%)			28 (26.4%)		
1G/2G	57 (40.4%)	66 (45.2%)	N.S.	0.82 (0.42-1.59)	2 (20.0%)	N.S.	0.94 (0.17-5.26)	20 (40.0%)	N.S.	1.08 (0.40-2.88)	48 (45.3%)	N.S.	0.74 (0.36-1.49)
Total	141 (100%)	146 (100%)			10 (100%)			50 (100%)			106 (100%)		
Prevalence of 2G allele													
2G allele frequency	62.8%	54.1%	0.007		70.0%	N.S.		64%	N.S.		50.9%	0.002	
Carrier frequency of 2G allele	83%	76.7%	0.049		76.5%	N.S.		84%	N.S.		73.6%	0.026	

Fischer's *p*-value is for genotype comparisons; χ^2 *p*-value is for allele frequency comparisons; odds ratios (OR) are age-adjusted; N.S. not significant.

In the patient group, the detected carrier frequency of the 2G allele was not significantly different from that in the control group. On the contrary, the 2G allele frequency was significantly lower in the patient group compared to that of controls (55.1% and 62.8% respectively, $p=0.01$). A significant decrease was also detected in certain subgroups of patients in comparison to controls ($p<0.05$). Specifically, a statistical difference in mutant allele and carrier frequencies was observed in the subgroups of patients a) in early (I, II) stages of cancer ($p=0.004$ and $p=0.046$, respectively), b) with positive family history of thrombophilia ($p=0.008$ and $p=0.009$, respectively), c) with tobacco abuse ($p=0.007$ and $p=0.049$, respectively) and e) without alcohol abuse ($p=0.002$ and $p=0.026$, respectively). A significant difference in only 2G allele frequency was also observed in the subgroup of patients a) without positive family history of cancer ($p=0.007$) and b) without positive family history of thrombophilia ($p=0.031$). The significant difference in the 2G allele frequency was mainly because of the decrease in the number of 2G/2G homozygotes in the above mentioned subgroups and the total group of patients. Finally, there were no significant differences due to categorizations of gender, age, and age at onset of oral cancer.

Discussion

MMP-1 is one of the principal endopeptidases that degrade most components of the extracellular matrix including the interstitial collagens types I, II and III (7, 9). It is usually expressed at low levels by most normal cells, while its expression reaches high levels in the connective tissue destruction observed in many diseases, such as arthritis and atherosclerosis (33-35). High levels of MMP-1 in various neoplasias may contribute to the invasive and aggressive behavior of the tumor (17-19). Overexpression of MMP-1 has also been associated with a poor prognosis in oral and esophageal cancer (20, 21).

A polymorphism in the promoter region of MMP-1 gene alters its expression. The 2G "mutant" allele at the -1607 1G/2G site increases gene expression and, as a consequence, its presence has been associated with the development of ovarian, colorectal, lung and breast cancer, but not with gastric carcinoma (25-29). In a French population this polymorphism was reportedly associated with head and neck squamous cell carcinoma (32). The same polymorphism in Chinese patients with squamous cell carcinoma in the oral region was reportedly associated with oral cancer, but not with esophageal cancer (30, 31).

The purpose of this study was to investigate whether the -1607 1G/2G polymorphism might indeed be related to an increased risk for oral squamous cell carcinoma in Europeans. The subjects under study were patients who had developed oral cancer and their genotypes were compared to those of healthy controls with matched age, gender and ethnicity. The observed 2G allele frequency was significantly lower in the patient group in comparison to that of the control group, although no significant difference was observed in the detected carrier frequency of the 2G allele. This observation was mainly due to significant decrease in 2G/2G homozygotes despite a small increase in 1G/2G heterozygotes. The same pattern of significance was also detected in several subgroups of patients including those without positive family history of cancer or thrombophilia. This trend was maximum when significantly decreased carrier frequency was observed in subgroups with early stages of cancer, with positive family history of thrombophilia, with tobacco abuse and without alcohol abuse.

Based on these results, it seems that low levels of MMP-1 may not be a major contributing factor in the development of oral tumors, but might indeed have a secondary effect in response to other mechanisms of oral oncogenesis. Such mechanisms may include reduced activation of MMPs by increased levels of plasminogen activator inhibitor 1, which has been strongly associated with high risk for oral cancer (5, 36). In support to these findings, pharmaceutical trials of matrix metalloproteinase inhibitors failed to suppress oral tumor progression (37).

Furthermore, a previous report in a French Caucasian population indicated an association of-1607 1G/2G polymorphism with risk for head and neck squamous cell carcinoma (32). That study also found that the high expression 2G allele frequencies were significantly lower in 129 patients than in 249 controls, in accordance to the present study (32). Although the French study investigated head and neck instead of specifically oral squamous cell carcinoma, it practically detected the same effect of the -1607 1G/2G polymorphism in oncogenesis that the present study did.

The discrepancy of the results of the present study and the report for the strong association of increased 2G allele frequency with oral cancer in Chinese patients (31) may be explained by the diverse ethnic background of the two studied populations. Another point of difference is the fact that their patient sample was 60% smaller than ours. In addition, about two thirds of the Chinese patients had tongue cancer, while only 7.8% such patients existed in our series. It is unclear though, whether this difference in oral cancer location may account for the contradicting results. Interestingly, another Chinese study reported absence of any association of the -1607 1G/2G polymorphism with esophageal cancer (30).

In conclusion, this study shows a significant involvement of the MMP-1 -1607 1G/2G polymorphism in increasing the risk for oral cancer in the 1G allele European carriers, also in accordance to a previous study. It is of great importance to perform further genetic studies regarding the contribution of angiogenesis and thrombosis related factors to predisposition for oncogenesis in the oral region. Such knowledge might safeguard the health status and lives of people at risk.

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