IN VIVO *39*: 1314-1324 (2025)
doi: 10.21873/invivo.13935

Association of Matrix Metalloproteinase-7 Genotypes With Nasopharyngeal Carcinoma Risk

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Abstract

Background/Aim: Nasopharyngeal carcinoma (NPC) is a multifactorial malignancy influenced by Epstein-Barr virus (EBV) infection, genetic susceptibility, and environmental factors. Matrix metalloproteinase-7 (MMP-7), a key regulator of extracellular matrix remodeling, has been implicated in NPC progression. This study investigated the association between *MMP-7* rs11568818 and rs11568819 genotypes and NPC susceptibility in a Taiwanese cohort consisted of 208 NPC cases and 416 cancer-free controls.

Materials and Methods: The genotypic patterns of *MMP-7* rs11568818 and rs11568819 were revealed by utilizing PCR-RFLP methodology. In addition, the interaction between *MMP-7* genotypes and lifestyle factors (including smoking, alcohol consumption, and betel quid chewing) was also analyzed in a stratified manner.

Results: Genotypic distribution analysis of *MMP-7* rs11568818 showed no significant association with NPC risk (p for trend=0.4641). Individuals carrying the AG (OR=1.22, 95%CI=0.79-1.90, p=0.4384) or GG (OR=1.74, 95%CI=0.52-5.79, p=0.5539) genotypes exhibited a modestly elevated, but statistically non-significant, risk compared to AA carriers. Similarly, allelic frequency analysis indicated that the G allele did not significantly contribute to NPC susceptibility (OR=1.28, 95%CI=0.87-1.87, p=0.2433). Stratified analysis revealed a significant interaction between *MMP-7* rs11568818 and smoking status (p for trend=0.0018). Among smokers, AG and GG genotypes were associated

continued

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Received February 20, 2025 | Revised March 4, 2025 | Accepted March 5, 2025

with an increased NPC risk (AG: OR=2.70, 95%CI=1.34-5.44, *p*=0.0076; GG: OR=9.27, 95%CI=1.01-84.66, *p*=0.0345), which remained significant after adjusting for confounders (adjusted OR=2.53, 95%CI=1.27-4.88; adjusted OR=7.89, 95%CI=1.02-47.38). No interactions were observed with alcohol consumption or betel quid chewing. Additionally, no polymorphic genotypes were detected for *MMP-7* rs11568819 in the studied population.
Conclusion: While *MMP-7* rs11568818 does not directly influence NPC susceptibility in a Taiwanese population, its interaction with smoking may contribute to elevated NPC risk.

Keywords: Genotype, matrix metalloproteinase-7, nasopharyngeal carcinoma, polymorphism, smoking; stratified analysis, Taiwan.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor arising from the mucosal lining of the nasopharynx, with a multifactorial etiology encompassing genetic predisposition, environmental influences, and viral infections (1, 2). According to the International Agency for Research on Cancer (IARC) in 2022, NPC accounted for approximately 120,416 newly diagnosed cases worldwide, representing 0.6% of all cancer incidences that year. The disease led to an estimated 73,476 fatalities, with both incidence and mortality rates significantly higher in males than in females (3). The pathogenesis of NPC is highly intricate, with Epstein-Barr virus (EBV) infection, host genetic variations, and environmental exposures recognized as key contributors (4). Although genome-wide association studies (GWAS) have identified several susceptibility loci associated with NPC (5, 6), the discovery of clinically applicable biomarkers remains a critical challenge. In particular, population-specific markers, such as those relevant to the Taiwanese cohort, require further investigation (7-11). Advancing precision medicine in NPC diagnosis, prognosis, and treatment remains contingent on translational research aimed at identifying more effective and clinically relevant biomarkers.

Matrix metalloproteinases (MMPs), also referred to as matrixins, constitute a family of peptidases that play a pivotal role in modulating extracellular matrix (ECM) components, thereby influencing inflammation, tumorigenesis, and cancer cell migration (12, 13). Among them, MMP-7, the smallest member of the MMP family, is a secreted zinc- and calcium-dependent endopeptidase alternatively known as matrilysin, matrilysin-1, putative metalloproteinase, or punctuated metalloproteinase (PUMP1). The *MMP-7* gene, located on chromosome 11q21-q22, comprises 13 exons (14).

Physiologically, MMP-7 is predominantly expressed in bronchial, ductal, glandular, urogenital, gastrointestinal, and endometrial tissues (15). In contrast, its expression is relatively low in the lungs, gallbladder, and bladder under normal conditions. However, aberrant upregulation of MMP-7 has been documented in pathological states, particularly in malignancies (16-18). Functionally, MMP-7 exhibits proteolytic activity against various ECM proteins, including collagen IV, fibronectin, laminin, and tenascin-C, as well as non-ECM substrates such as E-cadherin, tumor necrosis factor-α, and other MMPs (19-21). Through these proteolytic activities, MMP-7 plays a crucial role in cellular processes such as proliferation, inflammation, tissue remodeling, carcinogenesis, and angiogenesis (22-26).

Elevated MMP-7 expression has been observed in various malignancies, including digestive cancers (27), prostate cancer (28), bladder cancer (29), and renal cell carcinoma (30). Mechanistically, MMP-7 facilitates tumor progression by inhibiting apoptosis (31), reducing cell adhesion (32), and promoting angiogenesis (33). In NPC 5-8F and CNE-2 cells, MMP-7, together with cyclin D1, can regulate proliferation, migration and invasion (34-36). Collectively, these findings highlight MMP-7 as an oncogenic factor driving tumor initiation and progression through its multifaceted regulatory functions.

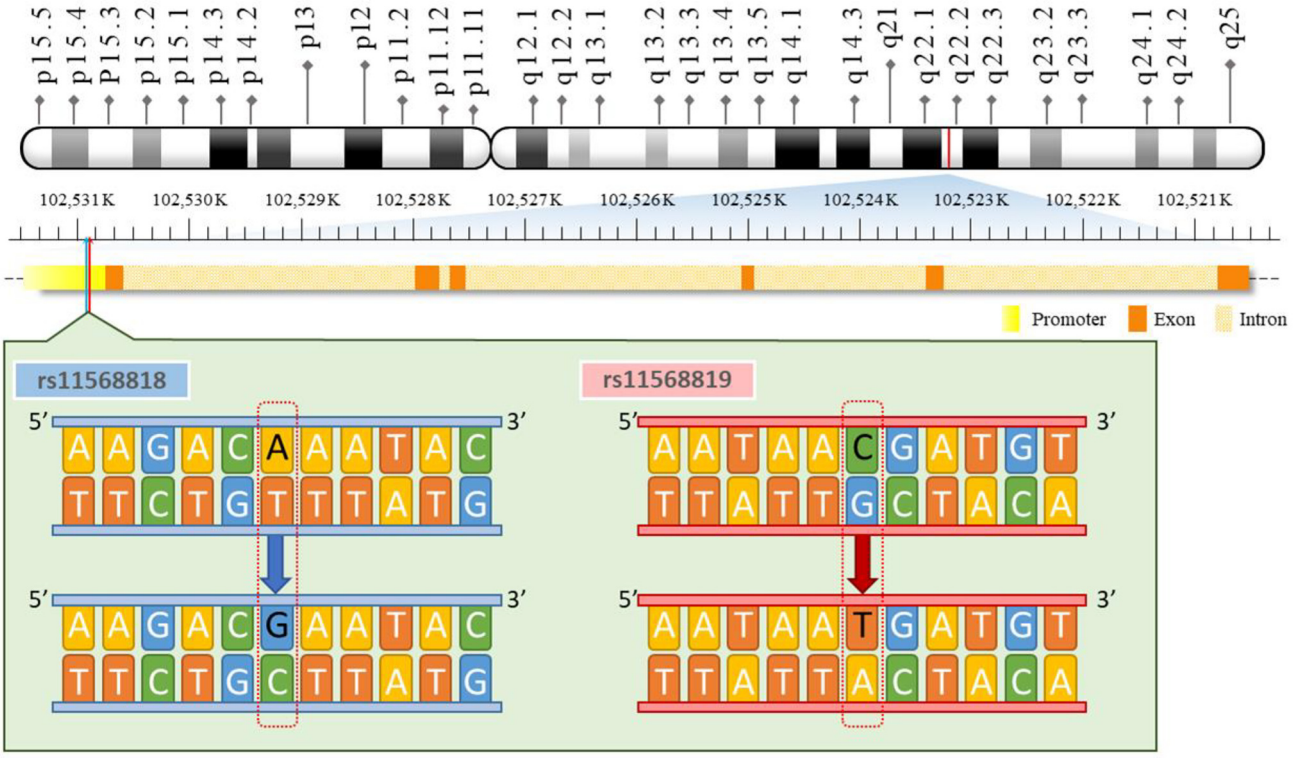

Figure 1. *Location of the MMP-7 rs11568818 and rs11568819 polymorphic sites together with the neighboring DNA sequences.*

In terms of the genotype-phenotype correlation, increased MMP-7 activity was observed in promoter variants *MMP-7* rs11568818 and rs11568819 alleles (37). Previous literature has examined the association of *MMP-7* genotypes with various cancers, such as oral cancer (38), esophageal cancer (39), gastric cancer (40), liver cancer (41), colorectal cancer (42), lung cancer (43), breast cancer (44), bladder cancer (45), prostate cancer (28), astrocytoma (46), renal cell carcinoma (47) and childhood leukemia (48). However, the investigation of *MMP-7* genotypes in relation to NPC is quite limited (49).

Based on the aforementioned information, our study aimed to assess the potential correlation between *MMP-7* rs11568818 and rs11568819 genotypes (Figure 1) and the susceptibility to NPC among a Taiwanese cohort consisting of 208 NPC cases and 416 healthy controls. Furthermore, our objectives encompass exploring conceivable interactions between *MMP-7* rs11568818 genotypes and lifestyle factors, including smoking, alcohol consumption, and betel quid chewing.

Materials and Methods

Collection of NPC cases and non-cancer controls. A cohort of 208 NPC patients was recruited from the Department of General Surgery at China Medical University Hospital in Taichung, Taiwan. Each participant voluntarily enrolled in the study, completed a structured self-administered questionnaire, and provided a peripheral blood sample. For the control group, non-cancer individuals were selected at a 2:1 ratio relative to cases, ensuring meticulous matching based on sex, age (±5 years), and lifestyle behaviors, including smoking, alcohol consumption, and betel quid chewing. Controls were excluded if they had a history of malignancy, metastatic cancer of uncertain or non-NPC origin, or any hereditary or genetic disorders. To ensure

Table I. *Demographic characteristics of the 416 control subjects and 208 nasopharyngeal carcinoma patients.*

Characteristics	Cases (n=208)			Controls (n=416)			*p*-Value[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			50.6 (11.0)			49.9 (11.5)	0.4639[a]
Sex							
Male	153	73.6%		306	73.6%		1.0000
Female	55	26.4%		110	26.4%		
Personal behaviors							
Cigarette smoking	85	40.9%		158	38.0%		0.5422[b]
Alcohol drinking	95	45.9%		168	40.4%		0.2399[b]
Areca chewing	80	38.6%		156	37.5%		0.8840[b]
Classification							
KSCC (WHO type I)	8	3.8%					
NKC (WHO type II)	200	96.2%					
NKDC (WHO type IIa)	32	16.0%					
NKUC (WHO type IIb)	168	84.0%					

SD: Standard deviation; KSCC: keratinizing squamous cell carcinoma; NKC: non-keratinizing carcinoma; NKDC: non-keratinizing differentiated carcinoma; NKUC: non-keratinizing undifferentiated carcinoma; [a]Based on Student's *t*-test, [b]Based on Chi-square test with Yates' correction.

consistency in data collection, information regarding smoking, alcohol intake, and betel quid use was gathered through the same self-reported questionnaire used for NPC patients. Individuals were classified as "ever" users if they engaged in any of these habits more than twice per week for at least one year. The frequency and extent of these behaviors were systematically evaluated and categorized as discrete variables. All study participants were of Taiwanese ethnicity. Ethical approval was granted by the Institutional Review Board of China Medical University Hospital (DMR101-IRB1-306), with all procedures adhering strictly to the principles of the Declaration of Helsinki. A summary of key demographic and clinical characteristics for both cases and controls is presented in Table I.

MMP-7 genotyping methodology. Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp Blood Mini Kit (Qiagen, Hilden, Germany), following protocols outlined in previous studies (50-52). The design of primers, selection of restriction enzymes, and optimization of PCR conditions for genotyping *MMP-7* rs11568818 and rs11568819 adhered to methodologies established in our earlier publications (28). To ensure accuracy and reliability, genotyping of *MMP-7* rs11568818 and rs11568819 was performed independently by at least two experienced researchers under double-blind conditions. Each sample underwent multiple rounds of genotypic analysis, with all repeated tests yielding results that were 100% concordant.

MMP-7 statistical analytical methodology. To evaluate whether the control group was representative of the general population, Hardy-Weinberg equilibrium was tested using the goodness-of-fit approach to identify potential deviations in *MMP-7* genotype frequencies. Differences in mean age between cases and controls were assessed using the unpaired Student's *t*-test. The distribution of *MMP-7* genotypes across subgroups was analyzed through Pearson's Chi-square test with Yates' correction or, when expected cell counts were below five, Fisher's exact test. Statistical significance was set at $p<0.05$ for all comparisons. Logistic regression models were applied to determine odds ratios (ORs) and 95% confidence intervals (CIs), estimating the association between specific genotypes and NPC susceptibility. Stratified analysis for the interactions of *MMP-7* genotypes and lifestyle behaviors were adjusted with confounding factors, such as age, sex, and other lifestyle behaviors.

Table II. *Distribution of matrix metalloproteinase-7 variant genotypes among the controls and patients with nasopharyngeal carcinoma.*

Genotype	Frequency, n (%)		OR (95%CI)	*p*-Value[a]
	Cases (n=208)	Controls (n=416)		
rs11568818				
AA	165 (79.3)	345 (82.9)	1.00 (Reference)	
AG	38 (18.3)	65 (15.6)	1.22 (0.79-1.90)	0.4384
GG	5 (2.4)	6 (1.5)	1.74 (0.52-5.79)	0.5539
AG+GG	43 (20.7)	71 (17.1)	1.27 (0.83-1.93)	0.3227
p_{trend}				0.4641
p_{HWE}				0.1548
rs11568819				
CC	208 (100.0)	416 (100.0)	1.00 (Reference)	
CT	0 (0.0)	0 (0.0)	--	
TT	0 (0.0)	0 (0.0)	--	

OR: Odds ratio; CI: confidence interval. [a]Based on chi-square test with Yates' correction. p_{trend}, *p*-Value for trend analysis; p_{HWE}, *p*-Value for Hardy-Weinberg Equilibrium.

Results

Comparison of baseline characteristics between NPC cases and controls. Table I summarizes the distribution of key demographic and lifestyle characteristics for the 208 NPC patients and 416 cancer-free controls. Frequency matching was employed to ensure comparable age and sex distributions between the two groups (*p*=0.4639 and 1.0000, respectively). This matching approach also resulted in similar proportions of smokers (40.9% *vs*. 38.0%), alcohol consumers (45.9% *vs*. 40.4%), and betel quid users (38.6% *vs*. 37.5%) between cases and controls. Among the NPC cases, eight individuals (3.8%) were diagnosed with keratinizing squamous cell carcinoma (WHO type I), while the remaining 200 (96.2%) had non-keratinizing carcinoma (WHO type II). Within the type II subgroup, 32 patients (16.0%) were classified as having non-keratinizing differentiated carcinoma (WHO type IIa), whereas 168 (84.0%) were categorized as non-keratinizing undifferentiated carcinoma (WHO type IIb) (Table I).

Association between MMP-7 rs11568818 and rs11568819 genotypes and NPC susceptibility. Table II outlines the genotypic distributions of *MMP-7* rs11568818 and rs11568819 among 208 NPC cases and 416 cancer-free controls. The genotype frequencies of *MMP-7* rs11568818 in the control group were consistent with Hardy-Weinberg equilibrium (*p*=0.1548), confirming their representativeness. A comparative analysis revealed no significant differences in *MMP-7* rs11568818 genotype distributions between NPC patients and controls (*p* for trend=0.4641). Although the heterozygous AG and homozygous variant GG genotypes appeared to be associated with an increased risk of NPC, neither reached statistical significance (AG: OR=1.22, 95%CI=0.79-1.90, *p*=0.4384; GG: OR=1.74, 95%CI=0.52-5.79, *p*=0.5539). Similarly, analysis under the dominant genetic model (AA *vs*. AG+GG) did not indicate a significant association with NPC risk (OR=1.27, 95%CI=0.83-1.93, *p*=0.3227, Table II).

Allelic frequency distribution of MMP-7 rs11568818 and its association with NPC risk. To further validate the preliminary findings presented in Table II, an allelic frequency analysis was conducted to assess the potential contribution of *MMP-7* rs11568818 to NPC susceptibility. Consistent with the genotypic analysis, the distribution of the variant G allele did not significantly differ between NPC patients and cancer-free controls (*p*=0.2433). Individuals carrying the G

Table III. *Allelic frequencies for matrix metalloproteinase-7 genotypes in the control and nasopharyngeal carcinoma patient groups.*

Allelic type	Frequency, n (%)		OR (95%CI)	*p*-Value[a]
	Cases (n=416)	Controls (n=832)		
rs11568818				
Allele A	368 (88.5)	755 (90.7)	1.00 (Reference)	
Allele G	48 (11.5)	77 (9.3)	1.28 (0.87-1.87)	0.2433
rs11568819				
Allele C	416 (100.0)	832 (100.0)	1.00 (Reference)	1.0000
Allele T	0 (0.0)	0 (0.0)	--	

CI: Confidence interval; OR: odds ratio. [a]Based on chi-square test with Yates' correction.

allele exhibited a modestly elevated, though statistically non-significant, risk of NPC (OR=1.28, 95%CI=0.87-1.87) compared to those with the wild-type A allele (Table III). Collectively, the findings from Table II and Table III suggest that neither the AG nor GG genotype of *MMP-7* rs11568818 substantially influences NPC susceptibility in the Taiwanese population.

Stratified analysis of MMP-7 rs11568818 genotypes in relation to lifestyle factors. To assess the combined impact of *MMP-7* rs11568818 genotypes with smoking, alcohol consumption, and betel quid chewing on NPC susceptibility, a stratified analysis was performed (Table IV, Table V, Table VI). Notably, a significant interaction was observed between *MMP-7* rs11568818 and smoking status (*p* for trend=0.0018, Table IV). Among smokers, individuals carrying the AG or GG genotype exhibited a markedly higher risk of NPC compared to AA carriers (AG: OR=2.70, 95%CI=1.34-5.44, *p*=0.0076; GG: OR=9.27, 95%CI=1.01-84.66, *p*=0.0345). These associations remained statistically significant even after adjusting for age, sex, alcohol consumption, and betel quid chewing (adjusted OR=2.53, 95%CI=1.27-4.88; adjusted OR=7.89, 95%CI=1.02-47.38, Table IV). Conversely, no significant interaction was detected between *MMP-7* rs11568818 genotypes and alcohol consumption, regardless of drinking status (Table V). Similarly, no notable association was found between *MMP-7* rs11568818 genotypes and NPC risk among betel quid chewers or non-chewers (Table VI).

Discussion

MMP-7 is one of the proteins highly expressed in NPC tissues (53). In NPC, the Wnt signaling pathway has been reported to enhance MMP-7 expression and promote cell invasion (35). Hence, it is reasonable to hypothesize that the up-regulation of MMP-7 may be influenced by its inherited *MMP-7* rs11568818 and rs11568819 polymorphisms, both located in the promoter region, which regulates MMP-7 expression. As early as 2007, Zhou and his colleagues conducted a comprehensive investigation into the effects of promoter polymorphisms in various *MMP* genes on the risk of NPC (49). Among the *MMP-1*, *MMP-2*, *MMP-3*, *MMP-7*, *MMP-9*, *MMP-12*, and *MMP-13* genes examined, only the CC genotype of *MMP-2* C-1306T (rs243865) and C-735T (rs2285053) was significantly associated with an increased risk of NPC. In contrast, *MMP-7* G-181A showed no apparent correlation with NPC susceptibility. Their study included NPC cases collected from Guangxi and Guangdong provinces in southern China, comprising 593 patients with NPC and 480 controls (49). This is the only pivotal study investigating the association between the *MMP-7* genotype and the risk of NPC. In the present study, we observed that the variant genotypes of *MMP-7* rs11568818 *a*re not significantly associated with altered risk of NPC (Table II). This finding aligns with previous investigations conducted in South China NPC cohorts (49). Both Zhou's and our teams reported that the AG and GG variant genotypes of *MMP-7* rs11568818 were

Table IV. *Distribution of matrix metalloproteinase-7 rs11568818 genotypes among 208 nasopharyngeal carcinoma cases and 416 controls after stratification by smoking status.*

Genotype	Non-smokers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value	Smokers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
AA	206	105	1.00 (ref)	1.00 (ref)		139	60	1.00 (ref)	1.00 (ref)	
AG	47	17	0.71 (0.39-1.30)	0.75 (0.44-1.21)	0.3305	18	21	2.70 (1.34-5.44)	2.53 (1.27-4.88)	**0.0076**
GG	5	1	0.39 (0.05-3.40)	0.57 (0.18-3.04)	0.6676	1	4	9.27 (1.01-84.66)	7.89 (1.02-47.38)	**0.0345**
Total	258	123				158	85			
p_{trend}					0.3794					**0.0018**

N: Number; OR: odds ratio; CI: confidence interval; [a]Based on Chi-square with Yate's correction test; [b]Based on Chi-square with Yate's correction test (when every n≥5) or Fisher exact test (when any n<5) after adjustment for age, sex, alcohol drinking, and betel quid chewing status. Bold values indicate statistical significance.

Table V. *Distribution of matrix metalloproteinase-7 rs11568818 genotypes among 208 nasopharyngeal carcinoma cases and 416 controls after stratification by alcoholism status.*

Genotype	Non-drinkers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value	Drinkers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
AA	210	89	1.00 (ref)	1.00 (ref)		135	76	1.00 (ref)	1.00 (ref)	
AG	36	23	1.51 (0.84-2.69)	1.37 (0.62-2.48)	0.2143	29	15	0.92 (0.46-1.82)	0.99 (0.73-1.64)	0.9443
GG	2	1	1.18 (0.11-13.18)	1.23 (0.17-10.65)	1.0000	4	4	1.78 (0.43-7.31)	1.51 (0.66-5.39)	0.4674
Total	248	123				168	95			
p_{trend}					0.3767					0.6882

N: Number; OR: odds ratio; CI: confidence interval; [a]Based on Chi-square with Yate's correction test; [b]Based on Chi-square with Yate's correction test (when every n≥5) or Fisher exact test (when any n<5) after adjustment for age, sex, smoking, and betel quid chewing status.

not the primary determinants of NPC susceptibility in representative East Asia cohorts. It is noteworthy that the etiological factors contributing to NPC in East Asia (China and Taiwan) may be different from other regions, necessitating further investigations across diverse populations to validate these findings. Regarding the *MMP-7* rs11568819 polymorphism, there was no polymorphic genotype at all in Taiwanese; all the subjects investigated were of CC genotype at *MMP-7* rs11568819 (Table II).

In addition to assessing the contribution of *MMP-7* rs11568818 genotypes to NPC risk, our investigation extended to exploring potential interactions between *MMP-7* rs11568818 genotypes and other factors related to NPC susceptibility. There was no discernible difference in susceptibility among individuals with variant *MMP-7* rs11568818 genotypes with or without alcohol consumption or betel quid chewing habits for NPC risk (Table V and Table VI). Interestingly, our primary findings revealed higher proportions of NPC smokers with *MMP-7* rs11568818 AG and GG genotype compared to smokers in the control group (Table VI, right part). Currently, the underlying mechanisms by which *MMP-7* rs11568818 genotypes contribute to altered NPC risk in smokers or non-smokers are largely unclear.

The World Health Organization has divided NPC into three pathological subtypes, including keratinizing squamous, non-keratinizing, and basaloid squamous. Further, non-keratinizing nasopharyngeal carcinoma can be divided into differentiated and undifferentiated tumors (1, 54, 55). Based on this classification, we analyzed the association between the *MMP-7* rs11568818 genotype and pathological subtypes of NPC but observed no significant

Table VI. *Distribution of matrix metalloproteinase-7 rs11568818 genotypes among 208 nasopharyngeal carcinoma cases and 416 controls after stratification by betel quid chewing status.*

Genotype	Non-chewers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value	Chewers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
AA	212	98	1.00 (ref)	1.00 (ref)		133	67	1.00 (ref)	1.00 (ref)	
AG	45	27	1.30 (0.76-2.21)	1.22 (0.83-2.05)	0.4124	20	11	1.09 (0.49-2.41)	1.03 (0.57-2.28)	0.9894
GG	3	3	2.16 (0.43-10.91)	1.56 (0.51-7.88)	0.3886	3	2	1.32 (0.22-8.11)	1.15 (0.37-7.26)	1.0000
Total	260	128				156	80			
p_{trend}					0.4245					0.9361

N: Number; OR: odds ratio; CI: confidence interval; [a]Based on Chi-square with Yate's correction test; [b]Based on Chi-square with Yate's correction test (when every n≥5) or Fisher exact test (when any n<5) after adjustment for age, sex, smoking and alcohol drinking status.

differences among the three subtypes (data not shown). This lack of association may be attributed to the relatively low frequency of the homozygous variant genotype. Further studies with larger NPC cohorts will be necessary to clarify the potential relationship between *MMP-7* rs11568818 genotype and NPC pathological subtypes. Aging is also a recognized risk factor for NPC (56, 57). Globally, the highest proportion of patients with NPC is in people older than 50 years of age (58). Across all age groups, it is reported that the relative risk of nasopharyngeal carcinoma peaks at age 55 (59). We conducted a stratified analysis to assess the association between age and *MMP-7* rs11568818 genotype but found no significant differences among age-stratified subgroups (data not shown). Similarly, no significant association was observed between sex and *MMP-7* rs11568818 genotype (data not shown).

In 2012, Chen and his colleagues investigated the role of RNA Binding Motif, Single-Stranded Interacting Protein 3 (RBMS3) in NPC cell lines. They observed that RBMS3 was consistently downregulated in all three NPC cell lines examined, as well as in the majority (13/15) of primary NPC tissues. This downregulation may be mediated through the suppression of MMP-2 and β-catenin, leading to the inactivation of its downstream targets, including cyclin D1, c-Myc, MMP-7, and MMP-9. Notably, MMP-7 is a well-established downstream target of β-catenin and has been reported to play a crucial role in cancer invasion and metastasis (60, 61). In their study, MMP-7 expression was effectively downregulated following the introduction of RBMS3 into NPC cells, further supporting its regulatory role in tumor progression. However, the precise role of MMP-7 in the carcinogenesis of NPC remains unclear. Further studies are required to elucidate how *MMP-7* genotypes contribute to its overexpression in NPC tumor tissues, as well as the underlying genotype-phenotype relationship in NPC pathogenesis.

In conclusion, our findings suggest that the variant genotypes of *MMP-7* rs11568818 may exert a modest influence on NPC susceptibility. Specifically, the *MMP-7* rs11568818 AG and GG genotypes appear to confer a synergistic effect, particularly among individuals who consume tobacco cigarette as a habit. Further investigations involving larger sample sizes and diverse populations are imperative to corroborate and expand the application of *MMP-7* genotypes in clinical prediction.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Research design: Shih LC, Chen KY, Bau DT, and Tsai CW; patient and questionnaire summaries: Shih LC, Hsu SW, Chen KY, Hsu CL, and Liu YF; experimental work: Hsu SW, Wang YC, Shih HY, Chang WS, and Tsai CW; data clearance and identification: Chen KY, Shih LC, Hsu SW, and Hsu CL;

statistical analysis: Bau DT, Hsu SW, and Chang WS; literature review and manuscript writing: Chen KY, Shih LC, Hsu SW, Tsai CW and Bau DT; review and revision: Tsai CW and Bau DT.

Acknowledgements

The Authors are grateful to Yu-Hsin Yen and Yu-Cheng Lou for their excellent technical assistance. This study was supported by Taichung Armed Forces General Hospital (TCAFGH-D-113018), Taichung Veterans General Hospital (TCVGH-1124903B), and Asia and China Medical University (CMU113-ASIA-06). The funders were not involved in the study design, data collection, analysis, or annotation of the manuscript.

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