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The Association of *MMP7* Genotype With Pterygium

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Abstract. *Background/Aim: In literature, few studies have examined the diagnostic or prognostic potential of matrix metalloproteinases (MMP) in pterygium, whose formation and progression are closely related to imbalance in the extracellular microenvironment. In this study, we investigated the contribution of MMP7 promoter (A-181G and C-153T) polymorphic genotypes to pterygium risk. Materials and Methods: A total of 134 cases and 268 controls were collected and their MMP7 genotypes at A-181G and C-153T were examined by polymerase chain reaction-restriction fragment length polymorphism methodology. Results: The AA, AG and GG genotypes at MMP7 promoter A-181G were non-significantly differentially distributed between the two groups at 85.8, 11.2 and 3.0%, respectively, in pterygium cases and 88.4, 9.7 and 1.9% in controls, respectively (p for trend=0.6822). There was no polymorphic genotype for MMP7 C-153T among our Taiwanese cohort. Conclusion: A-181G and C-153T genotypes at MMP7 do not have a direct role in determining Taiwanese susceptibility to pterygium.*

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Pterygium is a disease presenting an abnormal wing-shaped outgrowth of fibrovascular conjunctival tissues invading the clear cornea. The etiology of pterygium is still largely unclear. The incidence of pterygium is epidemiologically due to several factors, such as overexposure to sunshine, UV light, heat, dust, and other particles in the atmosphere (1-3). In the past two decades, mounting evidence has supported the concept that variations in our genome play a critical role in the determination of the etiology and development of pterygium (4-11). Many theories for pterygium have been proposed, such as imbalances in immunological mechanisms, growth factors, cytokines, apoptosis, angiogenesis (12-15), and most interestingly but complicatedly, an imbalance in the extracellular microenvironment and the involvement of matrix metalloproteinases (MMPs) (16-19).

MMPs are a group of zinc-binding endopeptidases responsible for regulating the components of the extracellular matrix microenvironment (20). The activation of MMPs generally takes place in the extracellular space, and interacts with various other proteases, teaming up to regulate the behaviors of cancer cells including viability, cell differentiation, programmed cell death, angiogenesis, immune surveillance, invasiveness and migration capacity (21, 22).

The smallest MMP member, MMP7 (matrilysin), is responsible for the metabolism of a broad spectrum of substrates including fibronectin, vitronectin, elastin, collagen IV, aggrecan, and proteoglycans (23). In addition, MMP7 is involved in inflammatory responses *via* its capacity to promote cell-surface processing of cytokines such as tumor necrosis factor a (24). MMP7 activation was first proposed to be involved in the pathogenesis of pterygium as early as 2001 by Girolamo and colleagues (25). In their analysis of cultured pterygial and conjunctival tissues from eight pterygium cases at Wales hospital in Sydney, basal and activated MMP7 levels were 1.4- and 2.7-fold higher, respectively, in pterygia

compared with conjunctiva (25). In 2007, Kato and colleagues examined the mRNA expression of the β-catenin-driven gene *MMP7* in pterygial and corneal limbal epithelium, and found that MMP7 was uniquely expressed in all of the four pterygium samples examined (26). They were also interested in investigating the contribution of MMP7 to pterygium at the DNA level, however, their limited sample size was unsuitable for that purpose.

Since the two promoter polymorphic sites of *MMP7*, A-181G and C-153T, may be in charge of controlling the level of MMP7 expression, we aimed to examine the association of *MMP7* A-181G and C-153T polymorphisms with the susceptibility to pterygium in the current study.

Materials and Methods

Collection of patients with pterygium and selection of controls. The well-designed protocol of the investigation was approved by the Institutional Review Board of Changhua Christian Hospital (number: 151225) and written informed consent was obtained from all of the patients. In total, 134 pterygium cases were recruited into the current study with the help of all the colleagues in Department of Ophthalmology at Changhua Christian Hospital in central Taiwan. All of the clinical characteristics for each of the patient such as their histological and surgical records, were identified by at least two expert surgeons at Changhua Christian Hospital. All of the pterygium cases voluntarily took in part, completed a questionnaire (containing personal age, gender, life-style and environmental exposure, *etc*.), and provided 3 to 5 ml of their peripheral blood. The inclusion criteria for the pterygium cases were the science of the apex of the pterygium invading the cornea by at least 1 mm. For the control group, all of those enrolled were healthy volunteers aged 45 years or more without pterygium or any type of cancer who visited the Department of Ophthalmology at Changhua Christian Hospital. In the final pool, the case group included 78 males and 56 females (age range of 48 to 89 years, with an average age of 64.4 years). Finally, 268 healthy participants without pterygium and without cancer were selected in order to match the population structure of the pterygium population (we doubled the number of cases and matched for their ages and genders). The overall agreement rate in the sampling of both the case and control groups was more than 85%. Selected basal characteristics of both the pterygium and control groups are presented in Table I.

Methodology for determining MMP7 genotypes. Genomic DNA from peripheral blood leukocytes of each participant was carefully extracted within 12 h after sample collection, then aliquoted and stored as we previously described (27). The *MMP7* genotyping methodology is the same as our recently published article (28). The genotyping polymerase chain reaction (PCR) cycling conditions *via* My Cycler (Biorad, Hercules, CA, USA) for *MMP7* were set as: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 57˚C for 30 s and 72˚C for 30 s; a final extension at 72˚C for 10 min; kept at 25˚C if needed overnight.

Methodology for statistical analysis. Typical Pearson's chi-square test without Yates' correction (when all frequencies were ≥5) and Fisher's exact test (when any number was less than 5) was applied to compare the distribution of gender, and *MMP7* genotypes and alleles between the two groups. The unpaired Student's *t*-test was applied for the comparison of distribution of the ages between the two groups. The associations between the *MMP7* genotypes and allelic types with the risk for pterygium were estimated by evaluating the odds ratios (ORs) as well as their 95% confidence intervals (CIs) using unconditional logistic regression with adjustment for possible confounding factors including age and gender.

Results

Comparison of age and gender between the patient and control groups. The percentage of males and females was 58.2% and 41.8% in both groups. Since we matched the age and gender when recruiting the controls into the study, there was no significant difference between the two groups regarding these data, as expected ($p>0.05$) (Table I).

Association analysis of MMP7 A-181G and C-153T promoter genotypes with pterygium risk. The results of PCR-RFLP-based genotypic analysis of the *MMP7* promotor A-181G and C-153T among the pterygium cases and controls are presented and compared in Table II. Firstly, the genotypic frequency distributions for *MMP7* A-181G did not statistically differ between the groups (p for trend=0.6822) (Table II). In detail, the *MMP7* A-181G heterozygous AG and homozygous GG genotypes seemed not to be associated with risk for pterygium among Taiwanese (adjusted OR=1.11 and 1.28, 95% CI=0.56-2.21 and 0.47-5.36; $p=0.6141$ and 0.4844, respectively; Table II). Even combining the G-carrying genotypes to compare with the AA genotype, risk for pterygium was unaltered ($p=0.4544$) (Table II). Secondly, we noted that there were no bearers of the polymorphic genotype at *MMP7* C-153T among any of the examined Taiwanese subjects (Table II). Overall, *MMP7* A-181G and C-153T genotypes do not play a direct role in determining personal susceptibility to pterygium among Taiwanese.

Association analysis of MMP7 A-181G and C-153T allelic frequencies with pterygium risk. We have further conducted the allelic frequency analysis for *MMP7* promoter A-181G and C-153T with pterygium risk to confirm the findings in Table II, and the results are shown in Table III. Supporting the preliminary findings in Table II, there was still no differential distribution of the allelic frequencies between the pterygium and control groups for the *MMP7* A-181G site (Table III). The adjusted OR for those carrying the variant G allele at *MMP7* promoter A-181G was 1.34 (95% CI=0.77-2.32, $p=0.3389$), compared to those carrying the wild-type A allele (Table III). As for the analysis of allelic frequency for *MMP7* C-153T, there was no association between the

Table I. *Distribution of selected demographics of the 134 pterygium patients and the 268 non-pterygium controls.*

Characteristic		Controls (n=268)	Patients (n=134)	*p*-Value
Age at onset, years	Mean±SD	64.3±6.0	64.4±7.0	0.9660[a]
Gender, n (%)	Male	156 (58.2%)	78 (58.2%)	>0.99[b]
	Female	112 (41.8%)	56 (41.8%)	

SD: Standard deviation. [a]Student's *t*-test; [b]chi-square test.

Table II. *Distribution of matrix metalloproteinase (MMP7) A-181G and C-153T genotypic frequencies among patients with pterygium and healthy controls.*

MMP7 polymorphism	Patients, n (%)	Controls, n (%)	Adjusted OR (95% CI)[a]	*p*-Value[b]
A-181G				
AA	115 (85.8)	237 (88.4)	1.00 (Reference)	
AG	15 (11.2)	26 (9.7)	1.11 (0.56-2.21)	0.6141
GG	4 (3.0)	5 (1.9)	1.28 (0.47-5.36)	0.4844
AG+GG	19 (14.2)	31 (11.6)	1.19 (0.49-2.64)	0.4544
p_{trend}				0.6822
C-153T				
CC	134 (100.0)	268 (100.0)	--	
CT	0 (0.0)	0 (0.0)	--	
TT	0 (0.0)	0 (0.0)	--	
p_{trend}				

OR: Odds ratio; CI: confidence interval. [a]Data adjusted for confounding factors age and gender. [b]Based on chi-square test without Yates' correction or Fisher exact test when n<5.

Table III. *Allelic frequencies for matrix metalloproteinase (MMP7) A-181G and C-153T polymorphisms among patients with pterygium and healthy controls.*

MMP7 polymorphism	Patients, n (%) n=268	Controls, n (%) n=536	Adjusted OR (95% CI)[a]	*p*-Value[b]
A-181G				
Allele A	245 (91.4)	500 (93.3)	1.00 (Reference)	
Allele G	23 (8.6)	36 (6.7)	1.34 (0.77-2.32)	0.3389
C-153T				
Allele C	268 (100.0)	536 (100.0)	--	
Allele T	0 (0.0)	0 (0.0)	--	

OR: Odds ratio; CI: confidence interval. [a]Data have been adjusted for confounding factors age and gender. [b]Based on chi-square test without Yates' correction.

genotypes with pterygium since all individuals investigated carried only C alleles (Table III).

Discussion

Under normal conditions, MMP7 is secreted by the cells in the ductal epithelium of glands in the skin, salivary glands, pancreas, glandular epithelium of intestine and reproductive organ, liver, and breast of human body (29). Since MMP7 is responsible for the metabolism of extracellular macromolecules such as casein, type I-V gelatins, fibronectins and proteoglycans (29), it is reasonably hypothesized that hereditary variations of *MMP7* may determine personal risk for inflammatory processes, tumor initiation, invasion and metastasis (30). The supporting evidence comes from several sources: a) MMP7 is found to be highly expressed in the

luminal surface of dysplastic glands in human colorectal cancer (29); b) In clinical practice, MMP7 inhibitors can potentially be applied to control the invasive capacity of cancer cells (30); c) MMP7 has been found to be highly overexpressed in advanced colorectal adenomas and involved in converting colorectal adenomas into a malignant state and facilitating rapid growth of the tumor (31).

In the current study, the results showed that the G allele at *MMP7* A-181G was not significantly associated with an increased risk for pterygium (Tables II and III). As far as we are concerned, the present study is the first one to reveal a lack of genotypic contribution of *MMP7* promoter genotype to pterygium in a representative population. In literature, the A-181G genotypes of *MMP7* have been examined for their association with various types of cancer, including oral, breast, esophageal, gastric, colorectal, gallbladder, bladder, cervical cancer, leukemia and renal cell carcinoma (28, 32-46). The lack of association of *MMP7* genotype with pterygium in the current study, together with those in bladder (34), renal cell (44), oral (35), colorectal (28), and lung (46) cancer in Taiwan supports the concept that MMP7 may influence Taiwanese susceptibility to these diseases *via* other mechanisms, such as regulation of translation or protein–protein interaction, and simply not through the regulation at the transcriptional level *via* polymorphic variations in the promoter region. Notably, while the AG genotype at *MMP7* promoter A-181G was associated with an OR of 1.22 (95% CI=0.91-1.63, p=0.2235), the GG genotype had an OR of 2.84 (95% CI=1.64-7.48, p=0.0007) compared to those carrying the AA wild-type genotype among a very large Taiwan population with 1,232 patients with breast cancer and 1,232 non-cancer controls (32). In addition, boys carrying the *MMP7* A-181G GG and AG/GG genotypes had 8.79- and 2.04-fold odds (p=0.0150 and 0.0413, respectively) of childhood acute lymphoblastic leukemia compared to those in Taiwan carrying the wild-type AA genotype (33). In our investigated population, the carriers of the G allele at *MMP7* A-181 were also non-significantly prone to have a higher pterygium risk (Tables II and III). Thus, from the pilot data we collected here, we still cannot provide any association of *MMP7* A-181 with pterygium, while we cannot exclude the possibility that other *MMP7* polymorphisms may serve as a biomarker for the prediction of pterygium.

There are several directions for prospective investigations. Firstly, the collection of precious pterygium samples should be continuously conducted to be as representative for the whole population with pterygium as possible. Moreover, validations with larger sample sizes at multiple centers and various populations are needed. Secondly, the genotype–phenotype correlation for MMP7 can only be revealed after phenotypic measurements of *MMP7* transcripts, protein level and activity with the primarily cultured pterygia and conjunctiva cells from patients with pterygium. Thirdly, any contribution of MMP7 genotype and phenotype to pterygium can be further understood in the stratification of the pterygium population into several subgroups according to their clinical characteristics, such as severity. There are already several classification systems for stratifying patients with pterygium. For example, pterygium can be separated into atrophic, intermediate and fleshy types according to its translucence (47). It is possible to analyze the interaction of *MMP7* genotypes and some clinical indices, such as the metastasis status, severity and the level of translucence, in order to understand the role of MMP7 in the etiology and development of pterygium.

In conclusion, the results of this pilot study suggest that neither A-181G nor C-153T genotype of the promoter of *MMP7* significantly confer a differential pattern of personal susceptibility to pterygium among Taiwanese. Further investigations elucidating the contribution of the genotypes of other members of *MMP*s to pterygium initiation and progression are needed and the findings in the current study should be validated in other ethnic populations and larger cohorts.

Conflicts of Interest

All the Authors have no conflicts of interest to declare.

Authors' Contributions

Research design: Hu PS and Liao CH; patient and questionnaire summarize: Hu PS and Hsia NY; experiments: Wang YC and Chang WS; statistical analysis: Wu MF, Yang JS and Yu CC; article writing: Tsai CW and Bau DT; review and revision: Chang WS, Tsai CW and Bau DT.

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