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Contribution of Matrix Metalloproteinase-2 Genotypes to Taiwan Pterygium Risk

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Abstract. *Background/Aim: In the literature, the studies about the role of matrix metalloproteinase-2 (MMP-2) in pterygium diagnosis are mainly based on its protein expression. The role of MMP-2 variants has never been examined. The aim of this study was to examine the association of MMP-2 genotypes with pterygium risk. Materials and Methods: MMP-2 rs243865 and rs2285053 were genotyped in 140 pterygium cases and 280 non-pterygium controls by typical polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) genotyping technology. Results: The genotypic frequency of MMP-2 rs243865 CC, CT and TT were 86.4%, 12.9% and 0.7% in the pterygium group and 81.1%, 17.1% and 1.8% in the non-pterygium group (p for trend=0.3389). The variant CT and TT carriers had a 0.70- and 0.38-fold pterygium risk (95%CI=0.39-1.26 and 0.04-3.25, p=0.2982 and 0.6686, respectively). As for MMP-2 rs2285053, the genotypic frequency of CC, CT and TT were 67.1%, 28.6% and 4.3% in the pterygium group, non-significantly different from those in non-pterygium group (p for trend=0.7081). The CT and TT carriers had a 0.88- and 0.71-fold pterygium risk (95%CI=0.56-1.38 and 0.27-1.88, p=0.6612 and 0.6456, respectively). The allelic analysis results showed that MMP-2 rs243865 variant T allele was not associated with pterygium risk (7.1% versus 10.4%, OR=0.67, 95%CI=0.39-1.13, p=0.1649). As for MMP-2 rs2285053, the T allele was not associated with pterygium risk either (18.6% versus 21.1%, OR=0.85, 95%CI=0.59-1.23, p=0.4136). Conclusion: The genotypes at MMP-2 rs243865 or rs2285053 played minor role in determining individual susceptibility for pterygium among Taiwanese.*

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Pterygium is a prevalent ocular surface condition characterized by aberrant epithelial and fibrovascular proliferation, invasion, and matrix remodeling (1, 2). The development of fibrovascular tissues that excessively proliferate, resulting in an anomalous wing-shaped growth, resembles the overgrowth observed in tumors (3). The migration of these wedge-shaped abnormal tissues from the bulbar conjunctiva onto the cornea also shares certain tumorigenesis characteristics seen in solid cancers (4). Pterygium's multifactorial nature, influenced by factors, such as heat, dust, atmospheric particles, immunological cytokines, extracellular matrix reorganization, UV radiation, and growth factors, contributes to the intricate etiology of this condition (5-13). Furthermore, a handful of studies have provided evidence indicating that genetic variations also play

Table I. *Demographics of the pterygium patients and the non-pterygium subjects.*

Characteristic	Controls (n=280)			Cases (n=140)			*p*-Value
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			62.3±7.4			62.2±7.9	0.2980[a]
<60	99	35.4%		56	40.0%		0.4109[b]
≥60	181	64.6%		84	60.0%		
Sex							
Male	162	57.9%		81	57.9%		1.0000
Female	118	42.1%		59	42.1%		

SD: Standard deviation; [a]based on unpaired Student's *t*-test; [b]based on Chi-square test with Yates' correction.

a pivotal role in determining individual susceptibility to pterygium (14-17). Nonetheless, a practical and easily accessible marker for pterygium is still conspicuously absent.

The equilibrium between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) plays a crucial role in regulating the extent of connective tissue degradation and remodeling. The extracellular matrix (ECM) is a network of interconnected macromolecules that form a dynamic scaffold outside of the cells (18-20). Numerous studies have reported up-regulated expression of various MMP types in pterygium samples. Elevated MMP levels have been linked to the dissolution of Bowman's layer, leading to angiogenesis and the invasion and migration of pterygium tissues onto the cornea (21-28). Two known risk factors for pterygium, namely, UV radiation and inflammatory cytokines, have been shown to increase the expression levels of MMPs in both epithelial cells and fibroblasts (22, 28, 29).

MMP-2, also known as type IV collagenase or gelatinase A, is situated on chromosome 16q21 and encodes the MMP-2 enzyme (30, 31). One of its main functions is the degradation of type IV collagen, contributing to the maintenance of balanced extracellular matrix components and concentrations (32, 33). Prior research has predominantly concentrated on the roles of MMPs in pterygium etiology by comparing MMP expression levels in surgically excised pterygia with those from normal controls. However, studies examining the transcriptional or translational expression of MMP-2 in cultured pterygium fibroblasts have yielded conflicting results (21-23, 25, 27, 34-36). The previous sample collection methods and the involvement of unpredictable confounding factors during primary culture have compelled us to explore alternative strategies for identifying clinically feasible predictive markers from a genomic perspective.

The literature contains reports indicating that *MMP-2* polymorphic variants, specifically rs243865 and rs2285053, have the potential to influence mRNA and protein expression levels of MMP-2 in various cancer types, including oral cancer (37), esophageal cancer (38), breast cancer (39), colorectal cancer (40), and leukemia (41). However, the genetic variations of *MMP-2* have not been explored in relation to pterygium, and the genotype-phenotype connection of *MMP-2* remains uncharted. Given the above information, this study aimed to investigate whether *MMP-2* rs243865 and rs2285053 genotypes contribute to the risk of pterygium in a representative Taiwanese population, which contains 140 pterygium cases and 280 non-pterygium controls.

Materials and Methods

Recruited pterygium and non-pterygium population. The research concepts, association hypotheses, and experimental protocols of the present study have received approval from the Changhua Christian Hospital Institutional Review Board. Additionally, informed consent has been signed and obtained from all the subjects. A total of 140 individuals diagnosed with pterygium and 280 non-pterygium control subjects, were recruited for this study. All participants willingly completed a questionnaire and provided peripheral blood samples for genotyping. The non-pterygium control subjects were selected based on the absence of pterygium, endometriosis, myoma, or any type of cancer. The demographic characteristics of all participants are summarized in Table I.

MMP-2 genotyping methodologies. DNA was extracted from the peripheral blood of each subject as we routinely conduct (42-45). The patterns of *MMP-2* rs243865 and rs2285053 genotypes among 140 pterygium cases and 280 non-pterygium controls were accessed *via* polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) genotyping methodology. The design of primer sequences was as we previously published (46, 47). Also, the PCR conditions have been as we previously published (46, 47). The PCR fragments were digested by restriction enzymes *Xsp* I and *Hinf* I overnight for *MMP-2* rs243865 and rs2285053, respectively. After the enzyme digestion, the genotyping profiles of *MMP-2* rs243865 and rs2285053 of each sample were identified by two independent researchers after 3% agarose gel electrophoresis.

MMP-2 statistical analysis methodologies. The ages between the pterygium patient and non-pterygium control groups are shown as the mean±standard deviation (SD), and unpaired Student's *t*-test was applied for the statistical comparison. Pearson's chi-square (when n≥5) or Fisher exact test (when n<5) was used for evaluating of the

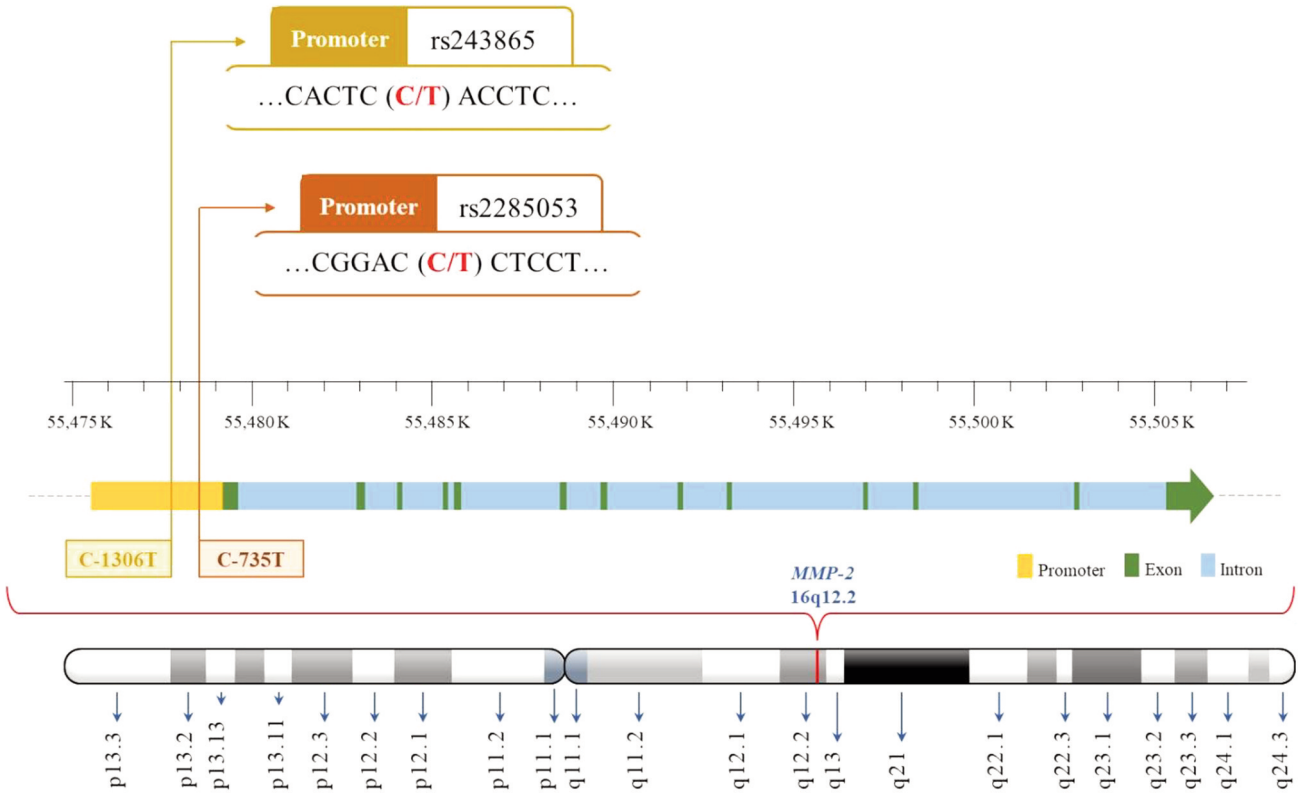

Figure 1. *Physical map of matrix metalloproteinase-2 rs243865 and rs2285053 polymorphic sites.*

contributions of *MMP-2* polymorphisms to pterygium risk. The associations were also checked using odds ratios (ORs) and individual corresponding 95% confidence intervals (CIs). Any consequence was taken as statistically significant when the outcome *p*-value was less than 0.05.

Results

Comparison of age and sex distributions between the pterygium patient and non-pterygium control groups. First, it is essential to examine the age distributions between the pterygium and non-pterygium groups. The mean age of the pterygium and non-pterygium groups was assessed, and the results indicated no significant difference between the two groups (p=0.2980). This observation remained consistent even after stratifying the data using a threshold age of 60 years (p=0.4109). Second, it's worth noting that, as part of our recruitment process, we matched the pterygium and non-pterygium groups, ensuring there is no disparity in the distribution of men and women between these groups (p=1.0000).

Association of MMP-2 genotypes and pterygium risk. The physical map illustrating the locations of *MMP-2* polymorphisms is presented in Figure 1. First, the genotypic frequencies of *MMP-2* polymorphisms of the control group fit the Hardy-Weinberg equilibrium hypothesis (p=0.1988 and 0.1998, respectively) (Table II). Second, the genotypic frequencies for *MMP-2* rs243865 (CC, CT, and TT) in the pterygium group were 86.4%, 12.9%, and 0.7%, respectively. When compared to the non-pterygium group with frequencies of 81.1%, 17.1%, and 1.8%, no significant difference was observed (p for trend=0.3389). In specific terms, carriers of the CT and TT variants exhibited a 0.70- and 0.38-fold risk for developing pterygium (95%CI=0.39-1.26 and 0.04-3.25, p=0.2982 and 0.6686, respectively). CT+TT carriers showed a 0.67-fold risk for pterygium (95%CI=0.38-1.19, p=0.2165) (Table II, top section). Third, concerning *MMP-2* rs2285053, the genotypic frequencies of CC, CT, and TT in the pterygium group were 67.1%, 28.6%, and 4.3%, respectively. There was no significant difference compared to the non-pterygium group (p for trend=0.7081). In detail, carriers of the CT and TT variants had a 0.88- and 0.71-fold risk for developing pterygium (95%CI=0.56-1.38 and 0.27-1.88, p=0.6612 and 0.6456, respectively). CT+TT carriers exhibited a 0.85-fold risk for pterygium (95%CI=0.56-1.31, p=0.5393) (Table II, bottom section).

Table II. *Genotypic frequency distributions of matrix metalloproteinase-2 rs243865 and rs2285053 among pterygium patients and non-pterygium subjects.*

Genotypes	Controls, n (%)	Cases, n (%)	OR (95%CI)	*p*-Value[a]
Promoter -1306				
rs243865				
CC	227 (81.1)	121 (86.4)	1.00 (Reference)	
CT	48 (17.1)	18 (12.9)	0.70 (0.39-1.26)	0.2982
TT	5 (1.8)	1 (0.7)	0.38 (0.04-3.25)	0.6686
CT+TT	53 (18.9)	19 (13.6)	0.67 (0.38-1.19)	0.2165
p_{trend}				0.3389
p_{HWE}				0.1988
Promoter -735				
rs2285053				
CC	178 (63.6)	94 (67.1)	1.00 (Reference)	
CT	86 (30.7)	40 (28.6)	0.88 (0.56-1.38)	0.6612
TT	16 (5.7)	6 (4.3)	0.71 (0.27-1.88)	0.6456
CT+TT	102 (36.4)	46 (32.9)	0.85 (0.56-1.31)	0.5393
p_{trend}				0.7081
p_{HWE}				0.1998

OR: Odds ratio; CI: confidence interval; [a]data based on Chi-square test with Yates' correction (n≥5) or Fisher's exact test (n<5); p_{trend}: *p*-value based on trend analysis; p_{HWE}: *p*-value based on Hardy-Weinberg Equilibrium.

Table III. *Allelic frequencies for matrix metalloproteinase-2 rs243865 and rs2285053 polymorphisms among pterygium patients and non-pterygium subjects.*

Genotypes	Controls, n (%)	Cases, n (%)	Odds ratio (95% Confidence internal)	*p*-Value[a]
rs243865				
Allele C	502 (89.6)	260 (92.9)	1.00 (Reference)	
Allele T	58 (10.4)	20 (7.1)	0.67 (0.39-1.13)	0.1649
rs2285053				
Allele C	442 (78.9)	228 (81.4)	1.00 (Reference)	
Allele T	118 (21.1)	52 (18.6)	0.85 (0.59-1.23)	0.4136

[a]Data based on Chi-square test with Yates' correction.

Association of MMP-2 allelic frequencies and pterygium risk. The results of allelic frequency analysis indicated that the variant T allele at *MMP-2* rs243865 does not appear to be associated with pterygium risk (7.1% *versus* 10.4%, OR=0.67, 95%CI=0.39-1.13, *p*=0.1649) (Table III). Similarly, in the case of *MMP-2* rs2285053, the results suggest that the variant T allele does not seem to be associated with an increased risk for pterygium either (18.6% *versus* 21.1%, OR=0.85, 95%CI=0.59-1.23, *p*=0.4136) (Table III).

Discussion

There is a lack of consensus among ophthalmologists regarding the optimal understanding of pterygium etiology and its management. This is partly attributed to the multitude of risk factors involved, and the absence of a reliable marker for personalized therapeutic strategies. Early investigations into protein and mRNA expression patterns by translational scientists revealed an over-expression of MMPs, particularly MMP-1 (22, 23, 29, 48, 49), MMP-2 (29, 34) and MMP-3 (22, 23, 29). However, the genomic roles of MMPs have rarely, if ever, been investigated. In the current study, we investigated the potential contribution of *MMP-2* rs243865 and rs2285053 genotypes to pterygium susceptibility in a representative Taiwanese population (control:case=280:140). As far as we know, there is significant potential in identifying a genetic target within MMP-2 for the development of therapeutic strategies for pterygium.

In the current dataset, it is evident that the T allele of *MMP-2* rs243865 does not appear to be a significant contributor to individual pterygium susceptibility (Table II and Table III). However, it's noteworthy that both *MMP-2* rs243865 variant CT and TT genotypes were less prevalent

in the pterygium group compared to the non-pterygium group (12.9% *versus* 17.1% and 0.7% *versus* 1.8%). This finding raises considerable interest, and a larger pterygium population could help validate the results for *MMP-2* rs243865. Furthermore, our current study is the first to demonstrate the potential contribution of *MMP-2* rs243865 genotypes to pterygium susceptibility on a global scale. As for *MMP-2* rs2285053, no association has been found between *MMP-2* rs2285053 genotypes and pterygium (Table II and Table III). The minor allelic frequencies of *MMP-2* rs243865 along with rs2285053 in our study are 10.4% and 21.1%, respectively (Table III). These frequencies closely resemble those reported on the NCBI website for East Asian populations, with minor allelic frequencies of 10.9% among 1,712 subjects and 23.7% among 1,170 subjects (50, 51). This information, coupled with the adherence of the two polymorphic sites to Hardy-Weinberg Equilibrium, suggests that our collection of pterygium samples can be considered representative of the broader Taiwanese population.

In 2000, Solomon and his research team initiated the development of standardized pterygium fibroblast culture systems, enabling investigations into mRNA and protein expression levels in pterygium (23). Their initial study focused on MMP-2 and cytokines, revealing that the transcriptional expression of MMP-2 was relatively high but showed no significant difference between primary pterygium body fibroblasts and normal human conjunctival fibroblasts (23). In 2001, Li *et al*. conducted a comprehensive analysis of transcriptional and translational MMP expression in cultured human pterygium head, body, and subconjunctival fibroblasts from 6 non-pterygium subjects and 14 pterygium cases (22). Their findings indicated that only MMP-1 and MMP-3 proteins and activity decreased progressively from pterygium head to body to subconjunctival fibroblasts. Notably, there was no significant difference in the transcript and protein expression of MMP-2 or other targets (22). In 2009, Yang and his colleagues provided evidence showing significantly higher MMP-2 and MMP-9 expression in pterygium fibroblasts compared to normal conjunctival specimens (34). However, their sample size remained limited, with only 15 cases collected and cultured. They further compared paired cultured fibroblasts from the same cases and tentatively proposed that the expression of MMP-2, along with MMP-9, might increase in conjunction with the progression of pterygium (34). In the near future, it is essential to investigate whether the mRNA and protein expression levels of MMP-2 correlate with the genotypes of *MMP-2* rs243865 and/or rs2285053. Furthermore, exploring whether MMP-2 expression levels are up-regulated in line with the progression of pterygium stages is an area of interest.

In summary, this study investigated the genotypic variations of *MMP-2* rs243865 and rs2285053 in the Taiwanese population and found that neither of them significantly contributes to an individual's susceptibility to pterygium among Taiwanese. It is worthwhile to validate these findings in larger and more diverse populations.

Conflicts of Interest

All the Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Research design: Hu PS, Hsia NY, Wang ZH, Bau DT; patient and questionnaire summaries: Hu PS, Hsia NY, Chen HC, Hsia TC; experimental work: Wang ZH, Chang WS, Tsai CW, Wang YC; statistical analysis: Wang ZH, Lin ML, Wang YC; manuscript writing: Tsai CW, Bau DT; manuscript checking and discussing: Hu PS, Hsia NY, Wang ZH, Chen HC, Hsia TC, Lin ML, Wang YC, Chang WS, Bau DT, Tsai CW.

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