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The Significant Association of *MMP-1* Genotypes With Taiwan Pterygium

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Abstract. *Background/Aim: Few studies have examined the contribution of matrix metalloproteinases (MMP) to either diagnosis or prognosis of pterygium. The aim of this study was to investigate the contribution of MMP-1 genotypes to pterygium risk. Patients and Methods: A total of 134 cases and 268 controls were included and their MMP-1 -1607 (rs1799705) genotypes were examined by polymerase chain reaction-restriction fragment length polymorphism. Results: The percentages of 2G/2G, 1G/2G, and 1G/1G for rs1799705 genotypes were 48.5, 36.6 and 14.9% among patients and 33.9, 44.8, and 21.3% among controls (p trend=0.0167). The odds ratios (ORs) after adjusting for age and gender for 1G/2G and 1G/1G genotypes at rs1799705 were 0.54 (95%CI=0.33-0.89, p=0.0168) and 0.46 (95%CI=0.27-0.88, p=0.0192), respectively. Consistently, the adjusted OR for those carrying the 1G allele at MMP-1 -1607 was 0.61 (95%CI=0.41-0.78, p=0.0167), compared with the wild-type 2G allele. Conclusion: The genotypes at rs1799705 play a role in determining personal susceptibility to pterygium.*

Pterygium is the formation of fibrovascular tissues consisting of highly vascularized epithelial and subepithelial cells that proliferate excessively and generate an abnormal wing-shaped growth from the conjunctiva over the ocular surface (1). Epidemiologically, population-based reports have shown that heat, dust, particles in the atmosphere, immunological mechanisms, and agents inducing extracellular matrix reorganization, growth factors, cytokines, and those affect apoptosis and angiogenesis are risk factors for pterygium (2-10). In recent decades, several reports have demonstrated that inherited genomic variants play a significant role in the determination of individual susceptibility to pterygium (11-14).

Matrix metalloproteinases (MMPs), also known as matrixins or matrix metallopeptidases, comprise the major calcium-dependent zinc-containing protein family responsible for regulating the components of extracellular matrix (15). MMPs are also function in cell proliferation, differentiation, apoptosis, invasion, adhesion, dispersion, migration, angiogenesis and immune surveillance (16, 17). It has been shown that polymorphic genotypes of *MMPs* may associate with the personal susceptibility to several types of cancer (18-21). However, the obstacle in recruiting pterygium patients and matched controls has retarded the progress in deciphering the role of MMPs in pterygium etiology and only limited reports with a small size of pterygium samples have provided evidence for MMPs' involvements in the initiation and progression of pterygium (22-24).

The most commonly studied *MMP-1* polymorphic site is the rs1799750, which is located at -1607 of the promoter of the *MMP-1* gene. The variants at this polymorphic site may be consist of the "2G" insertion polymorphism, which has been reported to lead to higher transcriptional activity of *MMP-1*, potentially to higher levels or rates of collagen breakdown, and higher levels of MMP-1 in the serum than the 1G/1G genotype (25). In a meta-analysis published in 2012 investigating about 10,000 cancer cases, half of which metastasized, concluded that *MMP-1* rs1799750 2G/2G genotypes carriers may have a slightly higher overall metastasis rate (26). As far as pterygium

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is concerned, MMP-1 and MMP-3 have been reported to be overexpressed at the levels of both mRNA and protein in Pterygium head fibroblasts (22). Thus, it is reasonable to hypothesize that the variant genotypes at the promoter region at *MMP-1* rs1799750 may play a role in determining the expression levels of MMP-1, and personal susceptibility for pterygium. Since the promoter polymorphic site of *MMP-1* may control the expression levels of MMP-1 and consequently the levels of extracellular matrix components, we aimed at investigating the association of *MMP-1* rs1799750 genotypes with the susceptibility of pterygium in Taiwan.

Materials and Methods

Collection of pterygium patients and matched controls. The protocols of the study were approved by the Institutional Review Board of Changhua Christian Hospital and written informed consent was obtained from one or both parents of all participants (Changhua Christian Hospital IRB numbers: 151225). Totally, 134 cases diagnosed with pterygium were recruited in this study. They voluntarily participated, completed a questionnaire, and provided their peripheral blood samples. At the same time, healthy subjects, aged 45 years or more without pterygium or any type of cancer were enrolled as controls. There were 78 males and 56 females in the pterygium group (age range between 48-89 years and average age of 64.4 years). At last, 268, double the number of the cases, healthy participants were included into the control group matching the population structure (matched for their ages with difference no larger than 5 years and genders). Selected characteristics of the participants both in pterygium and control groups are summarized and compared in Table I.

MMP-1 rs1799750 genotyping. The genomic DNA from peripheral blood leukocytes of each subject was extracted, aliquoted and stored in –80˚C as previously described (13, 14). The *MMP-1* genotyping methodology is the same as described in our recently published papers (19, 27). The polymerase chain reaction (PCR) protocols set at My Cycler (Biorad, Hercules, CA, USA) for *MMP-1* were one cycle at 94˚C for 5 min; 35 cycles at 94˚C for 30 s, one cycle at 57˚C for 30 s and one cycle at 72˚C for 30 s and a final extension at 72˚C for 10 min.

Statistical analysis. Typical Pearson's Chi-square test without Yates' correction (when all numbers were equal to or larger than 5) and Fisher's exact test (when any number was less than 5) was applied to compare the distribution of the gender, *MMP-1* genotypic and allelic distributions between pterygium and control groups. Also, the unpaired Student's *t*-test was applied for the comparison of distribution of the ages between the case and control groups. In addition, the associations between the *MMP-1* polymorphisms and pterygium risk were estimated by computing odds ratios (ORs) as well as their 95% confidence intervals (CIs) from unconditional logistic regression analysis with the adjustment for possible confounding factors including age and gender (Tables II and III).

Results

Well-match of ages and genders between the pterygium patient and control groups. The distributions of the age and gender for the 134 pterygium patients and the 268 non-pterygium controls are shown and compared in Table I. The average onset age of the pterygium patients was 64.4 years old, and the percentages of males and females were 58.2% and 41.8% in control and case groups, respectively. Since we originally matched the age and gender in our research design, there was no significant difference between the two groups as for the frequencies of age or gender as expected (both $p>0.05$) (Table I).

Association analysis of MMP-1 promoter genotypes at rs1799750 with pterygium risk. The results of genotypic analysis of the *MMP-1* promoter rs1799750 polymorphism among the pterygium cases and non-pterygium controls are presented and compared in Table II. First, the genotypic frequency distributions at *MMP-1* rs1799750 were statistically different between the pterygium and control groups (p for trend=0.0167) (Table II, top panel). In detail, the *MMP-1* rs1799750 heterozygous 1G/2G and homozygous 1G/1G variant genotypes were both associated with lower risk for pterygium than the wild-type 2G/2G genotype among the investigated population (p=0.0168 and 0.0192, adjusted OR=0.54 and 0.46, 95%CI=0.33-0.89 and 0.27-0.88, respectively; Table II, top panel). In the recessive model, the combination of the wild-type 2G/2G and heterozygote 1G/2G genotypes (2G/2G+1G/2G) at *MMP-1* rs1799750 conferred an unaltered risk for pterygium compared to 1G/1G genotype (p=0.1276) (Table II, middle panel). In the dominant model, the 1G/1G+1G/2G carriers at *MMP-1* rs1799750 conferred lower risk of pterygium compared to the 2G/2G genotype carriers (p=0.0048, aOR=0.53 and 95%CI=0.35-0.81) (Table II, bottom panel). Overall, the *MMP-1* rs1799750 genotypes play a critical role in determining personal susceptibility to pterygium among Taiwanese.

Association analysis of MMP-1 rs1799750 allelic frequencies with pterygium risk. The allelic frequency analysis of *MMP-1* rs1799750 with pterygium risk was also conducted to confirm the findings in Table II. The results are shown in Table III. Consistent with the major finding in Table II, there is a significant difference in the distribution of allelic frequencies between the pterygium and control groups regarding *MMP-1* rs1799750 (Table III). In detail, the adjusted OR for the subjects carrying the variant 1G allele at *MMP-1* rs1799750 was 0.61 (95%CI=0.41-0.78, p=0.0167), compared to those carrying the wild-type 2G allele (Table III).

Discussion

MMPs play a critical role in the homeostasis of extracellular matrix components, and any imbalance of the extracellular microenvironment may be related to the initiation and progression of pterygium. It has been reported that in early-stage pterygium the levels of MMP-2 or MMP-9 were low

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

Characteristics	Controls (n=268)			Patients (n=134)			*p*-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age at onset (years old)			64.3 (6.0)			64.4 (7.0)	0.9660
Gender							1.0000
Male	156	58.2%		78	58.2%		
Female	112	41.8%		56	41.8%		

[a]Based on Student's *t*-test; bbased on Chi-square test; SD: standard deviation.

Table II. *Distributions of matrix metalloproteinase-1 rs1799750 genotypic frequencies among the pterygium patients and healthy controls.*

	Pterygiums, n (%)	Controls, n (%)	Adjusted OR (95%CI)[a]	*p*-Value[b]
rs1799750				
2G/2G	65 (48.5)	91 (33.9)	1.00 (Reference)	
1G/2G	49 (36.6)	120 (44.8)	**0.54 (0.33-0.89)**	**0.0168***
1G/1G	20 (14.9)	57 (21.3)	**0.46 (0.27-0.88)**	**0.0192***
p_{trend}				**0.0167***
Carrier comparison				
2G/2G+1G/2G	114 (85.1)	211 (78.7)	1.00 (Reference)	
1G/1G	20 (14.9)	57 (21.3)	0.63 (0.36-1.18)	0.1276
2G/2G	65 (48.5)	91 (33.9)	1.00 (Reference)	
1G/1G +1G/2G	69 (51.5)	177 (66.1)	**0.53 (0.35-0.81)**	**0.0048***

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. *Bold values show significance.

Table III. *Allelic frequencies for matrix metalloproteinase-1 rs1799750 polymorphisms among the pterygium patients and healthy controls.*

Allelic type	Pterygiums, n (%) n=268	Controls, n (%) n=536	Adjusted OR (95%CI)[a]	*p*-Value[b]
rs1799750				
Allele 2G	179 (66.8)	302 (56.3)	1.00 (Reference)	
Allele 1G	89 (33.2)	234 (43.7)	**0.61 (0.41-0.78)**	**0.0167***

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. *Bold values show significance.

or undetectable in tissues and cultured fibroblasts. On the contrary, in advanced-stage pterygium, the levels of MMP-2 and MMP-9 were higher in pterygium tissues and fibroblasts (28). In addition, Kim and his colleagues have reported that down-regulation of the expression levels of MMP-3 and MMP-13 resulted in suppression of the proliferation and migration of pterygium fibroblasts (29). These findings support the idea that *MMPs* may play an important role in the progression of pterygium, and polymorphisms of MMPs may serve as valuable predictive biomarkers for the risk of pterygium.

The positive association of *MMP-1* rs1799750 genotypes with pterygium in the current study (Tables II and III), supports the concept that polymorphic variations in *MMP-1* promoter region may influence personal susceptibility to pterygium by regulating MMP-1 expression at the transcription level. This is consistent with the findings in childhood leukemia (30), and gastric cancer (31). However, in several types of cancer, the genotypes of *MMP-1* rs1799750 may not directly contribute to the risk determination (20, 32-34), which indicates that the *MMP-1* rs1799750 genotypes may be indirectly involved in

carcinogenesis. The detailed mechanisms of how MMP-1 rs1799750 genotypes interact with other molecules leading to pterygium need further investigation.

In conclusion, this is the first study that has provided evidence on the association of polymorphisms at *MMP-1* rs1799750 with pterygium. Our results suggest that the variant genotypes of the rs1799750 at the promoter of *MMP-1* significantly confer personal susceptibility to pterygium among Taiwanese. Further studies elucidating the contribution of the genotypes of other members of *MMPs*, such as *MMP-2*, *-9* (28), *-3, -13* (29) and *-27*, to pterygium are needed and the findings in the current study should be validated in other studies to strengthen their value.

Conflicts of Interest

All the Authors have declared no conflicts of interest regarding this study.

Authors' Contributions

Research design: Tsai CB, Wang YC and Yin MC; patient and questionnaire summaries: Tsai CB and Hsia NY; experimental work: Wang YC, CHIN YC and Huang TL; statistical analysis: Wang ZH, Chang WS and Yu CC; article writing: Tsai CW and Bau DT; review and revision: Chang WS, Tsai CW and Bau DT.

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