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Exploring the Genetic Role of Matrix Metalloproteinase-13 Variants in Pterygium Risk

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Abstract

Background/Aim: Pterygium is a common ocular surface disorder characterized by abnormal fibrovascular growth and extracellular matrix remodeling, yet its precise molecular etiology remains unclear. Matrix metalloproteinases (MMPs) have been implicated in pterygium pathogenesis. However, the genetic contribution of *MMP13* remains unexplored.

Materials and Methods: This case–control study evaluated the association between *MMP13* promoter rs2252070 and intronic rs478927 with pterygium susceptibility, in a cohort comprising 160 patients and 320 age- and sex-matched controls by genotyping via polymerase chain reaction-restriction fragment length polymorphism methodology. The interaction between *MMP13* genotype and age or sex were accessed by stratified analysis.

Results: The genotypic distributions of *MMP13* rs2252070 showed no significant differences between cases (AA: 33.1%, AG: 42.5%, GG: 24.4%) and controls (AA: 28.4%, AG: 45.6%, GG: 26.0%; *p* for trend=0.5720). Compared to the AA genotype, the odds ratios (ORs) for pterygium in association with AG and GG were 0.80 (95% CI=0.51-1.25, *p*=0.3829) and 0.81 (95% CI=0.48-1.34, *p*=0.4856), respectively. Under dominant and recessive models, no significant associations were observed (dominant: OR=0.80, 95% CI=0.53-1.21, *p*=0.3417; recessive: OR=0.92, 95% CI=0.59-1.43, *p*=0.7953). Similarly, rs478927 showed no significant genotypic or allelic associations with pterygium risk (all *p*>0.05). Stratified analyses indicated no effect modification by age or sex.

continued

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Conclusion: These findings suggest that *MMP13* genetic variants rs2252070 and rs478927 do not significantly contribute to pterygium susceptibility. Given the known involvement of other MMPs, future studies should focus on alternative genetic markers to better understand pterygium pathogenesis and improve early detection strategies.

Keywords: Age, sex, genotype, matrix metalloproteinase-13, polymorphism, pterygium, Taiwan.

Introduction

Pterygium is a chronic and degenerative ocular surface disorder of unclear etiology, predominantly affecting populations in hot and arid climates (1). While its global prevalence is estimated at approximately 12% (2), marked regional and ethnic disparities exist, with incidence rates ranging between 1% and 30% (3). As one of the most frequently encountered ocular surface abnormalities worldwide, its precise molecular mechanisms and factors contributing to recurrence after treatment remain incompletely elucidated (4). The biological behavior of pterygium bears several similarities to that of neoplastic diseases, including aberrant fibrovascular expansion, corneal invasion, remodeling of the extracellular matrix (ECM), and a high likelihood of postoperative regrowth (5-7). The characteristic triangular extension of the lesion onto the corneal surface mimics the invasive properties typically observed in solid tumors (8). Histologically, the subepithelial compartment of pterygium is marked by a pronounced accumulation of ECM components, both fibrillar and non-fibrillar, that are not present in adjacent healthy conjunctival tissue. This abnormal matrix deposition is believed to be a key contributor to disease initiation and progression (9). Although advances in omics-based approaches have expanded our understanding of the molecular landscape of pterygium, progress is still hindered by the limited availability of adequately powered patient cohorts (10-14).

As previously highlighted, dysregulation of ECM represents a defining feature in the pathophysiology of pterygium (15). Nevertheless, the specific molecular events governing these alterations remain incompletely defined. Since the early 2000s, a growing body of evidence has implicated matrix metalloproteinases (MMPs), along with their endogenous antagonists, tissue inhibitors of metalloproteinases (TIMPs), as central mediators in the processes of inflammation, ECM remodeling, degradation of Bowman's layer, and subsequent corneal invasion. Despite over two decades of investigation, the individual roles of distinct MMP isoforms in pterygium development remain only partially delineated. Among these, MMP1, -2, and -9 have been consistently reported to facilitate the enzymatic degradation of Bowman's layer, a critical step that promotes angiogenesis and enables the progressive extension of the lesion onto the corneal surface (16-18). Both MMP2 and MMP9 have been further associated with active ECM remodeling and the stimulation of neovascularization (19). In vitro investigations by Solomon *et al.* (20) and Li *et al.* (21) demonstrated that the proinflammatory cytokines interleukin-1β and tumor necrosis factor-α significantly increased the transcription and protein levels of MMP1 and MMP3 in primary fibroblast cultures derived from pterygium tissue (20, 21). At around the same time, Di Girolamo and colleagues provided the first experimental evidence for the overexpression of MMP7 in cultured pterygium specimens (22). Subsequent comprehensive profiling confirmed the upregulation of a broader array of MMPs, including MMP1, -2, -3, -7, -8, -9, and -14, in excised pterygium tissues (23). Moreover, transcriptomic studies using microarray platforms revealed that UV-induced stress enhances MMP9 expression, thereby accelerating pterygium progression (24, 25). One proposed mechanism involves post-transcriptional regulation by the RNA-binding protein human antigen R, which stabilizes *MMP9* mRNA in response to interleukin-1β, amplifying its proinflammatory and pro-invasive effects (26). It was also

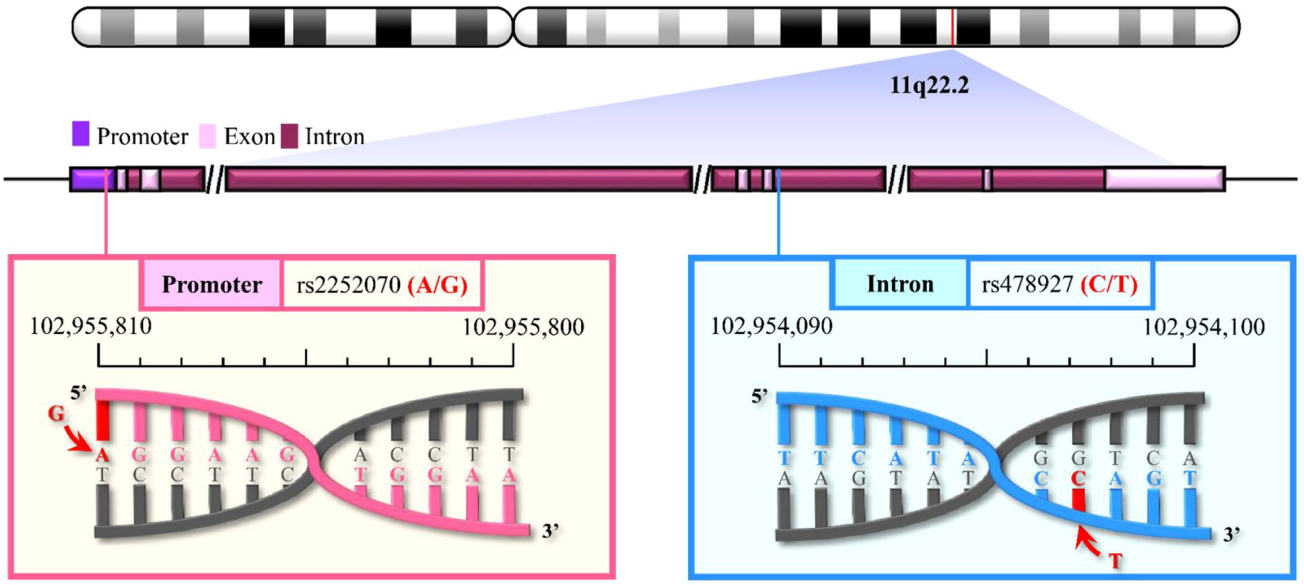

Figure 1. *Physical map of matrix metalloproteinase-13 rs2252070 and rs478927 polymorphic sites.*

shown that fibroblasts migrating within pterygium lesions express significantly elevated levels of MMP3 and MMP13 (27). This finding introduces MMP13, a relatively underexplored member of the MMP family, as a potential player in the pathogenesis of pterygium, warranting further functional and mechanistic investigation.

MMP13, also known as collagenase-3, is encoded by the *MMP13* gene located at chromosome 11q22 (28). This enzyme possesses broad substrate specificity, capable of degrading not only fibrillar collagens but also a range of non-collagenous ECM components, including fibronectin and laminin (29). Although the proteolytic activity and involvement of MMP13 in tissue remodeling are well documented (30), its genetic contributions to ocular surface disorders remain largely unexplored. Notably, to our knowledge, no prior investigations have assessed the potential role of *MMP13* polymorphisms in modulating susceptibility to pterygium. To address this knowledge gap, we conducted the first hospital-based, case–control study aimed at elucidating the association between *MMP13* genetic variants and the risk of developing pterygium in a Taiwanese population. The study cohort comprised 160 clinically diagnosed pterygium cases and 320 age- and sex-matched controls without a history of pterygium. We specifically genotyped two single nucleotide polymorphisms within the *MMP13* locus, one located in the promoter region (rs2252070) and another within an intronic region (rs478927) (Figure 1).

Materials and Methods

Recruitment of study participants. The enrollment of participants with and without pterygium was conducted under a study protocol approved by the Institutional Review Board of China Medical University Hospital (no. CMUH111-REC1-176). The study design, including its objectives, hypotheses, and experimental procedures, underwent rigorous ethical and methodological review. Written informed consent was obtained from the parents or legal guardians of all participants prior to inclusion in the study. A total of 160 individuals clinically diagnosed with pterygium were recruited, along with a control group comprising 320 individuals without a history of the disease. All participants were ethnic Taiwanese and voluntarily completed a structured questionnaire capturing demographic and lifestyle data. Additionally,

Table I. *Demographics of the pterygium cases and individuals without pterygium.*

Characteristic		Non-pterygium controls (N=320)	Pterygium cases (N=160)	*p*-Value
Age, years	Mean±SD	61.4±7.8	61.5±7.3	0.9006[a]
	<60 Years, n (%)	125 (39.1%)	72 (45.0%)	0.2509[b]
	≥60 Years, n (%)	195 (60.9%)	88 (55.0%)	
Sex, n (%)	Male	182 (56.9%)	91 (56.9%)	1.0000[b]
	Female	138 (43.1%)	69 (43.1%)	

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

Table II. *The primer sequences, methodologies for identifying matrix metalloproteinase-13 rs2252070 and rs478927 polymorphic genotypes.*

Polymorphic site (rs number)	Primer sequences	Restriction endonuclease	Polymorphic genetic pattern	DNA fragment size (bp)
rs2252070	F: 5'-GTCATGGAGCTTGCTGCATT-3'	*BsrI*	A	527
	R: 5'-CGTGAACTTCAGGTAGACAC-3'		G	115+412
rs478927	F: 5'-CTCAAGCCACAGTGACAGAT-3'	*SpeI*	C	410
	R: 5'-ACCTGTGCTAAGTACTCCTG-3'		T	167+243

F: Forward; R: reverse.

peripheral blood samples were collected from each individual for subsequent genetic analysis. To ensure the integrity of the control group, stringent exclusion criteria were applied. Individuals with a prior medical history of pterygium, endometriosis, uterine leiomyoma, or any form of malignancy were not eligible for inclusion. An overview of the demographic characteristics of the case and control groups is presented in Table I.

MMP13 genotyping processes. Following the acquisition of informed consent, each participant provided a peripheral blood sample (3-5 ml), from which genomic DNA was extracted from leukocytes within 12 h of collection. The isolated DNA was diluted and aliquoted for short-term storage at −20˚C in accordance with previously validated protocols (31, 32). The genotyping methodology for *MMP13* was established at the Terry Fox Cancer Research Laboratory and included the design of specific primers, selection of restriction enzymes, and optimization of polymerase chain reaction (PCR) conditions. Detailed information on primer sequences, enzymes used, and the expected sizes of DNA fragments before and after enzymatic digestion is summarized in Table II. PCR amplification was performed using a T100 Thermal Cycler (Bio-Rad, Hercules, CA, USA) under the following cycling parameters: an initial denaturation at 94˚C for 5 minutes; followed by 35 cycles of 94˚C for 30 s (denaturation), 59˚C for 30 s (annealing), and 72˚C for 30 s (extension); and a final elongation step at 72˚C for 10 min. The resulting PCR products corresponding to *MMP13* rs2252070 and rs478927 loci were digested with *BsrI* and *SpeI*, respectively, and separated on a 3% agarose gel to determine genotype-specific fragment patterns.

Statistical analysis. Comparative analyses of continuous variables between case and control groups were performed using the unpaired Student's *t*-test to assess significant differences in means. Genotypic and allelic distributions of *MMP13* polymorphisms between individuals with and without pterygium were evaluated using the Pearson chi-square test based on two-sided contingency tables. To estimate the strength of association between *MMP13* variants and pterygium risk, odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated. All statistical tests were two-tailed, and a *p*-value of less than 0.05 was considered statistically significant.

Table III. *Genotypic frequency distributions of matrix metalloproteinase-13 polymorphisms among the pterygium cases and individuals without pterygium.*

Polymorphism	Genotype	Cases, n (%)	Controls, n (%)	OR (95% CI)	*p*-Value[a]
rs2252070	AA	53 (33.1)	91 (28.4)	1.00 (Reference)	
	AG	68 (42.5)	146 (45.6)	0.80 (0.51-1.25)	0.3829
	GG	39 (24.4)	83 (26.0)	0.81 (0.48-1.34)	0.4856
	p_{trend}				0.5720
	p_{HWE}				0.1199
	AA	53 (33.1)	91 (28.4)	1.00 (Reference)	
	AG+GG	107 (66.9)	229 (71.6)	0.80 (0.53-1.21)	0.3417
	AA+AG	121 (75.6)	237 (74.0)	1.00 (Reference)	
	GG	39 (24.4)	83 (26.0)	0.92 (0.59-1.43)	0.7953
rs478927	CC	54 (33.8)	95 (29.7)	1.00 (Reference)	
	CT	71 (44.3)	148 (46.3)	0.84 (0.54-1.31)	0.5172
	TT	35 (21.9)	77 (24.0)	0.80 (0.48-1.35)	0.4777
	p_{trend}				0.6479
	p_{HWE}				0.1974
	CC	54 (33.8)	95 (29.7)	1.00 (Reference)	
	CT+TT	106 (66.2)	225 (70.3)	0.83 (0.55-1.24)	0.4224
	CC+CT	125 (78.1)	243 (76.0)	1.00 (Reference)	
	TT	35 (21.9)	77 (24.0)	0.88 (0.56-1.39)	0.6747

CI: Confidence interval; OR: odds ratio. [a]Based on chi-square test with Yates' correction; p_{trend}: From trend analysis; p_{HWE}: Based on fitness with Hardy–Weinberg equilibrium.

Results

Age and sex matching between case and control groups. Preliminary analyses revealed no statistically significant difference in mean age between individuals diagnosed with pterygium and those in the control group (p=0.9006). This finding remained consistent even when participants were stratified by age using 60 years as a cutoff threshold (p=0.2509). This shows the rigorous sex matching employed during participant selection resulted in identical sex distribution for the two groups (p=1.0000), ensuring methodological robustness and minimizing selection bias.

Association between MMP13 genotypic variants and pterygium susceptibility. The genotypic frequencies of *MMP13* rs2252070 and rs478927 polymorphisms in the control group were consistent with those under Hardy–Weinberg equilibrium (p=0.1199 and 0.1974, respectively; Table III), supporting the validity of the genotyping results. Among pterygium cases, the distribution of *MMP13* rs2252070 genotypes was 33.1% AA, 42.5% AG, and 24.4% GG. These frequencies closely mirrored those observed in the control group, of 28.4%, 45.6%, and 26.0%, respectively, with no significant trend detected across genotypes (p for trend=0.5720).

Using the AA genotype as the reference, the ORs for individuals with AG and GG genotypes were 0.80 (95% CI=0.51-1.25, p=0.3829) and 0.81 (95% CI=0.48-1.34, p=0.4856), respectively (Table III, upper section). Under the dominant genetic model (AG+GG *vs.* AA), carriers of at least one G allele exhibited a non-significant 0.80-fold reduced risk of developing pterygium (95% CI=0.53-1.21, p=0.3417). Similarly, under the recessive model (GG *vs.* AA+AG), the GG genotype was associated with a 0.92-fold risk compared to carriers of the A allele (95% CI=0.59-1.43, p=0.7953) (Table III, upper section). For the *MMP13* rs478927 variant, similarly no significant differences in genotypic distributions were observed between cases and controls under any inheritance model, co-dominant, dominant, or recessive (all p>0.05) (Table III, lower section).

Table IV. *Allelic frequencies for matrix metalloproteinase-13 polymorphisms among the pterygium cases and healthy individuals of this study.*

Polymorphism	Allele	Cases, n (%)	Controls, n (%)	OR (95% CI)	*p*-Value[a]
rs2252070	A	174 (54.4)	328 (51.3)	1.00 (Reference)	
	G	146 (45.6)	312 (48.7)	0.88 (0.67-1.15)	0.8959
rs478927	C	179 (55.9)	338 (52.8)	1.00 (Reference)	
	T	141 (44.1)	302 (47.2)	0.88 (0.67-1.15)	0.3970

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

Table V. *Distribution of matrix metalloproteinase-13 rs2252070 genotypes among 160 pterygium cases and 320 non-pterygium controls after stratification by age.*

	<60 Years, n (%)				≥60 Years, n (%)			
Genotype	Controls	Cases	OR (95% CI)	*p*-Value[a]	Controls	Cases	OR (95% CI)	*p*-Value[a]
AA	38 (30.4)	22 (30.6)	1.00 (Reference)		53 (27.2)	31 (35.2)	1.00 (Reference)	
AG	52 (41.6)	31 (43.0)	1.03 (0.52-2.05)	0.9335	94 (48.2)	37 (42.1)	0.67 (0.38-1.21)	0.2372
GG	35 (28.0)	19 (26.4)	0.94 (0.44-2.02)	0.8092	48 (24.6)	20 (22.7)	0.71 (0.36-1.41)	0.4237
Total	125	72			195	88		
p_{trend}				0.9673				0.3848

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

Association between MMP13 allelic variants and pterygium susceptibility. Allelic frequency analysis revealed no significant association between either MMP13 rs2252070 or rs478927 variants and the risk of developing pterygium. Specifically, the presence of the rs2252070 G allele did not significantly alter susceptibility when compared to the wild-type A allele (OR=0.88, 95% CI=0.67-1.15, p=0.8959; Table IV, upper section). Likewise, for the rs478927 polymorphism, carriers of the variant T allele exhibited no statistically significant difference in risk relative to the wild-type C allele (OR=0.88, 95% CI=0.67-1.15, p=0.3970; Table IV, lower section).

Association between MMP13 genotypes and age or sex in relation to pterygium risk. To explore potential effect modification by demographic factors, stratified analyses were conducted to assess interactions between *MMP13* rs2252070 and rs478927 genotypes with age and sex in relation to pterygium susceptibility. No statistically significant associations were identified between rs2252070 genotypes and pterygium risk when stratified by either age or sex (all p>0.05; Table V and Table VI). Similarly, for rs478927, genotype-specific risk did not significantly differ across age or sex subgroups (all p>0.05; Table VII and Table VIII). These findings suggest that neither age nor sex modifies the relationship between *MMP13* variants and pterygium risk in this Taiwanese cohort.

Discussion

There remains considerable debate among ophthalmologists and translational medical scientists regarding the precise molecular mechanisms driving pterygium development. A widely supported hypothesis posits that disruptions in the homeostasis of ECM components play a central role in pterygium pathogenesis, with MMPs and their endogenous inhibitors critically regulating ECM remodeling. MMPs have been implicated not only in pterygium but also across a spectrum of malignancies, highlighting their versatile involvement in tissue remodeling and pathological invasion (33-36). Nonetheless, the specific functional roles of individual MMPs in pterygium remain incompletely

Table VI. *Distribution of matrix metalloproteinase-13 rs2252070 genotypes among 160 pterygium cases and 320 non-pterygium controls after stratification by sex.*

	Males, n (%)				Females, n (%)			
Genotype	Controls	Cases	OR (95% CI)	*p*-Value[a]	Controls	Cases	OR (95% CI)	*p*-Value[a]
AA	49 (26.9)	29 (31.9)	1.00 (Reference)		42 (30.4)	24 (34.8)	1.00 (Reference)	
AG	84 (46.2)	37 (40.7)	0.74 (0.41-1.36)	0.4172	62 (44.9)	31 (44.9)	0.88 (0.45-1.70)	0.8207
GG	49 (26.9)	25 (27.4)	0.86 (0.44-1.68)	0.7889	34 (24.7)	14 (20.3)	0.72 (0.32-1.60)	0.5461
Total	182	91			138	69		
p_{trend}				0.6253				0.7234

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

Table VII. *Distribution of matrix metalloproteinase-13 rs478927 genotypes among 160 pterygium cases and 320 non-pterygium controls after stratification by age.*

	<60 Years, n (%)				≥60 Years, n (%)			
Genotype	Controls	Cases	OR (95% CI)	*p*-Value[a]	Controls	Cases	OR (95% CI)	*p*-Value[a]
CC	36 (28.8)	22 (30.6)	1.00 (Ref)		59 (30.3)	32 (36.4)	1.00 (Ref)	
CT	60 (48.0)	35 (48.6)	0.95 (0.49-1.87)	0.8925	88 (45.1)	36 (40.9)	0.75 (0.42-1.35)	0.4197
TT	29 (23.2)	15 (20.8)	0.85 (0.37-1.92)	0.8481	48 (24.6)	20 (22.7)	0.77 (0.39-1.51)	0.5524
Total	125	72			195	88		
p_{trend}				0.9204				0.5946

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

Table VIII. *Distribution of matrix metalloproteinase-13 rs478927 genotypes among 160 pterygium cases and 320 non-pterygium controls after stratification by sex.*

	Males, n (%)				Females, n (%)			
Genotype	Controls	Cases	OR (95% CI)	*p*-Value[a]	Controls	Cases	OR (95% CI)	*p*-Value[a]
CC	53 (29.1)	29 (31.9)	1.00 (Reference)		42 (30.4)	25 (36.2)	1.00 (Reference)	
CT	90 (48.5)	44 (48.3)	0.89 (0.50-1.59)	0.8155	58 (42.0)	27 (39.1)	0.78 (0.40-1.53)	0.5866
TT	39 (21.4)	18 (19.8)	0.84 (0.41-1.73)	0.7780	38 (27.6)	17 (24.7)	0.75 (035-1.60)	0.5828
Total	182	91			138	69		
p_{trend}				0.8841				0.6987

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

characterized. Previous investigations have documented overexpression of multiple MMP family members in pterygium tissues, including MMP1 (20, 21, 37-39), MMP2 (37), MMP3 (20, 21, 37), MMP9 (40), MMP10 (40), MMP14 (41). Despite these insights, research on other MMP family members remains limited, often constrained by small sample sizes. Moreover, the scarcity of well-characterized genetic markers for pterygium is compounded by challenges in obtaining sufficient tissue specimens and appropriate control samples. In recent years, our research group has systematically examined the genotypic profiles of several MMPs, including *MMP1* (42), *MMP2* (43), *MMP7* (44), *MMP8* (45), *MMP9* (46) and *MMP11* (47), within a representative Taiwanese pterygium cohort. Notably, our

findings identified the *MMP1* rs1799705 2G and *MMP11* rs738792 C alleles as potential predictive biomarkers for pterygium susceptibility (42, 47).

The *MMP13* rs2252070 single nucleotide polymorphism is the result of consolidation of many other designations, including rs2119649325, rs2119649320, rs2119649300, rs2119649296, rs386562614 rs58991848, rs17860523, and rs17174356 (48); the *MMP13* rs478927 polymorphism was similarly merged from rs61236945 and rs17860532 (49).

To date, as far as we are aware, the genetic involvement of *MMP13* in pterygium pathogenesis has not been investigated. In this study, we conducted the first comprehensive analysis examining the association between *MMP13* polymorphisms, namely the promoter variant rs2252070 and the intronic variant rs478927, and pterygium susceptibility in a well-characterized Taiwanese cohort consisting of 160 pterygium patients and 320 matched controls (Table I). Genotyping results demonstrated no significant association between either heterozygous or homozygous genotypes of *MMP13* rs2252070 or rs478927 and altered risk of developing pterygium (Table III). These findings were corroborated by allelic frequency analyses (Table IV). Furthermore, stratified analyses revealed no significant interaction effects between *MMP13* genotypes and demographic factors such as age or sex in relation to pterygium risk (Table V, Table VI, Table VII and Table VIII). To our knowledge, this study represents the first global effort to evaluate the potential genetic contribution of *MMP13* to pterygium susceptibility. However, no positive associations or genotype-demographic interactions were identified.

In our Taiwanese cohort, the observed frequency of the variant G allele at rs2252070 was 48.70%, closely matching the 48.38% reported for 1,170 East Asians in the 1000 Genomes Project Phase 3 dataset (48). However, it exhibits considerable variation across ethnic groups. For instance, the frequency of the G allele at *MMP13* rs2252070 is reportedly 28.00% out of 1,786 Africans, 29.94% from 1,266 Europeans, and 35.00% out of 980 Americans (49). Several studies have implicated the *MMP13* rs2252070 G allele in susceptibility to diverse diseases, including ovarian cancer (50), esophageal cancer (51), oral/oropharyngeal cancer (52), lung cancer (53), colorectal cancer (54), and endometriosis (55). In contrast, the MMP13 rs478927 polymorphism, merged from rs61236945 and rs17860532, has been scarcely investigated. To date, only a single study has reported a significant association between the rs478927 TT genotype and an increased risk of dental caries (56). It is important to emphasize that these associations were identified in disease contexts other than pterygium. These ethnic differences and disease-specific findings underscore the need for further investigations of *MMP13* genetic variants in diverse populations to validate their potential role as risk factors for pterygium beyond the Taiwanese cohort.

As previously noted, migrating fibroblasts within pterygium lesions have been shown to exhibit markedly elevated expression of both MMP3 and MMP13 (27). However, investigations directly assessing MMP13 expression or function in primary pterygium tissues remain lacking. The complex interplay within the MMP network is intriguing but not yet fully elucidated. For example, MMP3 functions as a critical activator of several pro-MMPs, including MMP1, MMP7, MMP9, and MMP13, thereby facilitating ECM remodeling, cell migration, and tissue restructuring processes (57, 58). Furthermore, exploring genotype–phenotype correlations involving *MMP13* polymorphisms rs2252070 and rs478927 holds considerable promise for elucidating molecular mechanisms underlying human diseases beyond pterygium.

In summary, neither *MMP13* rs2252070 nor rs478927 genotypes were found to be significantly associated with altered susceptibility to pterygium. Moreover, no combined effects of these genotypes with age or sex were observed in relation to pterygium risk. These results indicate that *MMP13* genetic variants may have a less prominent role in pterygium pathogenesis compared to other MMP family members and are unlikely to serve as

reliable biomarkers for early detection. Future investigations should prioritize other MMPs to identify genetic markers that might facilitate early prediction and diagnosis of pterygium.

Conflicts of Interest

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

Authors' Contributions

Funding acquisition: NYH, HCC, and PSH and TCH; supervision: DTB and CWT; experimental work: YCW, HYS, PSH and WSC; validation: HCC, CWT and PSH; statistical analysis: TCH and HCC; writing – original draft: HCC, NYH, CWT and DTB; writing – review and editing: CWT and DTB.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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