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Original Article

Genetic analysis of TGFBI variants in the Taiwanese population: from granular corneal dystrophy type 1 to a broader phenotypic spectrum

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Abstract: Objectives: Granular corneal dystrophy type 1 (GCD1) is an autosomal dominant hereditary corneal disorder caused by pathogenic variants in the TGFBI gene. However, the population distribution of TGFBI (Transforming Growth Factor Beta Induced) variants in Taiwan remains incompletely characterized. This study aimed to investigate the spectrum and population frequency of coding variants in TGFBI within the Taiwanese population using genomic data from the Taiwan Biobank. Methods: Whole genome sequencing (WGS) data from Taiwan Biobank participants were analyzed to identify exonic single-nucleotide polymorphisms (SNPs) causing coding sequence alterations in the TGFBI gene. Allele frequencies were estimated and compared against probe-based SNP array data and East Asian population reference data from the 1000 Genomes Project. Phenotypic information was obtained from self-reported questionnaire data available within the Taiwan Biobank. Results: A total of 22 exonic SNPs causing coding sequence alterations were identified in TGFBI. One variant, rs121909212 (p.P501T) was observed at a notably higher allele frequency (0.003) compared to other identified variants. The estimated allele frequency of rs121909212 in the Taiwanese population was approximately 0.003, which is comparable to the frequency reported in the Japanese population. Furthermore, WGS-based allele frequency estimates showed greater consistency with reference population data than SNP array-based genotyping. Conclusions: Our findings provide a population-level overview of TGFBI coding variation in the Taiwanese population and identify rs121909212 as a rare variant prevalent in East Asian populations. The study also highlights the utility of WGS for accurately characterizing rare pathogenic variants in population-scale genomic datasets.

Keywords: Granular corneal dystrophy type I, growth factor beta-induced, SNP array, Taiwan Biobank, Whole genome sequencing

Introduction

Groenouw type I, also known as granular corneal dystrophy type 1 (GCD1), is an autosomal dominant genetic disorder characterized by scattered, well-defined protein deposits within the corneal stroma that gradually impair visual function [1]. Clinically, GCD1 presents as bilateral, symmetrical granular opacities, primarily located in the central cornea. Under slit-lamp biomicroscopy, these diagnostically significant lesions appear as small, white-to-gray deposits, resembling “breadcrumbs” or “snowflakes” in appearance. The natural course of this dystrophy involves the continuous accumulation and fusion of stromal deposits, leading to increased optical density and ultimately a significant decrease in visual acuity, often accompanied by photophobia due to impaired corneal transparency [2]. The molecular pathogenesis of GCD1 is attributed primarily to pathogenic mutations in the transforming growth factor β-induced gene- Transforming Growth Factor Beta Induced (*TGFBI*), located on chromosome 5q31 [3, 4]. The *TGFBI* gene encodes a protein called keratoepithelin (also known as Big-h3 or βig-h3). Keratoepithelin is a secreted extracellular matrix protein that plays a crucial regulatory role in corneal homeostasis and stromal structure by interacting with various matrix

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components, including collagen fibers, fibronectin, and other structural glycoproteins [5-7]. This protein is a major mediator of corneal transparency, promoting the proper organization of the extracellular matrix and regulating cell adhesion processes essential for corneal structural integrity.

The diagnosis of GCD1 is determined through a combination of clinical assessment and auxiliary diagnostic methods. Slit-lamp biomicroscopy is the primary diagnostic technique for identifying characteristic stromal deposits. Molecular genetic analysis targeting *TGFBI* mutations provides definitive diagnostic confirmation, helps to accurately differentiate it from phenotypically similar dystrophies, and allows for comprehensive genetic counseling for affected individuals and their families [8, 9]. Contemporary treatment strategies for Groenouw type I employ a stepwise approach, focusing primarily on symptom relief and visual rehabilitation. Initial management typically involves conservative interventions, such as optical correction with glasses or specialized contact lenses, to optimize remaining vision [10-12]. However, progressive disease with significant visual impairment often requires surgical intervention through various corneal procedures. Surgical options include: phototherapeutic keratectomy (PTK) targeting superficial lesions [13]; deep anterior lamellar keratoplasty (DALK) for cases requiring stromal replacement while preserving endothelial function [14]; and penetrating keratoplasty (PKP) for advanced cases involving full-thickness corneal replacement [15]. While these surgeries show initial efficacy in restoring corneal transparency and improving visual outcomes, long-term prognosis remains guarded due to the inherent tendency for stromal deposits to recur. This recurrence is attributed to an underlying genetic defect in TGFBI, which leads to the persistent production of abnormal protein deposits in transplanted or treated corneal tissue, thus requiring repeated interventions and ongoing clinical monitoring.

Several cases of GCD1 have been reported in the Taiwanese population, providing valuable insights into the genetic heterogeneity and clinical spectrum of this disease in East Asian populations. For example, Chen et al. reported a comprehensive case study in 2003 involving a 45-year-old female patient who presented with bilateral visual impairment and recurrent ocular discomfort during adolescence [16]. This patient's ophthalmological examination revealed numerous diffuse granular opacities distributed in the superficial corneal stroma. Family history revealed that three of her male offspring also had similar symptoms and clinical presentations, consistent with an autosomal dominant inheritance pattern. The clinical diagnosis was established as autosomal dominant granular dystrophy based on its characteristic phenotype and familial aggregation. Subsequently, molecular genetic analysis of two affected family members, using single-strand conformation polymorphism (SSCP) and direct DNA sequencing, identified a pathogenic R555W mutation in the *TGFBI* protein. In 2012, the same research team conducted a broader generational study encompassing eleven patients diagnosed with granular corneal dystrophy disease from nine unrelated families. These patients exhibited phenotypic heterogeneity, presenting with diverse punctate or spotted opacities, while sharing core clinical features. Additionally, comprehensive genetic analysis of the *TGFBI* gene revealed two distinct pathogenic variants: the R124H mutation was identified in five families, while the R555W mutation was detected in four families [17].

To further characterize the spectrum of genetic variation in the *TGFBI* gene in the Taiwanese population, we used comprehensive whole genome sequencing data and SNP array from the Taiwan Biobank. Through systematic analysis of the complete TGFBI coding region, this study aimed to characterize the genetic variation landscape of TGFBI and identify candidate variants of potential clinical relevance, which may warrant further investigation as susceptibility alleles in the Taiwanese population.

Materials and methods

The Taiwan Biobank is a comprehensive repository that collects a large amount of health-related data and biological samples from individuals in Taiwan [18, 19]. This population-based biobank aims to promote biomedical research and precision medicine in Taiwan. To investigate the mutation spectrum of GCD1 and *TGFBI*, we selected single-nucleotide polymorphisms (SNPs), obtained from SNP array or whole-genome sequencing (WGS), of the TGFBI gene from the Taiwan Biobank. For WGS quality control, SNPs selected from VCF (variant call file) were based on the Depth (Reads coverage) ≥ 30, GQ (Genotype Quality) ≥ 20, QD (QualByDepth) ≤ 2.0, and QUAL (Quality) ≤ 30.

Table 1. Nonsynonymous SNPs of TGFBI in Taiwan biobank

Chr	Pos	dbSNP ID	Ref	Alt	ExonicFuncChange	AAChange
chr5	136033818	rs767980992	A	C	nonsynonymous	exon2:c.A190C:p.N64H
chr5	136046343	rs774697241	C	A	nonsynonymous	exon4:c.C307A:p.L103I
chr5	136046358	rs188322933	G	A	nonsynonymous	exon4:c.G322A:p.E108K
chr5	136046403	rs541270955	G	C	nonsynonymous	exon4:c.G367C:p.D123H
chr5	136046482	rs76212104	C	T	nonsynonymous	exon4:c.C446T:p.A149V
chr5	136046862	rs558785543	C	G	nonsynonymous	exon5:c.C471G:p.D157E
chr5	136046905	rs374172528	C	T	nonsynonymous	exon5:c.C514T:p.R172C
chr5	136046953	rs753369803	G	A	nonsynonymous	exon5:c.G562A:p.G188S
chr5	136047283	rs1224788277	G	T	nonsynonymous	exon6:c.G634T:p.V212L
chr5	136047310	rs533509858	G	A	nonsynonymous	exon6:c.G661A:p.D221N
chr5	136047340	rs755263822	C	T	nonsynonymous	exon6:c.C691T:p.L231F
chr5	136049494	rs757860567	C	T	nonsynonymous	exon7:c.C827T:p.T276M
chr5	136053021	rs770981462	T	A	nonsynonymous	exon8:c.T1028A:p.M343K
chr5	136053972	rs747929238	T	A	nonsynonymous	exon9:c.T1156A:p.S386T
chr5	136053991	rs534142584	T	C	nonsynonymous	exon9:c.T1175C:p.I392T
chr5	136054017	rs750693052	G	A	nonsynonymous	exon9:c.G1201A:p.G401S
chr5	136054742	rs554088498	A	G	nonsynonymous	exon10:c.A1291G:p.T431A
chr5	136054763	rs148555720	C	T	nonsynonymous	exon10:c.C1312T:p.H438Y
chr5	136055708	rs192398905	C	T	nonsynonymous	exon11:c.C1439T:p.A480V
chr5	136055770	rs121909212	C	A	nonsynonymous	exon11:c.C1501A:p.P501T
chr5	136055803	rs370523274	G	A	nonsynonymous	exon11:c.G1534A:p.D512N
chr5	136059131	rs1459036254	G	A	nonsynonymous	exon13:c.G1720A:p.G574S

Due to mutation effects are characterized easily when occur in the coding region (exon), which encodes the amino acid sequence of the protein. Synonymous mutations SNPs (protein residues would not change) were filtered out, leaving only nonsynonymous variants (protein residues would change), which result in an alteration in the amino acid sequence of the encoded protein.

After identifying these variants, additional gene-related information, including population frequency, clinical classification, and predicted effects on protein function, was annotated using ANNOVAR software (version 2023Nov2) [20, 21]. Population frequencies including African, American, East Asian, European, and South Asian were compared using the 1000 Genomes Project build in 2015Aug [22]. Clinical classifications followed ClinVar (2024 version) records [23, 24]. Functional damage predictions for protein variants were made using SIFT version 2022 Mar [25], PolyPhen-2 version 2021 Jul 2 [26], and CADD version 2024 Feb 2 [27].

Genotype counts were performed based on the genetic combinations (AA, Aa, and aa). For the calculation of population allele frequency, the following equation formulas:

$$Frequency = \frac{Counts\ of\ Minor\ Allele}{Counts\ of\ Minor\ Allele + Counts\ of\ Major\ Allele}$$

Fisher's exact test was used to compare allele frequencies, with all statistical computations performed using R version 4.3.3. Phenotypic data were extracted from self-reported questionnaires collected during enrollment in the Taiwan Biobank. Participants provided medical histories, including diagnosed ocular conditions; for each identified carrier, specific responses regarding visual impairment and cataract formation were reviewed.

Results

Comprehensive genomic analysis of the Taiwan Biobank dataset identified 22 SNPs characterized as missense variants within the TGFBI gene, localized to chromosomal region 5q31 (**Table 1**). The identified variants include rs767980992, rs774697241, rs188322933, rs541270955, rs76212104, rs558785543, rs374172528, rs753369803, rs1224788277, rs533-

Table 2. Clinvar profile and effects prediction of TGFBI nonsynonymous SNPs from Taiwan biobank

Chr	Pos	rsID	Ref	Alt	Clinvar	SIFT	Polyphen2	CADD
chr5	136033818	rs767980992	A	C	.	D	D	25.6
chr5	136046343	rs774697241	C	A	.	T	D	23.7
chr5	136046358	rs188322933	G	A	.	T	B	26.4
chr5	136046403	rs541270955	G	C	.	D	D	28.6
chr5	136046482	rs76212104	C	T	.	T	P	18.5
chr5	136046862	rs558785543	C	G	.	T	D	24.5
chr5	136046905	rs374172528	C	T	.	D	D	35.0
chr5	136046953	rs753369803	G	A	.	D	D	33.0
chr5	136047283	rs1224788277	G	T	.	D	D	26.7
chr5	136047310	rs533509858	G	A	.	T	D	24.3
chr5	136047340	rs755263822	C	T	.	D	D	29.9
chr5	136049494	rs757860567	C	T	.	D	D	28.8
chr5	136053021	rs770981462	T	A	.	T	B	13.6
chr5	136053972	rs747929238	T	A	.	T	D	21.6
chr5	136053991	rs534142584	T	C	.	T	B	4.5
chr5	136054017	rs750693052	G	A	.	T	B	3.2
chr5	136054742	rs554088498	A	G	.	D	B	1.8
chr5	136054763	rs148555720	C	T	Likely benign	D	D	32.0
chr5	136055708	rs192398905	C	T	.	T	P	16.8
chr5	136055770	rs121909212	C	A	Pathogenic	D	D	25.7
chr5	136055803	rs370523274	G	A	.	T	P	26.6
chr5	136059131	rs1459036254	G	A	.	T	P	23.6

D = Deleterious, T = Tolerated, P = Possibly damaging, B = Benign.

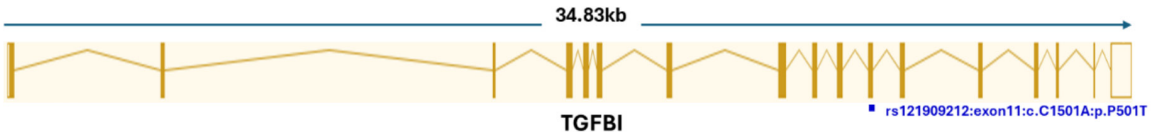

Figure 1. Genetic relationships of rs121909212 in TGFBI. The bold gold line represents the exons, and the thin golden line is introns. The blue line indicates the TGFBI gene transcription direction from left to right. SNP rs121909212 is located on exon 11; the transcription change is c.1501 C > A, and the protein change is p.P501T.

509858, rs755263822, rs757860567, rs770981462, rs747929238, rs534142584, rs750693052, rs554088498, rs148555720, rs192398905, rs121909212, rs370523274, and rs1459036254, all resulting in amino acid substitutions within the TGFBI protein sequence.

Pathogenicity assessment utilizing the ClinVar database and computational prediction algorithms, including SIFT, PolyPhen-2, and CADD scores, revealed that only variant rs121909212 demonstrated both an established pathogenic classification and high predicted deleterious functional effects (SIFT = Damaging, PolyPhen-2 = Probably Damaging, CADD score > 15) (**Table 2**). Detailed structural analysis using reference transcript ENST00000221930.6 indicated that this variant is located within exon 11, resulting in a nucleotide change of c.1501C > A and consequent amino acid substitution p.P501T at residue 501 of the TGFBI protein sequence (**Figure 1**).

Additionally, several variants lacking ClinVar pathogenic annotations nonetheless demonstrated high predicted deleterious effects based on computational analyses (rs767980992, rs541270955, rs374172528, rs753369803, rs1224788277, rs755263822, and rs757860567). Furthermore, the variant rs148555720, despite being classified as “Likely Benign” in ClinVar, still exhibited a high predictive molecu-

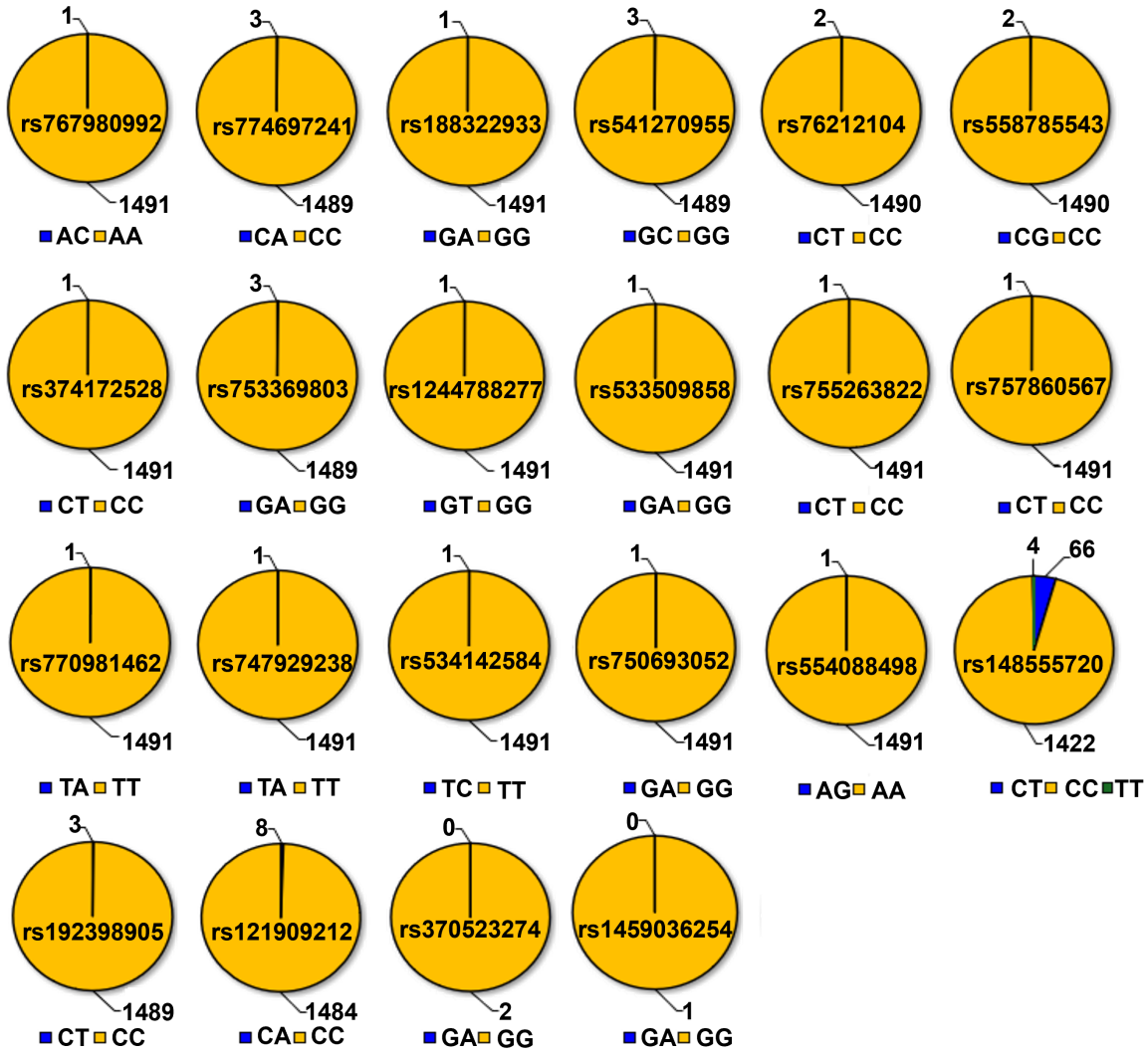

Figure 2. Genotype of TGFBI SNPs. Only rs148555720 exhibits a homozygous mutation (TT) and a higher count of heterozygous (CT) genotypes than other variants. The potential risk variant, rs121909212, has 8 heterozygotes, which is more frequent than other identified SNPs.

Table 3. Allele frequency of rs121909212 in TW biobank by a different screening platform

Allele count	SNP Array	WGS[a]	*p*-value[b]
C	13535	2976	< 0.001
A	475	8	
Frequency	0.035	0.003	

[a]Whole Genome Sequencing. [b]Calculated by Fisher's Exact Test.

lar effect (SIFT = Damaging, PolyPhen-2 = Probably Damaging, CADD > 30). This discrepancy necessitates additional functional validation studies to resolve these conflicting assessments.

Genotypic distribution analysis showed that, except for rs148555720, all identified variants presented in a heterozygous inheritance pattern, consistent with autosomal dominant inheritance (**Figure 2**). Notably, all heterozygous variants, except for rs121909212, had low carrier frequencies in the study population. Comparative analysis of the allele frequencies of rs121909212 using different genotyping platforms revealed differences. Among the 1,492 and 7,005 test samples obtained from WGS and array, respectively and the frequency of rs121909212 in probe-based frequencies is higher than in whole-genome sequencing (**Table 3**). The difference between these two plat-

Study	Population	Group	Sample Size	Ref Allele	Alt Allele
1000Genomes	Global	Study-wide	5008	C=0.9996	A=0.0004
1000Genomes	Arican	Sub	1322	C=1.0000	A=0.0000
1000Genomes	East Asian	Sub	1008	C=0.9980	A=0.0020
1000Genomes	European	Sub	1006	C=1.0000	A=0.0000
1000Genomes	South Asian	Sub	978	C=1.0000	A=0.0000
1000Genomes	American	Sub	694	C=1.0000	A=0.0000

Figure 3. Allele frequency of rs121909212 across different populations. Only East Asian populations present the C > A mutation.

Table 4. Eye Health of TW Biobank in participants with rs121909212

ID	Age	Sex	Genotype	Eye health of questionnaire
NGS1	33	M	A C	Blind
NGS2	34	M	A C	NA
NGS3	58	F	A C	NA
NGS4	69	F	A C	Cataract
NGS5	34	F	A C	NA
NGS6	63	M	A C	Xerophthalmia
NGS7	30	F	A C	Xerophthalmia
NGS8	61	M	A C	Allergic conjunctivitis

forms was significant by Fisher's Exact Test ($p < 0.001$).

Population genetic comparisons with the 1000 Genomes Project reference data revealed that the WGS-derived allele frequency of rs121909212 in this study was highly consistent with that observed in East Asian populations (**Figure 3**). This suggests that this variant represents a high-risk allele specific to populations susceptible to GCD1, particularly East Asian and Taiwanese cohorts.

Because phenotypic information in the Taiwan Biobank is derived primarily from questionnaire-based data, the findings from this analysis should be interpreted as exploratory population-level observations rather than definitive clinical evidence. A clinical relevance analysis was performed on eight Taiwan Biobank participants carrying the heterozygous rs121909212 mutation. Questionnaire-based self-reported data indicated that among the eight identified variant carriers, two participants (NGS1 and NGS4) reported visual impairment and cataract formation (**Table 4**). Although these self-reported findings cannot be definitively attributed to GCD1 in the absence of a formal ophthalmologic examination, they provide preliminary population-level observations that may warrant further clinical investigation, given that pathogenic TGFBI mutations are known to cause corneal stromal deposits leading to progressive corneal opacity and visual impairment.

Discussion

The molecular pathogenic mechanism of GCD1 involves dysregulation of the TGFBI protein, leading to disruption of extracellular matrix homeostasis and impairment of cellular mechanisms essential for maintaining corneal transparency [28]. TGFBI is a key mediator in the transforming growth factor-β signaling pathway, regulating corneal cell proliferation, differentiation, and extracellular matrix biosynthesis within the corneal stroma [29-31]. Under physiologic conditions, *TGFBI* functions as an adhesion molecule, promoting the proper organization of stromal collagen fibers and maintaining the structural integrity of the corneal extracellular matrix. However, pathogenic mutations in *TGFBI* produce misfolded protein structures, altering their biochemical properties and leading to aberrant aggregation tendencies. Consequently, these mutant proteins interact abnormally with stromal components - including type I and type V collagen and fibronectin - ultimately leading to progressive protein accumulation and the formation of characteristic granular deposits within the corneal stroma [7, 32, 33].

Traditionally, histopathologic examination is used to diagnose GCD1-associated stromal deposits. It reveals characteristic hyaline material, which appears eosinophilic under hematoxylin and eosin staining and is strongly positive for periodic acid-Schiff (PAS) staining. Immunohistochemical analysis has clearly confirmed the accumulation of mutated keratoepithelin (encoded by the *TGFBI* gene) within these pathologic deposits, directly demonstrating the causal relationship between *TGFBI* mutations and the pathogenesis of corneal dystrophy

[34]. However, histopathology has limited sensitivity compared to molecular genetic diagnostic methods; therefore, it is necessary to integrate advanced genomic technologies for definitive diagnosis.

Phenotypic heterogeneity associated with *TGFBI* mutations is a particularly intriguing aspect of corneal dystrophy pathogenesis. Different pathogenic variants within the *TGFBI* are associated not only with GCD1 but also with distinct clinically recognized phenotypes, including lattice corneal dystrophy type 1 (LCD1), granular corneal dystrophy type 2 (Avellino corneal dystrophy), and Reis-Bücklers corneal dystrophy. This genotype-phenotype association indicates that specific residue substitutions confer unique biochemical properties on mutant proteins, thereby influencing the morphologic characteristics of stromal deposits and the overall clinical presentation. The molecular basis for these phenotypic differences remains an active area of research, with current studies focusing on elucidating the structure-function relationships that determine disease presentation patterns [35, 36].

Mutations in the *TGFBI* gene cause a clinically heterogeneous spectrum of inherited corneal dystrophies, all characterized by the abnormal deposition of keratoepithelin within the corneal stroma. These include granular corneal dystrophy type 1 (GCD1), lattice corneal dystrophy type IIIA (LCD IIIA), and granular corneal dystrophy type 2, among others. Although these conditions differ in the morphology and distribution of corneal deposits, they share a common molecular basis: pathogenic *TGFBI* variants that disrupt normal protein folding and promote stromal protein aggregation. The most frequently reported mutation associated with classic GCD1 is p.Arg555Trp (R555W), which promotes abnormal granular aggregation. In contrast, the variant examined in this study, rs121909212 (p.Pro501Thr; P501T), was first reported by Munier et al. in 1997 in Japanese families with LCD IIIA, and subsequent studies confirmed its presence in additional LCD IIIA patients [37].

We characterized a rare pathogenic variant, rs121909212, which represents a distinct molecular lesion within the TGFBI gene. Population genetic data indicated that the allele frequency of rs121909212 is approximately 0.005 in Japan and 0.003 in the Taiwanese population based on Taiwan Biobank whole-genome sequencing data. Fisher's exact test revealed no significant difference between these frequencies ($P = 0.416$), suggesting this rare allele is distributed across East Asian populations at comparable frequencies. This variant results in the amino acid substitution p.P501T within the keratoepithelin protein sequence. The pathogenic significance of this variant was initially established by Munier et al. in 1997 through genetic analysis of Japanese families affected with LCD IIIA [37]. Subsequent validation studies in 1999 confirmed the presence of this mutation in additional Japanese patients [38]. Furthermore, a comprehensive population-based study by Mashima et al. in 2002 employed intragenic polymorphic marker analysis across 18 Japanese patients, revealing the universal presence of the P501T mutation among all examined individuals with the LCD IIIA phenotype [39].

However, it is now well established that *TGFBI*-associated corneal dystrophies exhibit complex and sometimes overlapping genotype-phenotype relationships. The same variant can produce variable clinical phenotypes across different individuals or families, and phenotypic reclassification of *TGFBI*-associated dystrophies has occurred as diagnostic criteria have evolved. Notably, both GCD1 and LCD IIIA involve the pathologic accumulation of keratoepithelin in the corneal stroma-categorizing them as stromal corneal dystrophies - and the distinction between subtypes relies primarily on deposit morphology observed under slit-lamp examination and histopathologic analysis [3]. In this context, the identification of p.P501T carriers in the Taiwanese population is significant not only for LCD IIIA but also for understanding the broader landscape of *TGFBI*-associated corneal dystrophy susceptibility in East Asian populations.

Whole-genome sequencing, employing next-generation sequencing (NGS) technology, is a powerful tool for comprehensive human genome analysis. It provides unprecedented depth and breadth of genomic information, making it invaluable for research and clinical diagnostics requiring complete genome characterization. Unlike probe-based genotyping methods, WGS can directly sequence and resolve virtually every nucleotide in an individual's entire

genome without relying on predetermined variant locations. The comprehensiveness of WGS allows it to detect all types of genetic variations at base-pair resolution, including single nucleotide variants (common, rare, and novel polymorphisms), small insertions and deletions (indels), large copy number variations, and complex structural variations (such as chromosomal inversions and translocations spanning broad genomic regions). This unbiased, hypothesis-free sequencing method provides complete genome coverage, including non-coding regulatory regions that are typically inaccessible to SNP microarray genotyping platforms. Consequently, WGS offers higher accuracy in variant detection and precise genotyping. This explains the superior accuracy of NGS compared to probe-based platforms in determining the rs121909212 allele frequency observed in this study.

Recent research has begun to explore innovative therapeutic modalities targeting the fundamental genetic defects of *TGFBI*. These modalities include gene therapy vectors for wild-type protein replacement, RNA interference strategies for mutant transcript knockout [40], and genome editing technology through CRISPR-Cas9 for directly correcting pathogenic mutations [41, 42]. These methods may demonstrate great therapeutic potential, but they are still in an experimental stage and require extensive preclinical validation and clinical trials before potential clinical applications.

Conclusion

This study analyzed genetic data from the Taiwan Biobank to characterize variation in the *TGFBI* gene within the Taiwanese population. Our findings provide a population-level overview of *TGFBI* variant distribution and highlight several rare alleles that may be candidates for further investigation as potential susceptibility variants for granular corneal dystrophy type 1 (GCD1).

As phenotypic information in the Taiwan Biobank is primarily derived from questionnaire-based self-reported data rather than formal ophthalmologic records, the observed associations should be regarded as exploratory and hypothesis-generating rather than definitive clinical evidence. Future studies incorporating clinically confirmed GCD1 cases and detailed slit-lamp ophthalmologic examinations will be essential to validate the pathogenic relevance of these variants and to clarify their contribution to disease susceptibility in the Taiwanese population.

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Disclosure of conflict of interest

None.

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