Original Article

Association of the TGF-beta1 polymorphism with primary open-angle glaucoma: a case-control study

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ABSTRACT

Background: Primary open-angle glaucoma (POAG) is characterized by increased resistance to aqueous humor outflow. Transforming growth factor beta-1 (TGF-beta1) contributes to this resistance by promoting synthesis and remodeling of the extracellular matrix in the trabecular meshwork, thereby reducing outflow facility. This study aimed to investigate the association between the TGF-beta1 gene polymorphism at position −800 G>A (rs1800468) and POAG in patients from Khorasan Razavi Province, Iran.

Methods: In this case-control study, patients with POAG referred to Khatam-al-Anbia Hospital were enrolled as the case group, and age-matched healthy individuals served as controls. Demographic and clinical data of participants were recorded, collecting 5 mL of whole blood from each individual. DNA was extracted, genotyping the TGF-beta1 −800 G>A polymorphism using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: We included 105 individuals diagnosed with POAG and 105 healthy controls, with comparable mean age and sex distribution between the two groups (both $P > 0.05$). In the case group, genotype frequencies were 88.6% GG (n = 93), 10.5% GA (n = 11), and 1.0% AA (n = 1), in the control group 79.0% GG (n = 83), 19.1% GA (n = 20), and 1.9% AA (n = 2). Allele frequencies were 94.0% G (n = 197) and 6.0% A (n = 13) in cases, compared to 88.6% G (n = 186) and 11.4% A (n = 24) in controls. No significant association was observed between genotype frequencies and POAG or between alleles and POAG (both $P > 0.05$). Analysis under various inheritance models (codominant, dominant, recessive, overdominant) showed no significant associations either ($P > 0.05$).

Conclusions: The TGF-beta1 −800 G>A polymorphism does not appear to play a significant role in POAG development in this population. Inheritance of the mutant A allele is not a risk factor for POAG in northeastern Iran.

KEYWORDS

primary open angle glaucoma, genetic association study, transforming growth factor-beta1, TGF-beta-1, gene polymorphism, polymerase chain reactions, PCR, restriction fragment length polymorphisms, RFLP, -800 G>A, rs1800468.

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INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide and the most common cause of irreversible blindness, characterized as a progressive optic neuropathy. Diagnosis is confirmed by optic disc cupping and visual field loss [1, 2]. Major risk factors include advanced age and elevated intraocular pressure (IOP), with additional factors such as reduced central corneal thickness, ethnicity, and family history [3]. Primary open-angle glaucoma (POAG), the most prevalent form, features an open anterior chamber angle and normal trabecular meshwork appearance [4]. Approximately 1–2% of individuals over 40 years of age are affected by POAG, posing a significant public health challenge [5]. The prevalence of glaucoma, elevated increased cup-to-disc ratio (CDR), and high IOP is notably higher among first-degree relatives of affected individuals compared to the general population [6].

Transforming growth factor beta-1 (TGF-β1) is a multifunctional cytokine of the TGF-β superfamily that plays key roles in immune regulation [7]. It exerts various immunomodulatory effects, including immunosuppressive, proinflammatory, and anti-inflammatory actions, such as promoting monocyte and macrophage recruitment, inhibiting lymphocyte proliferation, and facilitating tissue repair [8]. Accordingly, dysregulation of TGF-β1 has been implicated in a wide range of inflammatory and autoimmune disorders, including allergies, systemic lupus erythematosus, and related immune-mediated conditions [9–11]. Beyond its immunological functions, emerging evidence suggests that TGF-β contributes to oxidative stress-related signaling pathways [12]. Given that oxidative stress has long been recognized as a key pathogenic mechanism in glaucoma [13, 14], TGF-β may represent an important molecular link between immune dysregulation, oxidative stress, and glaucomatous neurodegeneration.

TGF-β1 is the predominant isoform in ocular tissues, with elevated levels detected in aqueous humor, vitreous, and tears. It regulates the production of extracellular matrix components, such as chondroitin sulfate proteoglycans, which influence aqueous humor outflow through the trabecular meshwork [11, 15]. Studies indicate higher TGF-β1 expression in the ciliary body epithelium of glaucoma patients compared to healthy individuals [16]. A key mechanism in POAG involves TGF-β1-mediated induction of proteoglycan synthesis in the trabecular meshwork extracellular matrix, leading to reduced outflow facility and elevated IOP [17]. Numerous polymorphisms in growth factor genes, including TGF-β1 on chromosome 19q13 [18], influence gene expression and extracellular matrix remodeling in the trabecular meshwork [19]. The promoter polymorphism −800 G>A is particularly relevant, as the A allele has been linked to increased TGF-β1 expression [20].

Given the high prevalence of POAG and the need for early diagnosis [21], this study investigated the association between the TGF-β1 −800 G>A polymorphism and POAG in patients from northeastern Iran, with the aim of identifying potential genetic risk factors.

METHODS

In this case-control study, we recruited consecutively patients aged > 40 years with POAG confirmed by a glaucoma specialist at the Glaucoma Clinic in Khatam-al-Anbia Eye Hospital from January to September 2018 in Mashhad, Iran. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (Approval No: IR.MUMS.MEDICAL.REC.1398.518) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

For the control group, we included individuals over age 40 who came to other clinics at the same hospital without having glaucoma or any family history of glaucoma. Diagnosis of POAG was based on raised IOP, glaucomatous visual field changes in perimetry, a large CDR, and a normal-looking angle on gonioscopy. We excluded individuals with history of eye injury, uveitis, eye surgery, or laser iridotomy and those with abnormal gonioscopy findings.

Demographics and detailed clinical characteristics of participants were recorded. All participants underwent a standardized comprehensive ophthalmic examination. Corrected distance visual acuity (CDVA) was measured using a Snellen chart (Auto Chart Projector CP-670; NIDEK Co., Ltd., Gamagori, Japan) and subsequently converted to logarithm of the minimum angle of resolution (logMAR) for statistical analysis. IOP was measured using Goldmann applanation tonometry (AT 900; Haag-Streit AG, Koeniz, Switzerland). Anterior segment examination was performed using a slit-lamp biomicroscope (BQ 900; Haag-Streit AG, Koeniz, Switzerland). Gonioscopy was conducted using a Goldmann three-mirror contact lens (Volk Optical Inc., Mentor, OH, USA). Fundus examination took place after pharmacologic pupil dilation using a +90 diopter lens (Volk Optical Inc., Mentor, OH, USA). Vertical CDR was assessed by indirect ophthalmoscopy and slit-lamp biomicroscopy. In accordance with ethical standards, no new samples were collected; analyses were conducted using previously archived specimens from the institutional DNA bank [22].

Table 1. Forward and reverse primer sequences, restriction enzyme, recognition site, PCR product size, and expected fragment patterns for genotyping the TGF-β1 −800 G>A (rs1800468) polymorphism using PCR-RFLP

Primers (5′>3′)	Restriction enzyme (Recognition site)	PCR product size	Genotype
Forward: ACAGTTGGCACGGGCTTTCG	NmuCI (5-GTSAC-3')	388 bp	AA: 388 bp GA: 388 bp + 200 bp + 188 bp GG: 200 bp + 188 bp
Reverse: TCAACACCCTGCGACCCCAT			

Abbreviations: PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; bp, base pairs.

To check if the TGF-β1 gene polymorphism at −800 G>A (rs1800468) tied into POAG, we drew 5 mL of blood from each person into EDTA tubes. We pulled out the DNA using the standard salting-out approach [23]. Genotyping of the TGF-β1 −800 G>A polymorphism was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis with the NmuCI restriction enzyme. Primer sequences and enzyme details are provided in Table 1. For the PCR, we started with denaturation at 94°C for 4 minutes, then ran 35 cycles: 94°C for 45 seconds to denature, 61°C for 50 seconds to anneal, 72°C for 45 seconds to extend, wrapping up with a final extension at 72°C for 5 minutes.

To figure out the genotypes, we digested the PCR products with NmuCI (Thermo Scientific Inc., USA)—primarily, 10 μL of each product mixed with 0.25–0.5 units of the enzyme, incubated at 37°C for 12–16 hours. To avoid star activity, digestion was performed under manufacturer-recommended buffer conditions (Buffer R) and glycerol concentration was kept below 5%. Complete digestion was verified by including known genotype controls and by confirming the absence of undigested bands on 2% agarose gel electrophoresis. No evidence of nonspecific cleavage or DNA degradation was observed. Next, we ran the digested fragments on a 2% agarose gel, separated them by size, and checked under UV light.

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 21; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]), and categorical variables as frequencies and percentages. Differences between two groups were assessed using the independent samples t-test or Mann-Whitney U-test for continuous variables. Associations between quantitative variables were assessed using the chi-square test or Fisher's exact test. Comparisons of continuous variables across more than two groups were performed using one-way analysis of variance (ANOVA). Genotype distributions were compared between groups under different genetic inheritance models, including codominant, dominant, recessive, overdominant, and allelic models, using the chi-square test or Fisher's exact test as appropriate. In cases of sparse genotype counts (e.g., low-frequency homozygous variants), Fisher's exact test was applied. A two-sided P-value < 0.05 was considered statistically significant. No formal correction for multiple comparisons across inheritance models was applied, so results should be interpreted cautiously.

RESULTS

We recruited 105 patients with POAG and 105 healthy controls of comparable age (mean [SD] age was 57.8 (13.9) years in the glaucoma group and 60.2 (12.8) years in controls; $P > 0.05$) and sex distribution (62.9% male in cases vs. 61.0% in controls; $P > 0.05$) (Table 2).

Genotype distributions for the TGF-β1 −800 G>A (rs1800468) polymorphism followed Hardy-Weinberg equilibrium in both groups ($P = 0.33$ in cases, $P = 0.62$ in controls) (Table 3).

In the glaucoma patients, the most common genotype was GG (n = 93, 88.6%), followed by GA (n = 11, 10.5%) and AA (n = 1, 1.0%). In controls, the frequencies were 79.0% GG (n = 83), 19.1% GA (n = 20), and 1.9% AA (n = 2). The difference in genotype distribution between the two groups did not reach statistical significance ($P > 0.05$) (Table 3).

The minor A allele was less frequent in patients (n = 13, 6%) than in controls (n = 24, 11.4%), but again this difference was not statistically significant ($P > 0.05$) (Table 3). We also looked at different inheritance models (dominant, recessive, overdominant); none showed a significant association with POAG (all $P > 0.05$) (Table 3).

We also checked whether genotype was related to disease severity in the glaucoma patients. There was no significant association between the −800 G>A genotypes and CDR, IOP, or CDVA in either eye or with the need for glaucoma surgery (all $P > 0.05$). These findings are presented in Table 4.

Table 2. Demographic and baseline characteristics of study participants

Variables	POAG group (n = 105)	Control group (n = 105)	*P*-value
Sex (Male/Female), n (%)	66 (62.9) / 39 (37.1)	64 (61.0) / 41 (39.0)	0.776
Age (y), Mean ± SD, Median (IQR)	57.77±13.91, 57 (48.5, 68)	60.24±12.84, 61 (51, 71)	0.183
CDVA (OD) (logMAR), Mean ± SD, Median (IQR)	0.38 ± 0.32, 0.31 (0.12, 0.62)	0.37 ± 0.38, 0.22 (0.04, 0.69)	0.50
CDVA (OS) (logMAR), Mean ± SD, Median (IQR)	0.40 ± 0.33, 0.31 (0.15, 0.62)	0.32 ± 0.32, 0.15 (0.04, 0.52)	**0.029**
IOP (OD) (mmHg), Mean ± SD, Median (IQR)	23.47 ± 11.71, 20 (16, 28)	11.78 ± 1.83, 12 (10, 13)	**0.0001**
IOP (OS) (mmHg), Mean ± SD, Median (IQR)	20.67 ± 9.02, 20 (15, 24)	11.84 ± 1.89, 12 (10, 14)	**0.0001**
CDR, Mean ± SD, Median (IQR)	0.72 ± 0.24, 0.8 (0.5, 0.9)	0.26 ± 0.07, 0.3 (0.2, 0.3)	**0.0001**

Abbreviations: POAG, primary open angle glaucoma; n, number of participants; n, number; %, percentage; y, years; SD, standard deviation; IQR, interquartile range; CDVA, corrected distance visual acuity; OD, right eye; OS, left eye; logMAR, logarithm of the minimum angle of resolution; IOP, intra ocular pressure; mmHg, millimeter of mercury; CDR, cup-to-disk ratio. Note: *P*-values < 0.05 are shown in bold.

Table 3. Genotype and allele frequencies of the TGF-β1 −800 G>A (rs1800468) polymorphism in patients with POAG and healthy controls, analyzed under codominant, dominant, recessive, and overdominant models

TGF-β1 -800 G >A (rs1800469)	Genotype/Allele	Glaucoma (n = 105)	Controls (n = 105)	*P*-value
Codominant, n (%)	G/G	93 (88.6)	83 (79.0)	0.17
	G/A	11 (10.5)	20 (19.1)	
	A/A	1 (1.0)	2 (1.9)	
Hardy-Weinberg *P*-value	-	0.33	0.62	
Dominant, n (%)	G/G	93 (88.6)	83 (79.0)	0.059
	G/A-A/A	12 (11.4)	22 (20.9)	
Recessive, n (%)	G/G-G/A	104 (99.0)	103 (98.1)	0.56
	A/A	1 (1.0)	2 (1.9)	
Overdominant, n (%)	G/G-A/A	94 (89.5)	85 (81.0)	0.078
	G/A	11 (10.5)	20 (19.1)	
Allele, n (%)	G	197 (94.0)	186 (88.6)	0.084
	A	13 (6.0)	24 (11.4)	

Abbreviations: POAG, primary open angle glaucoma; n, number of participants; %, percentage. Note: Hardy-Weinberg equilibrium was confirmed in both groups.

Table 4. Association between TGF-β1 −800 G>A (rs1800468) genotypes and clinical parameters in patients with POAG

Clinical parameter		GG (n = 93)	GA (n = 11)	AA (n = 1)	*P*-value
CDR, Mean ± SD	OD	0.72 ± 0.03	0.74 ± 0.08	0.70	0.88
	OS	0.71 ± 0.03	0.76 ± 0.07	0.75	0.85
IOP (mmHg), Mean ± SD	OD	23.5 ± 1.4	23.9 ± 3.2	20	0.90
	OS	20.9 ± 1.1	18.7 ± 2.1	20	0.78
CDVA (LogMAR), Mean ± SD	OD	0.39 ± 0.04	0.38 ± 0.07	0.40	0.70
	OS	0.41 ± 0.04	0.36 ± 0.09	0.52	0.65
Need for glaucoma surgery, n (%)	-	32 (34.4)	3 (27.3)	0 (0.0)	0.89

Abbreviations: POAG, primary open angle glaucoma; n, number of participants; %, percentage; SD, standard deviation; IOP, intraocular pressure; CDVA, corrected distance visual acuity; OD, right eye; OS, left eye;

DISCUSSION

Our findings showed no statistically significant association between TGF-β1 polymorphism and POAG. The minor A allele was somewhat less frequent in patients (6%) than in controls (11%), and the *P*-value of 0.084 for allelic comparison was close to the conventional threshold but did not meet the criterion for significance. Similarly, none of the inheritance models revealed a meaningful link. Within the patient group, the genotype was not associated with clinical parameters of disease severity. These negative results are consistent with a number of studies examining TGF-β1 polymorphisms in POAG [24, 25].

Table 5. Summary of published case-control studies evaluating the association between TGF-β1 gene polymorphisms and POAG

First Author (Year)	Country	Case / Control, n	Polymorphism (rs No.)	Genotyping Method	Main Findings	OR (95% CI)	Conclusion
Derakhshan (2019) [22]	Iran	POAG: 112/ Controls: 112	-509C>T (rs1800469)	PCR-RFLP (Bsu36I restriction enzyme)	Higher CT genotype in cases; T mutant allele significantly increased in POAG	TT: 2.54 (1.22–5.27); T allele: 1.73 (1.18–2.53)	Significant association between TGF-β1 gene polymorphism and POAG; mutant T allele is risk factor
Karmiris (2018) [24]	Greece	POAG: 88 / Controls: 55	+915G>C (Arg25Pro) (rs1800471)	PCR-based genotyping	No significant genotype or allele differences	Not significant	No significant association
Sahin (2025) [25]	Turkey	POAG:115 / Controls: 96	-509C>T	PCR amplification and sequencing analysis (on the Illumina Miniseq platform)	No significant association in allele/genotype or dominant/recessive models	Not significant	No significant association between TGFB1 -509C>T polymorphism and POAG
Zhou and Liu (2010) [29]	China	POAG: 37 / Controls: 100	TGF-β1 SNP (rs4803455)	Real time PCR with TaqMan assay (ABI Prism 7900HT)	No significant association for TGF-β1	Not reported	TGF-β1 not associated
Bamdad (2021) [30]	Iran	POAG:56 / Controls: 106	+869T>C	Amplification refractory mutation system-PCR	No overall significant association; CT genotype protective in females	OR=0.42 (0.18–0.96) (female subgroup)	No overall association; possible sex-specific protective effect
Sripriya (2007) [31]	India	POAG: 106 / Controls: 104	-509C>T	PCR-RFLP (Eco81I)	No significant allele or genotype differences	Not significant	No association

Abbreviations: TGF-β1, transforming growth factor beta-1; POAG, primary open-angle glaucoma; OR, odds ratio; CI, confidence interval; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism. Note: The table includes study population, sample size, SNP investigated, genotyping methods, and main findings, highlighting the heterogeneity of results across ethnic groups.

POAG remains a leading cause of irreversible blindness worldwide [1, 2]; much of the damage is thought to stem from changes in the extracellular matrix of the trabecular meshwork that impede aqueous outflow [26]. TGF-β1 is a key player in this process, promoting proteoglycan synthesis and matrix remodeling that can raise intraocular pressure [16]. Given that polymorphisms in the promoter region of TGF-β1 can influence its expression [27, 28], we set out to examine whether the −800 G>A variant (rs1800468) might contribute to POAG risk in our northeastern Iranian population [22].

Several case-control studies have investigated the association between TGF-β1 gene polymorphisms and POAG across different populations, yielding inconsistent findings. Among the six studies summarized in Table 5 [22, 24, 25, 29–31], only the Iranian study conducted by Derakhshan et al. [22] demonstrated a significant association between the −509C>T polymorphism and POAG, reporting the mutant T allele as a potential genetic risk factor. In contrast, studies from Greece [24], Turkey [25], China [29], and India [31] failed to identify any significant association between TGF-β1 polymorphisms and POAG susceptibility. Notably, Bamdad et al. [30] reported a possible sex-specific protective effect of the CT genotype of the +869T/C polymorphism in female patients, although no overall association was detected. The discrepancies among studies [22, 24, 25, 29–31] may be attributed to ethnic genetic diversity, differences in sample size, varying single nucleotide polymorphism loci examined, and methodological heterogeneity in genotyping techniques and statistical models. Given the known role of TGF-β1 in extracellular matrix regulation and trabecular meshwork remodeling [32], genetic variations may exert population-specific effects on glaucoma susceptibility. Larger multi-center studies with stratified analyses are warranted to clarify the precise contribution of TGF-β1 polymorphisms to POAG pathogenesis.

Karmiris et al. [24] found no significant genotypic association for the coding region variant G915C (Arg25Pro; rs1800471) in a Greek cohort, despite a slight increase in the C allele among cases [24]. Similarly, Sahin et al. [25] recently reported no association between the promoter variant −509C>T (rs1800469) and either POAG or primary angle-closure glaucoma in a Turkish population [25]. Zhou and Liu [29], investigating multiple metabolic syndrome-related genes

including TGF-β1 in a Chinese sample, also failed to identify strong links with POAG [29]. Bamdad et al. [30], working with another Iranian population (Shiraz), observed no association for the TGF-β1 869T/C polymorphism, though they noted a sex-dependent effect for a glutathione S-transferase variant [30]. These consistent null findings across diverse ethnic groups Greek [24], Turkish [25], Chinese [29], and Iranian [30] suggest that many TGF-β1 variants, including −800 G>A, may not exert a major independent effect on POAG susceptibility in most populations [31].

However, some studies have reported positive associations, highlighting potential population-specific differences [28, 33]. Notably, Cruz-Pavlovich et al. [33] identified the minor A allele of −800 G>A as a significant risk factor in a Mexican mestizo cohort, with odds ratios ranging from 3.18 to 3.46 across codominant, dominant, and overdominant models [33]. They found a protective effect for the −509C>T variant in the overdominant model, illustrating how different promoter polymorphisms may have opposing functional consequences [33]. Thakur et al. [28] reported a significant association of −509C>T with primary angle-closure glaucoma (but not POAG) in Indian, with a sex-specific effect in females, patterns that partially overlap with earlier findings from our center on −509C>T in northeastern Iran [22]. Saleh et al. extended the discussion to the related isoform TGF-β2, finding that the C allele of rs991967 was protective against POAG in an Iraqi cohort, accompanied by elevated serum TGF-β2 levels in patients [34]. The contrasting results, particularly the strong risk conferred by −800 G>A in Mexicans [33] versus the absence of association in our sample, may reflect ethnic variation in minor allele frequency, linkage disequilibrium with untyped causal variants, or gene-environment interactions [35].

Although the −800 G>A (rs1800468) polymorphism is located in the promoter region of TGFB1, upstream of exon 1 and outside the coding sequence, it does not alter the amino acid sequence of the resulting protein, including its three primary domains (signal peptide, latency-associated peptide [LAP], and mature TGF-β1) [7]. However, functional studies suggest that the minor A allele may enhance transcriptional activity, potentially leading to increased overall TGF-β1 production and higher levels of the pro-protein (containing LAP and mature domains) [7]. This hypothetical overexpression could indirectly amplify TGF-β1 signaling in the trabecular meshwork, promoting extracellular matrix remodeling and outflow resistance, though evidence remains inconsistent across populations and the mechanism is not definitively established [7] (Figure 1).

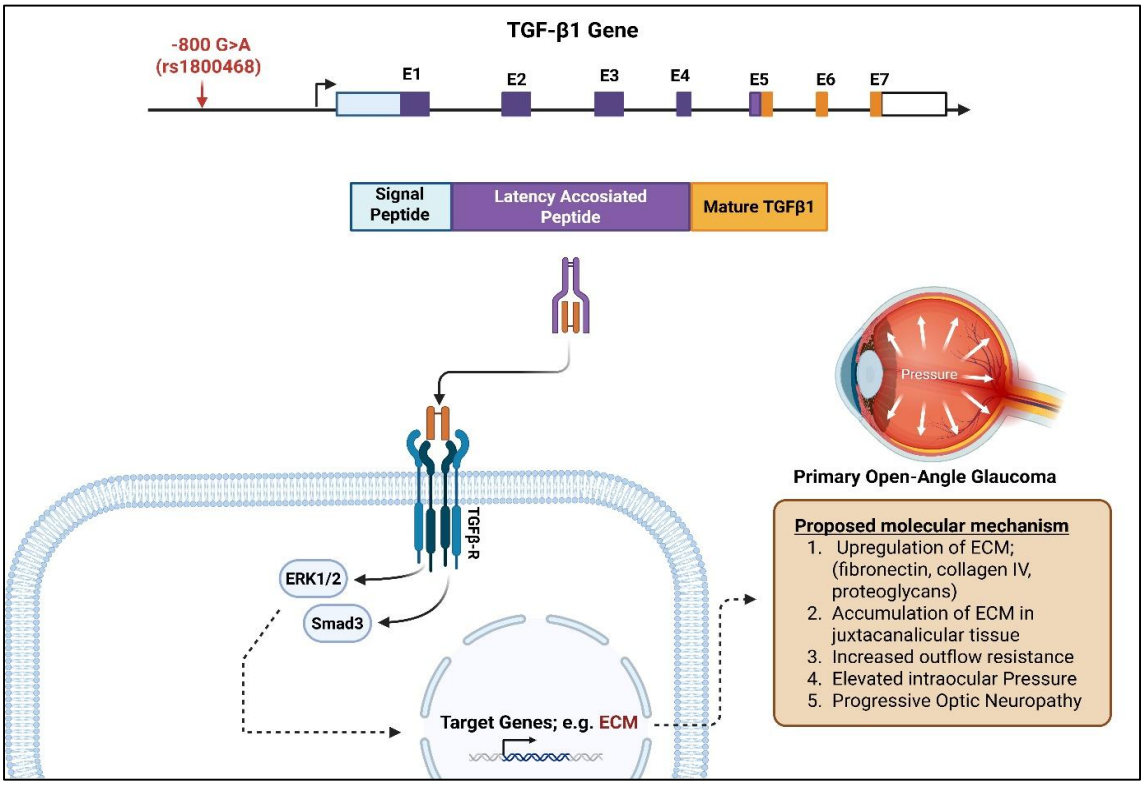

Figure 1. Proposed pathophysiological mechanism of POAG involving TGF-β1. The schematic illustrates the role of the TGF-β1 promoter polymorphism −800 G>A (rs1800468) in gene expression regulation and its potential impact on extracellular matrix remodeling in the trabecular meshwork, leading to increased outflow resistance and elevated intraocular pressure [created by biorender.com] [16, 36, 37]. Abbreviations: POAG, primary open-angle glaucoma; TGF-β1, transforming growth factor beta-1; E, exons; TGF-β-R, transforming growth factor beta receptor; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase.

Several limitations of our study warrant consideration. First, the sample size provides limited power for detecting small effect sizes; post-hoc calculations indicate approximately 50–60% power for an odds ratio of 2.0 at α=0.05. Second, we examined only a single polymorphism; haplotype-based or next-generation sequencing approaches could uncover combined effects across the promoter region. Third, recruitment from a single referral center may introduce selection bias, although demographic matching between groups minimizes confounding by age and sex. Despite these limitations, this study provides the first assessment of the TGF-β1 −800 G>A (rs1800468) polymorphism in a northeastern Iranian population, with careful phenotypic characterization of POAG patients and matched controls. Future studies with larger, multi-center cohorts and comprehensive genetic analyses are warranted to further explore the contribution of TGF-β1 promoter variants and potential gene-environment interactions in glaucoma susceptibility.

CONCLUSIONS

The TGF-β1 −800 G>A (rs1800468) polymorphism does not appear to be a significant genetic risk factor for POAG in northeastern Iran. Our results contribute to a growing body of evidence suggesting population-specific effects of TGF-β1 variants in glaucoma pathogenesis. Future large-scale, multi-ethnic studies incorporating haplotype analysis, functional assays of promoter activity, and gene-environment interactions are needed to fully elucidate the role of TGF-β1 in POAG and guide personalized risk assessment.

ETHICAL DECLARATIONS

Ethical approval: This study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (Approval no: IR.MUMS.MEDICAL.REC.1398.518). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment. No identifying personal data is included in this manuscript.

Conflict of interest: None.

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