Original Article

Association of *WDR36* polymorphisms with primary open-angle glaucoma

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ABSTRACT

Background: Various genes contribute to the pathophysiology of primary open-angle glaucoma (POAG). The WD repeat domain 36 (*WDR36*) gene may participate in T cell activation and, hence, in the pathogenesis of POAG. We investigated the association of two *WDR36* gene single nucleotide polymorphisms (SNPs) with POAG.

Methods: This cross-sectional study recruited patients aged > 40 years with POAG and investigated the rs10038177 and rs1971050 SNPs of *WDR36* using polymerase chain reaction and direct DNA sequencing. All participants underwent comprehensive ocular examination, visual field assessment using the Swedish Interactive Threshold Algorithm standard 24-2 threshold test, and measurement of peripapillary retinal nerve fiber layer thickness (RNFLT) using spectral domain optical coherence tomography.

Results: We enrolled 105 patients with a mean (standard deviation) age of 55.41 (8.56) years and a male-to-female ratio of 56 (53.3%) to 49 (46.7%), most of whom had a diagnosis of POAG for 2 to 5 years (60.0%). Most participants had diabetes (90.5%) but not hypertension (88.6%). There was a significant association of rs10038177 ($P < 0.05$), but not rs1971050 ($P > 0.05$), with family history of glaucoma. The association between rs10038177 and intraocular pressure was significant ($P < 0.05$), but that between rs1971050 and intraocular pressure was not ($P > 0.05$). No significant association was observed between mean cup-to-disc ratio and either SNP (both $P > 0.05$). For rs10038177, a significant association was found only with the RNFLT of the superior quadrant ($P < 0.05$), whereas for rs1971050, a significant association was found with the RNFLT of all four quadrants and average RNFLT (all $P < 0.05$). However, pairwise comparisons revealed no significant differences between genotypes ($P > 0.05$ for all pairwise comparisons). The association of rs10038177 with glaucoma severity was insignificant ($P > 0.05$), and most patients with the TC genotype (71.7%) had moderate severity. There was no significant association between rs1971050 and glaucoma severity ($P > 0.05$).

Conclusions: We observed genetic links between some, but not all, characteristics of POAG and the rs10038177 and rs1971050 SNPs of *WDR36*. Follow-up studies on these and other *WDR36* SNPs in populations with different genetic backgrounds are necessary to confirm this genetic association.

KEYWORDS

glaucomas, primary open angle glaucoma, *WD repeat-containing protein 36*, genetic polymorphism, single nucleotide polymorphism, optical coherence tomography, family medical history

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INTRODUCTION

Glaucoma is a group of ocular disorders that causes optic nerve damage and visual field defects [1]. It affects approximately 70 million people worldwide, a number expected to increase to 111.8 million by the year 2040 [2]. It is a leading cause of irreversible blindness globally [3].

Primary open-angle glaucoma (POAG) features a progressive optic neuropathy with loss of ganglion cells, open angles on gonioscopy, and specific visual field defects with or without elevated intraocular pressure (IOP) [4, 5]. Approximately 74% of all glaucoma cases are diagnosed as POAG [6]. There are multiple ocular and systemic factors in the development of glaucoma, including IOP, ocular perfusion pressure, ocular blood flow, myopia, age greater than 40 years, smoking, Black race [4, 7], family history of glaucoma, genetic factors, systemic hypertension, type 2 diabetes mellitus, obesity, stress, hypothyroidism, and primary vascular dysregulation [4].

In 4–16% of patients with POAG, more than one immediate family member is affected. This is because POAG is genetically passed from one generation to another, and various genes are known to contribute to the pathophysiology of POAG [8]. Multiple well-characterized groups of genes are recognized as susceptibility factors for POAG, including myocilin (*MYOC*), optineurin (*OPTN*), WD repeat domain 36 (*WDR36*), and forkhead box C1 (*FoxC1*) [9].

Studies using genome association methods and a number of single nucleotide polymorphisms (SNPs) have enabled the identification of genetic factors associated with susceptibility to various complex diseases including POAG [10]. The *WDR36* gene is found on chromosome 5q22.1 and is composed of 23 exons. It encodes 951 amino acids and a protein with multiple G-beta winged domain 40 repeats [11]. Mutations in this gene are associated with adult-onset POAG [11].

Although it has been hypothesized that *WDR36* may play a role in T cell activation, which subsequently causes optic nerve degeneration in patients with POAG, the role of *WDR36* in the pathogenesis of glaucoma remains incompletely understood [12]. In a systematic review and meta-analysis, Liu et al. concluded that existing data in the literature do not support a significant role for *WDR36* in the genetic susceptibility to POAG or its subtypes [13].

Some of the *WDR36* gene SNPs, namely rs11241095, rs10038177, rs17553936, rs13186912, rs13153937, and rs1971050, have been studied for their associations with POAG [14-17]. However, further replicative studies involving specific populations are warranted. Therefore, this study investigated the association of the rs10038177 and rs1971050 SNPs of the *WDR36* gene with the clinical and imaging characteristics of POAG.

METHODS

This cross-sectional study, which was conducted at Era's Lucknow Medical College, Lucknow, Uttar Pradesh, India, was approved by the Institutional Ethics Committee and adhered to the tenets of the Declaration of Helsinki. The study recruited all eligible patients aged > 40 years who presented to the eye clinic with POAG between the years 2018 and 2020. All patients provided informed consent prior to participation.

The inclusion criteria consisted of age > 40 years and the presence of glaucomatous optic neuropathy, open anterior chamber on gonioscopy, visual field defects consistent with those of glaucomatous optic neuropathy, and IOP consistently ≥ 22 mmHg. We excluded patients with types of glaucoma other than POAG, recent intraocular surgery, retinal changes due to pre-existing ocular or extraocular disorders, and non-glaucomatous visual field defects or optic disc changes.

Detailed medical and ocular histories, family histories of glaucoma (positive if a first-degree relative was affected [18]), and any previous medical or surgical treatment of glaucoma were recorded. Participants with blood pressure < 140/90 mmHg and ≥ 140/90 mmHg were categorized as normotensive and hypertensive, respectively [19]. The diagnosis of diabetes mellitus was based on a glycosylated hemoglobin (HbA1c) level ≥ 6.5%, fasting plasma glucose level ≥ 126 mg/dL, or two-hour postprandial plasma glucose level ≥ 200 mg/dL [20].

All recruited patients underwent a thorough ocular examination including best-corrected distance visual acuity measurement (LG 18.5-inch LED Vision Chart; Eye Care Products, Delhi, India), anterior segment examination using a slit-lamp (SI 115 Classic slit lamp; Carl Zeiss, Stuttgart, Germany), IOP measurement using Goldmann's applanation tonometry (L-5110; Inami & Co., Ltd., Bunkyo-ku, Tokyo, Japan), gonioscopy using a Sussman four mirror handheld gonioscope lens (Model G-4; Volk Optical Inc., Mentor, OH, USA) under a slit-lamp, and fundus examination under a slit-lamp using a Volk 90D lens (Volk Optical Inc.) and using a binocular indirect ophthalmoscope (Model AAIO-7; Appasamy Associates, India) using a Volk 20D lens (Volk Optical Inc.). The visual field test was performed using the Swedish Interactive Threshold Algorithm

Table 1. Hoddap–Parrish–Anderson glaucoma grading scale [21] for severity of glaucomatous visual field defects

Indices	Early defect	Moderate defect	Severe defect
Mean deviation	< - 6 dB	- 6 to - 12 dB	> - 12 dB
Pattern deviation plot	< 25% of points are depressed below the 5% level and < 10 points are depressed below the 1% level. No point within the central 5° has sensitivity < 15 dB.	< 50% of points are depressed below the 5% level and < 20 points are depressed below the 1% level. No point within the central 5° has sensitivity ≤ 0 dB.	> 50% of points are depressed below the 5% level or > 20 points are depressed below the 1% level. Any point within the central 5° has sensitivity ≤ 0 dB.
Hemifields	-	Only one hemifield have a point with sensitivity < 15 dB within 5° of fixation.	Both hemifields have points with sensitivity < 15 dB within 5° of fixation.

Abbreviations: %, percentage; dB, decibel.

standard 24-2 threshold test (Humphrey Field Analyzer 750 II-I; Carl Zeiss Meditec, Inc, Dublin, CA, USA). The peripapillary retinal nerve fiber layer thickness (RNFLT) was measured in four quadrants using spectral-domain optical coherence tomography (Cirrus™ HD-OCT 4000; Carl Zeiss Meditec). Glaucoma severity was assessed using the Hoddap–Parrish–Anderson (HPA) glaucoma grading scale (Table 1) [21].

For genetic evaluation, 3-mL peripheral blood samples from all participants were collected in EDTA [22] anticoagulant tubes (Peerless Biotech Pvt. Ltd., Chennai, Tamil Nadu, India). DNA was extracted from whole blood samples using the genomic DNA extraction technique [22]. DNA concentration and purity were measured by UV absorption at 260 and 280 nm, respectively, using a double-beam UV-VIS Spectrophotometer (Systronics Co., Ahmedabad, Gujarat, India). The amplification products of the *WDR36* gene SNPs rs10038177 and rs1971050 were 458 bp and 238 bp, respectively. Polymerase chain reaction (PCR) was used for amplification of the *WDR36* gene. The PCR protocol consisted of an initial denaturation step (95°C for 4 min), 35 cycles of denaturation (95°C for 30 s), annealing (50–62°C for 30 s), and elongation (70°C for 30 s). The final extension was performed at 72°C for 4 min. Products were digested using 10 µL of AluI (NEB #R0137S) restriction enzyme and were run on 3% regular agarose gels [23].

Data were collected and analyzed using IBM SPSS Statistics for Windows (version 21.0; IBM Corp., Armonk, NY, USA). Data were normally distributed according to the Kolmogorov–Smirnov test of normality. Quantitative and qualitative variables are expressed as mean (standard deviation [SD]) and frequency (percentage), respectively. Data were compared using the chi-square test and analysis of variance (ANOVA) if applicable. If by ANOVA a statistically significant difference between study groups was observed, a post-hoc analysis using Tukey's test was performed for multiple pairwise comparisons between genotypes. *P*-values < 0.05 were considered statistically significant.

RESULTS

We enrolled 105 patients with POAG with a mean (SD) age of 55.41 (8.56) years. Table 2 presents the characteristics of the study participants.

Table 3 summarizes the genotypic associations of the rs10038177 and rs1971050 SNPs with a family history of glaucoma. There was a significant association between rs10038177 and a family history of glaucoma ($P < 0.05$), but not between rs1971050 and family history ($P > 0.05$). The TT genotype of rs10038177 was more common (75.7%) in the patients without a family history of glaucoma (Table 3).

Table 4 displays the genotypic associations of the rs10038177 and rs1971050 SNPs with mean IOP and cup-to-disc ratio (CDR). There was a significant association between rs10038177 and IOP ($P < 0.001$), and the TC genotype (83.1%) of rs10038177 was more common in patients with an IOP ranging from 22.1–30 mmHg. However, the association between rs1971050 and IOP was not statistically significant ($P > 0.05$). Similarly, no significant association was found between the mean CDR and either SNP (both $P > 0.05$) (Table 4).

The association of rs10038177 with RNFLT (Table 5) was significant only for RNFLT in the superior quadrant ($P < 0.05$); however, for rs1971050, a significant association was found with the RNFLT in all four quadrants and the average RNFLT (all $P < 0.05$). Among the rs1971050 genotypes, the mean RNFLT of the CC genotype was the least, and that of the TT genotype was the greatest (Table 5). However, pairwise comparisons revealed no significant differences between genotypes ($P > 0.05$ for all pairwise comparisons).

On evaluating the associations between rs10038177 and rs1971050 and glaucoma severity (Table 6), we found no significant association with either of the SNPs (both $P > 0.05$). Most participants with the TC genotype of rs10038177 (71.7%) had moderate glaucoma severity, and rs10038177 genotypes of CC (60.0%) and TC (40.0%) were detected in all patients with severe glaucomatous visual field defects (Table 6).

Table 2. Demographic characteristics of participants with POAG

Variables	Values
Age (y), Mean ± SD (Range)	55.41 ± 8.56 (40 to 70)
Sex (Male / Female), n (%)	56 (53.3) / 49 (46.7)
BP (Normotensive / Hypertensive), n (%)	93 (88.6) / 12 (11.4)
Diabetic status (Diabetic / Non-diabetic), n (%)	95 (90.5) / 10 (9.5)
Duration of disease (y), n (%)	
< 2	22 (20.9)
2 – 5	63 (60.0)
6 – 10	20 (19.1)
> 10	0 (0.0)

Abbreviations: POAG, primary open-angle glaucoma; y, years; SD, standard deviation; n, number of participants; %, percentage; BP, blood pressure; mmHg, millimeters of mercury; mg/dL, milligrams per deciliter. Note: Participants with BP < 140/90 mmHg and ≥ 140/90 mmHg were categorized as normotensive and hypertensive, respectively [19]; the diagnosis of diabetes was based on glycosylated hemoglobin level ≥ 6.5%, fasting plasma glucose level ≥ 126 mg/dL, or two-hour postprandial plasma glucose level of ≥ 200 mg/dL [20].

Table 3. Genotypic associations of the rs10038177 and rs1971050 SNPs of *WDR36* with family history of glaucoma in participants with POAG

Genotypes	Family history (n = 31)	No family history (n = 74)	*P*-value
SNP: rs10038177			
CC, n (%)	3 (9.7)	4 (5.4)	**0.002**
TC, n (%)	14 (45.2)	14 (18.9)	
TT, n (%)	14 (45.2)	56 (75.7)	
SNP: rs1971050			
CC, n (%)	0 (0.0)	1 (1.4)	0.614
TC, n (%)	4 (12.9)	6 (8.1)	
TT, n (%)	27 (87.1)	67 (90.5)	

Abbreviations: *WDR36, WD repeat domain 36 gene*; SNP, single nucleotide polymorphism; POAG, primary open-angle glaucoma; n, number of participants; %, percentage. Note: *P*-values < 0.05 are shown in bold type.

Table 4. Genotypic associations of the rs10038177 and rs1971050 SNPs of *WDR36* with IOP and CDR in participants with POAG

Variables	Genotypes for SNP rs10038177			Genotypes for SNP rs1971050		
	TT, n (%)	TC, n (%)	CC, n (%)	TT, n (%)	TC, n (%)	CC, n (%)
IOP						
≤ 22 mmHg	2 (7.1)	10 (35.7)	16 (57.1)	6 (21.4)	10 (35.7)	12 (42.9)
22.1 – 30 mmHg	5 (8.5)	49 (83.1)	5 (8.5)	18 (30.5)	24 (40.7)	17 (28.8)
> 30 mmHg	3 (16.7)	5 (27.8)	10 (55.6)	6 (33.3)	9 (50.0)	3 (16.7)
***P*-value**	**< 0.001**			0.426		
CDR						
≤ 0.6	5 (16.1)	12 (38.7)	14 (45.2)	5 (16.1)	11 (35.5)	15 (48.4)
0.7 – 0.8	2 (3.5)	48 (84.2)	7 (12.3)	19 (33.3)	23 (40.4)	15 (26.3)
> 0.8	3 (17.6)	4 (23.5)	10 (58.8)	6 (35.3)	9 (52.9)	2 (11.8)
***P*-value**	0.092			0.067		

Abbreviations: *WDR36, WD repeat domain 36 gene*; SNP, single nucleotide polymorphism; POAG, primary open-angle glaucoma; IOP, intraocular pressure; mmHg, millimeters of mercury; CDR, cup-to-disc ratio; n, number of participants; %, percentage. Note: *P*-values < 0.05 are shown in bold type; CDR represents the average of the vertical and horizontal CDRs.

Table 5. Genotypic associations of the rs10038177 and rs1971050 SNPs of *WDR36* with RNFLT in participants with POAG

Variables	Genotypes			*P*-value
SNP: rs10038177	**TT (n = 10)**	**TC (n = 64)**	**CC (n = 31)**	
Average RNFLT (μm), Mean ± SD	68.63 ± 6.61	77.92 ± 15.45	75.55 ± 12.87	0.149
Superior RNFLT (μm), Mean ± SD	75.20 ± 14.88	92.42 ± 21.02	87.06 ± 17.27	**0.030**
Inferior RNFLT (μm), Mean ± SD	79.20 ± 8.34	88.53 ± 18.05	86.10 ± 16.95	0.266
Nasal RNFLT (μm), Mean ± SD	61.10 ± 12.71	65.83 ± 12.33	65.84 ± 12.98	0.528
Temporal RNFLT (μm), Mean ± SD	59.00 ± 10.21	64.91 ± 14.34	63.19 ± 12.43	0.417
SNP: rs1971050	**TT (n = 30)**	**TC (n = 43)**	**CC (n = 32)**	***P*-value**
Average RNFLT (μm), Mean ± SD	83.67 ± 16.47	75.23 ± 13.73	70.95 ± 9.51	**0.001**
Superior RNFLT (μm), Mean ± SD	100.30 ± 22.15	86.30 ± 19.34	82.69 ± 14.12	**0.001**
Inferior RNFLT (μm), Mean ± SD	93.73 ± 20.44	85.51 ± 16.63	82.44 ± 12.33	**0.026**
Nasal RNFLT (μm), Mean ± SD	70.97 ± 13.08	65.63 ± 12.73	59.81 ± 9.15	**0.002**
Temporal RNFLT (μm), Mean ± SD	69.67 ± 15.73	63.47 ± 13.28	58.88 ± 8.88	**0.006**

Abbreviations: *WDR36, WD repeat domain 36 gene*; SNP, single nucleotide polymorphism; POAG, primary open-angle glaucoma; RNFLT, retinal nerve fiber layer thickness; μm, micrometers; SD, standard deviation; n, number of participants. Note: *P*-values < 0.05 are shown in bold type.

Table 6. Genotypic associations of the rs10038177 and rs1971050 SNPs of *WDR36* with severity of glaucoma in participants with POAG

Severity	Genotypes			*P*-value
SNP: rs10038177	**TT, n (%)**	**TC, n (%)**	**CC, n (%)**	
Early	5 (11.9)	22 (52.4)	15 (35.7)	0.057
Moderate	5 (9.4)	38 (71.7)	10 (18.9)	
Severe	0 (0.0)	4 (40.0)	6 (60.0)	
SNP: rs1971050	**TT, n (%)**	**TC, n (%)**	**CC, n (%)**	
Early	12 (28.6)	15 (35.7)	15 (35.7)	0.582
Moderate	14 (26.4)	23 (43.4)	16 (30.2)	
Severe	4 (40.0)	5 (50.0)	1 (10.0)	

Abbreviations: *WDR36, WD repeat domain 36 gene*; SNP, single nucleotide polymorphism; POAG, primary open-angle glaucoma; n, number of participants; %, percentage. Note: The severities of glaucomatous visual field defects were assessed using the Hoddap-Parrish-Anderson glaucoma grading scale [21] (Table 1) and were categorized as early, moderate, and severe defects.

DISCUSSION

There is a proposed genetic predisposition to glaucoma when a family history of glaucoma is present [24]. Identification of the genes responsible for POAG is essential for assessing the risk for glaucoma and understanding the underlying pathogenic mechanisms [25, 26]. The *MYOC*, *OPTN*, and *WDR36* genes have been widely reported to be associated with POAG [9]. Several candidate SNPs have been explored with respect to POAG. Owing to the limited literature [14, 16], the current study was conducted in a population with variable profiles to identify the association of the rs1971050 and rs10038177 SNPs of *WDR36* with POAG. We enrolled 105 patients with POAG with a mean (SD) age of 55.41 (8.56) years and similar sex proportions. We observed genetic links between some, but not all, characteristics of POAG and the rs10038177 and rs1971050 SNPs of *WDR36*.

The high IOP and CDR in our participants were the result of glaucomatous changes [27]. Decreased RNFLT and visual field defects are correlated with the glaucomatous status of patients [28]. The TC genotype of rs10038177 was detected more frequently in patients with a family history of glaucoma and in those with moderate glaucoma severity. In this subgroup, a significant difference was observed in those within the IOP range of 22.1–30 mmHg. For rs1971050, no significant association was found with a family history of glaucoma, IOP levels, or CDR. Regarding the association with RNFLT, rs10038177 was associated only with superior RNFLT, and rs1971050 was associated with the RNFLT in all quadrants and the average RNFLT, with no significant difference between individual genotypes in pairwise comparisons. Among the rs1971050 genotypes, the mean RNFLT of the CC genotype was the least and that of the TT genotype was the greatest.

Su et al. [29] evaluated the association of a single SNP (rs10038177) by comparing polymorphisms in 61 patients with juvenile open-angle glaucoma and 61 controls. They concluded that *WDR36* was involved in the pathogenesis of POAG. Mookherjee et al. [30] enrolled patients with a mean age of 62 years and studied ten candidate SNPs of the *WDR36 gene*, two of which were investigated in our study (rs10038177 and rs1971050). The authors suggested a possible association with POAG. The combination of CC and TC genotypes of a single SNP (rs10038177) had a more deleterious effect than the CC genotype alone [30]. We detected the rs10038177 genotypes of CC (60.0%) and TC (40.0%) in all patients with severe glaucomatous visual field defects.

Another genome study on SNP rs10038177 was performed by Monemi et al. [11], in which 130 POAG families and 476 unaffected controls were included. There, the significance of *WDR36* gene mutations was reported for the first time; their occurrence was found in 1.6–17% of patients with POAG. These findings indicate a possible role of these genotypes in the pathogenesis and progression of glaucoma. As in our study, Taher et al. [14] found no significant association between IOP or CDR and the different genotypes of the rs1971050 SNP of *WDR36*.

Our study is limited by the lack of a control group and follow-up to document the progression of glaucomatous optic neuropathy, either by clinical assessment of CDR, deterioration in VF defects, or progressive thinning of the RNFLT. However, our findings remain interesting and illustrate the possible role of the rs1971050 and rs10038177 SNPs of the *WDR36* gene in some, but not all, characteristics of POAG. However, a substantial knowledge gap remains regarding the association of *WDR36* and POAG. Therefore, further multicenter studies on a global level are necessary to reach a final consensus.

CONCLUSIONS

We assessed the associations between the rs10038177 and rs1971050 SNPs of the *WDR36* gene and the clinical and imaging characteristics of POAG. We observed that these two SNPs were significantly associated with some, but not all, characteristics of POAG. To reach a robust conclusion concerning this observed genetic association, follow-up studies of these and other *WDR36* SNPs in populations with different genetic backgrounds are necessary.

ETHICAL DECLARATIONS

Ethical approval: The study, which was conducted at Era's Lucknow Medical College, Lucknow, Uttar Pradesh, India, was approved by the Institutional Ethics Committee and adhered to the tenets of the Declaration of Helsinki. All patients provided informed consent prior to participation.
Conflict of interests: None.

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