TP53 codon 72 polymorphism is associated with susceptibility to acute primary angle-closure in Brazilian patients

Polimorfismo do códon 72 do TP53 e a suscetibilidade ao fechamento angular primário agudo em pacientes brasileiros

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ABSTRACT

Objective: To compare the association between TP53 codon 72 polymorphism and primary angle-closure glaucoma in Brazilian patients, with emphasis on acute primary angle closure attack.

Methods: The TP53 codon 72 (exon 4) genotype status of 67 primary angle-closure glaucoma patients and 72 healthy (controls) was analyzed using polymerase chain reaction with the restriction fragment length polymorphism method and sequence analysis. The association of the polymorphism and primary angle-closure glaucoma with or without acute primary angle closure attack was evaluated using contingency tables with chi-square and Fisher's exact tests.

Results: No significant difference in genotype frequency for the TP53 polymorphism was observed between primary angle-closure glaucoma patients and controls (p = 0.39). Patients with previous acute primary angle closure attack showed a higher frequency of 72-PRO allele (p = 0.025).

Conclusion: TP53 codon 72 polymorphism was not associated with primary angle-closure glaucoma overall. Nevertheless, the higher frequency of the PRO allele among patients with acute primary angle closure suggests that TP53 may represent a genetic marker of susceptibility to acute angle-closure events, possibly related to ocular anatomical predisposition.

RESUMO

Objetivo: Comparar a associação entre o polimorfismo do TP53 no códon 72 e o glaucoma primário de ângulo fechado em pacientes brasileiros, com ênfase no glaucoma primário de ângulo fechado agudo.

Métodos: A análise genética do TP53 no códon 72 (exon 4) foi realizada em 67 pacientes com glaucoma primário de ângulo fechado e 72 controles, utilizando-se a reação em cadeia da polimerase para estudo do polimorfismo de fragmento de restrição e análise de sequenciamento. A associação dos polimorfismos e glaucoma primário de ângulo fechado com ou sem glaucoma primário de ângulo fechado agudo foi avaliada por meio de tabelas de contingência com teste do qui-quadrado e teste exato de Fisher.

Resultados: Não foi observada diferença significativa na frequência genotípica do polimorfismo do TP53 entre pacientes com glaucoma primário de ângulo fechado e controles (p = 0,39). Pacientes com glaucoma primário de ângulo fechado agudo prévio apresentaram maior frequência do alelo 72-PRO (p = 0,025).

Conclusão: O polimorfismo do códon 72 do TP53 não foi associado a glaucoma primário de ângulo fechado em geral. No entanto, a maior frequência do alelo PRO entre pacientes com glaucoma primário de ângulo fechado agudo sugere que o TP53 pode representar um marcador genético de suscetibilidade a eventos agudos de fechamento angular, possivelmente relacionado à predisposição anatômica ocular.

INTRODUCTION

Glaucoma is a group of optic nerve diseases presenting a progressive and irreversible loss of retinal ganglion cells commonly associated with elevated intraocular pressure (IOP) levels.[1] Primary angle-closure glaucoma (PACG) is a prevalent type of glaucoma, mainly in Asia, showing a higher risk of bilateral blindness than primary open-angle glaucoma (POAG).[2-6]

The peripheral apposition of the iris to the trabecular meshwork is a common feature of PACG. In fact, an iridotrabecular contact causing both the obstruction of trabecular outflow and IOP increases with subsequent glaucomatous optic neuropathy altogether depict the PACG clinical picture.[4]

The glaucomatous retinal ganglion cell damage is related to distinct local pathological processes. They can be triggered by several genetic players induced by loss of neurotrophic factors during high IOP periods and exposure to excessive excitatory amino acids as a consequence of optic nerve and retina ischemia.[7-9] The cellular damage is detected by sensor proteins that activate TP53 gene, a transcription factor that plays a significant role in apoptosis.[10-12] Several loci and genes have been linked to PACG in previous genetic studies from diverse countries.[13] Although Gupta et al.[11] have described the association between a higher risk of PACG and the Arg variant of TP53, no previous information on TP53 polymorphisms is available in patients with PACG and acute primary angle-closure attack (APAC).

Therefore, this study aimed to compare the association between TP53 codon 72 polymorphism and PACG in Brazilian patients, with emphasis on APAC.

METHODS

Participants

For this case-control study, PACG patients were recruited from the Glaucoma Outpatient Service of the *Hospital das Clínicas de Ribeirão Preto* of the *Faculdade de Medicina de Ribeirão Preto* of the *Universidade de São Paulo* and the Glaucoma Outpatient Service of the Department of Ophthalmology, State Civil Servant Hospital, São Paulo, Brazil. Healthy bone marrow donors at the Blood Center of Ribeirão Preto were included as a control group. This study followed the Declaration of Helsinki principles and was approved by the Local Ethics Committee of *Hospital das Clínicas de Ribeirão Preto* of the *Faculdade de Medicina de Ribeirão Preto* at USP (case number 8991/2001) and the National Commission of Ethics in Research (CONEP, process number 476/2002). Written informed consent was obtained from all participants.

The subjects underwent a comprehensive ophthalmological examination, including visual acuity assessment, refraction, slit-lamp examination, direct ophthalmoscopy, and IOP measurements (Goldmann applanation tonometry) and gonioscopy.

Patients were included in the study if the following criteria for PACG was fulfilled: typical glaucomatous optic neuropathy with corresponding evidence with typical changes in standard automated perimetry (pattern standard deviation with $p < 0.05$, and/or Glaucoma Hemifield Test results outside normal limits)[14] at least one IOP measurement above 21 mmHg, and closed angle on gonioscopy defined as Scheie grade III or IV. Those with secondary glaucoma or other ocular diseases were excluded. There were no limitations regarding age, gender or ethnicity.

Primary angle-closure glaucoma patients were divided into two groups: Group 1, including subjects with a documented history of APAC, and Group 2, including subjects with no history of APAC. Acute primary angle-closure attack was defined if there were the following symptoms and signs: severe ocular pain, acute visual acuity decreased, nausea and vomit, corneal edema, mydriasis, shallow anterior chamber, associated with high IOP levels.

Genotyping of TP53

Venipuncture was performed to obtain peripheral blood samples in all participants for genomic DNA extraction using modified salting-out method. For the polymerase chain reaction (PCR) analysis, the region of exon 4 of gene TP53 which contains the sequence of polymorphic DNA was amplified in all DNA samples extracted from patients and controls. Polymerase chain reaction was performed in a volume of 30 µL containing 1.5 µL purified DNA, 3.0 µL 10 x *Taq* buffer, 1.2 µl $MgCl_2$, 0.38 µL nucleotides, 0.2 µL *Taq* DNA polymerase, 21.92 µL sterile water, and 0.9 µL of each primer: Pro - (5' CGT GCA AGT CAC AGA CTT -3'l) and Arg + (5' TCC CCC TTG CCG TCC CAA -3'). The procedure was carried out as follows: one cycle at 94° C for 5 minutes with the sample heated for DNA denaturation, followed by 35 cycles at 94° C for 45 seconds, 60° C for 45 seconds, and 72° C for 45 seconds for primer hybridization, and a final cycle at 72° C for 4 minutes. The final PCR product consisted of a 279 bp DNA fragment resolved on a 10% polyacrylamide gel electrophoresis stained with 2% silver nitrate. The PCR product (7.0 µL) was then digested with the specific restriction enzyme BseDI (Fermentas,

USA) using the restriction fragment length polymorphism (RFLP) in a 3.0 µL reaction mixture in a water bath for 12 hours at 55° C. The digestion product was separated using 10% polyacrylamide gel stained with 2% silver nitrate. Bands containing TP53 codon 72 polymorphisms presented at the 94 bp were taken as proline and at the 138 bp as arginine. (Figure 1)

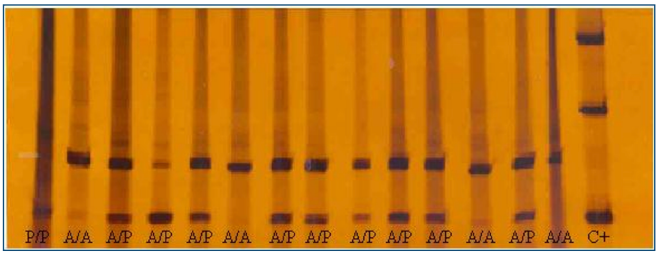

Figure 1. Polyacrylamide gel electrophoresis followed by silver nitrate staining.

Statistical analysis

Contingency tables were used for calculating the chi-square (χ^2) with Yates correction or by the two-tailed Fisher exact test when appropriate. All TP53 codon 72 polymorphisms results were tested to satisfy the Hardy-Weinberg equilibrium. Genotype frequency for the TP53 polymorphism (PRO / PRO, ARG / ARG and ARG / PRO) was compared between PACG and control subjects. The distribution of allelic frequency between patients with PACG and the controls, as well as between groups 1 and 2 were also compared using a significance level of $p < 0.05$. All tests were performed using the software StatCal (Epi Info, version 6.0).

RESULTS

The study evaluated 67 PACG patients (Group 1, 48 subjects; Group 2, 19 subjects) and 72 healthy controls. Mean ± standard deviation of age was 65.6 ± 10.3 years (range 34 to 84 years) for controls, 66.2 ± 8.7 years (ranging from 46 to 81 years) for Group 1, and 63.5 ± 13.8 years (range 34 to 84 years) for Group 2. Forty-five participants were female (62%) and 62 (92%) were categorized as white race.

Groups 1 and 2 were comparable regarding age, sex distribution, race, and best-corrected visual acuity in both eyes (all $p > 0.05$). A significant difference was observed in refractive status, with hyperopia being more frequent in Group 1 and myopia predominating in Group 2 ($p = 0.001$). Group 1 presented significantly larger vertical cup-to-disc ratios in both eyes compared with Group 2 (OD 0.7 ± 0.2 *versus* 0.5 ± 0.2; $p = 0.005$; OS 0.7 ± 0.2 *versus* 0.5 ± 0.2; $p = 0.018$). No significant differences were observed in the prevalence of glaucomatous visual field defects between groups in either eye (OD with $p = 0.759$; OS with $p = 0.859$). These findings indicate greater structural optic nerve damage in Group 1, while functional impairment, as assessed by visual field testing, was similar between the groups (Table 1).

Table 1. Baseline demographic and ocular characteristics according to history of acute primary angle-closure attack

Variable	Group 1 (n = 48)	Group 2 (n = 19)	p-value
Age	66.2 ± 8.7	63.5 ± 13.8	0.833
Gender			0.577
Female	34 (69.8)	11 (60.0)	
Male	14 (30.2)	8 (40.0)	
Race			0.742
White	45 (94.3)	17 (90.0)	
Mixed race	1 (1.9)	1 (5.0)	
Black	2 (3.8)	1 (5.0)	
Refractive error			0.001
Hyperopic	40 (81.1)	7 (40.0)	
Myopic	8 (18.9)	11 (60.0)	
BCVA OD	0.80 (0.35 - 0.87)	0.80 (0.65 - 1.00)	0.263
BCVA OS	0.70 (0.40 - 0.84)	0.75 (0.25 - 1.00)	0.593
VCDR OD	0.7 ± 0.2	0.5 ± 0.2	0.005
VCDR OS	0.7 ± 0.2	0.5 ± 0.2	0.018
Glaucomatous VFD OD	27 (56.6)	7 (35.0)	0.759
Glaucomatous VFD OS	29 (60.4)	11 (55.0)	0.859

Results expressed as mean ± SD, n (%) or median (interquartile range)
BCVA: best-corrected visual acuity; OD: right eye; OS: left eye; VCDR: vertical cup-to-disc ratio; VFD: visual field defect.

The absolute and relative genotype frequency of both PACG and control group, according to TP53 (codon 72) polymorphism is shown in Table 2. No significant difference was observed in genotype frequency for the TP53 polymorphism (PRO / PRO, ARG / ARG and ARG / PRO) between PACG cases and controls ($p=0.39$).

Genotype distributions for the TP53 codon 72 polymorphism were in Hardy-Weinberg equilibrium in both the control and PACG groups (all $p > 0.05$), supporting the quality and reliability of the genotyping data.

Table 2. TP53 codon 72 genotypes distribution in primary angle-closure glaucoma and healthy controls

Group	Genotype		
	CC (Pro-Pro)	GG (Arg/Arg)	CG (Pro/Arg)
PACG (67)	6 (8.9)	29 (43.3)	32 (47.8)
Controls (72)	4 (5.5)	39 (54.2)	29 (40.3)

Results expressed as n (%).
No significant difference was observed in genotype frequency for the TP53 polymorphism between primary angle-closure glaucoma cases and controls ($p = 0.39$).
PACG: primary angle-closure glaucoma.

The allelic frequency distribution between patients with PACG and controls showed no significant difference ($p = 0.1406$). However, the PRO allele frequency was significantly higher in patients from group 1 (with APAC history) compared to group 2 ($p = 0.025$; Table 3).

Table 3. Allele frequency in primary angle-closure glaucoma groups (1 if with, and 2 if without previous of acute primary angle closure) according to the TP53 polymorphism (codon 72)

	PRO	ARG
PACG group 1	38 (39.6)	58 (60.4)
PACG group 2	7 (18.4)	31 (81.6)

Results expressed as n (%).
The PRO allele frequency was significantly higher in patients from Group 1 (with APAC history) compared to Group 2 (p = 0.025).

DISCUSSION

In the present study, we investigated the association between TP53 codon 72 polymorphism and PACG in a Brazilian population, with particular emphasis on the occurrence of APAC. Although no significant differences in genotype or allele distribution were observed between PACG patients and healthy controls, a significantly higher frequency of the TP53 72-PRO allele was identified among PACG patients with a documented history of APAC.

A genetic etiology of glaucoma has been widely searched, particularly in POAG. In fact, several studies have observed genetic mutations related to POAG pathophysiology.[15-18]

Previous studies have showed a variable association of TP53 and POAG.[19] In a Chinese study, Lin et al.[20] found a predominance of the Pro / Pro in POAG patients, while Acharya et al.[21] described no association between TP53 polymorphism (codon 72) in Asian patients with POAG. Similarly, Silva et al.[22] evaluated the occurrence of that polymorphism in 104 patients with POAG and 58 controls and observed no significant difference between groups.

Considering that glaucoma is associated with apoptosis of retinal ganglion cells and TP53 is a transcription factor with a significant role in apoptosis,[23] we aimed to verify whether different TP53 genotypes were also associated with PACG. Although we observed no significant difference in genotype distribution between PACG and healthy controls, PACG patients with a previous history of APAC presented a higher frequency of Proline compared to those with no previous APAC history.

Gupta et al.[11] found similar results in PACG patients of no significant differences in genotypic distributions compared to control. Notwithstanding, after using additive (GG *versus* CC) and recessive (GG *versus* CG+CC) models, an increased risk of PACG was observed for ARG-72 homozygotes. Our results did not confirm significant difference in genotypic frequency between PACG and controls, but a significantly higher PRO-72 allelic frequency was observed in the group of patients with previous history of APAC.

The association of TP gene encoding for proline at codon 72 and POAG has already been described, including a potential relationship with early paracentral visual field defects.[20-24] To the best of our knowledge, there is no previous study demonstrating the association of TP53 polymorphisms nor risk factor for APAC or anatomic predisposition for angle closure in humans. Nevertheless, transgenic mice with mutant TP53 presented microphthalmia and changes in lens morphology.[25,26] Based on these animal findings, we speculate that humans expressing the PRO-72 allele may present smaller eyes with potential narrower anterior chamber that would facilitate an APAC event.

Although most previous studies on POAG and PACG suggested an association TP53 codon 72 polymorphism, particularly with ARG homozygosity, our study did no demonstrate differences between PACG and healthy controls. Nonetheless, this is the first study showing higher PRO allele frequency in PACG patients with previous history of APAC. Thus, beyond its potential role in retinal ganglion cell apoptosis, TP53 polymorphism may be associated with ocular developmental pathways that influence anatomical predisposition to angle closure and increase susceptibility to APAC.

Acute primary angle-closure attack is strongly associated with ocular anatomical characteristics, such as shallow anterior chamber depth, short axial length, and increased lens thickness. The significantly higher frequency of the PRO allele observed in PACG patients with APAC suggests that TP53 may contribute to a genetic background favoring these anatomical traits. Rather than acting primarily through enhanced retinal ganglion cell apoptosis, TP53 polymorphism in this context may influence ocular development in a manner that increases susceptibility to acute angle-closure events.

To our knowledge, this is the first study to demonstrate an association between TP53 codon 72 polymorphism and APAC. This observation introduces a novel perspective on the role of genetic factors in angle-closure disease, highlighting the potential importance of genes involved in ocular development and anatomical configuration, in addition to those directly related to neurodegeneration.

Some limitations of this study should be acknowledged. The sample size was modest, particularly in the subgroup without APAC, which may limit statistical power. Additionally, biometric parameters such as axial length and anterior chamber depth were not available for correlation with genetic findings. Future studies combining genetic analysis with detailed ocular biometry may further elucidate the mechanisms linking TP53 polymorphism to acute angle closure.

Despite these limitations, the consistent association between the PRO allele and APAC supports the hypothesis that TP53 codon 72 polymorphism may serve as a genetic marker of susceptibility to acute angle-closure events. This finding may contribute to improved understanding of individual risk profiles within the spectrum of primary angle-closure disease.

CONCLUSION

TP53 codon 72 polymorphism was not associated with primary angle-closure glaucoma overall. Nevertheless, the higher frequency of the PRO allele among patients with acute primary angle closure suggests that TP53 may represent a genetic marker of susceptibility to acute angle-closure events, possibly related to ocular anatomical predisposition.

AUTHOR CONTRIBUTION

Silva MJL, Paula JS, and Rodrigues MLV contributed to the conception and design of the study, analysis and interpretation of results, writing and critical revision of the manuscript content. Vargas MA, Dhegaide NHS, and Donadi EA contributed to the analysis and interpretation of data and critical revision of the manuscript content. Silva LFL contributed to the critical revision of the manuscript content. All authors approved the final version of the manuscript and are responsible for all aspects of it, including ensuring its accuracy and integrity.

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