Original Article

Association between the p53 codon 72 polymorphism and primary open-angle glaucoma risk: Meta-analysis based on 11 case–control studies

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The TP53 is important in functions of cell cycle control, apoptosis, and maintenance of DNA integrity. Studies on the association between p53 codon 72 polymorphism and primary open-angle glaucoma (POAG) risk have yielded conflicting results. Published literature from PubMed and Web of Science databases was retrieved. All studies evaluating the association between p53 codon 72 polymorphisms and POAG were included. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated. Eleven separate studies including 2541 cases and 1844 controls were pooled in the meta-analysis. We did not detect a significant association between POAG risk and p53 codon 72 polymorphism overall population except allele genetic model (C vs. G: OR = 0.961, 95% CI = 0.961–0.820, P = 0.622). In the stratified analysis for Asians and Caucasians, there was an association between p53 codon 72 polymorphism and POAG. In the dominant model in the overall population and by ethnicity subgroups, the highest elevated POAG risk was presented. In summary, these results indicate that p53 codon 72 polymorphism is likely an important genetic factor contributing to susceptibility of POAG. However, more case–controls studies based on larger sample size and stratified by ethnicity are suggested to further clarify the relationship between p53 codon 72 polymorphism and POAG.

Key words: Codon 72, meta-analysis, p53, polymorphism, primary open-angle glaucoma

Glaucoma is one of the leading causes of irreversible blindness worldwide, affecting 60 million people worldwide, with 8.4 million people with the disease being bilaterally blind.[1] The most common form is primary open-angle glaucoma (POAG), which is characterized by retinal ganglion cell apoptosis and visual field changes corresponding with the excavation of the optic disk and an open anterior chamber angle.[2,3]

It is suggested that glaucoma influenced by a combination of genetic and environmental risk factors.[4] This condition is attributed to several genes, the majority of which are yet unidentified.[5] Until now, linkage analysis in large affected families has yielded 25 chromosomal loci linked to POAG. The POAG-associated genes include atrial natriuretic peptide, apolipoprotein E, optic atrophy 1, p53, glutathione S-transferase (GST), interleukins, and tumor necrosis factor-α.[6] However, the role of these genes in the etiology of POAG is still controversial.[7] Recently, several genome-wide association studies have been performed for POAG, which revealed several genetic variants associated with the disease. Several chromosomal loci have now been reported as linked to POAG, such as p53 (MIM 602432).[6] However, the association of p53 with POAG has been a

source of controversy as reports published recently showed conflicting results.[8]

TP53 is a tumor suppressor that plays an important role in cell cycle regulation and the maintenance of genome integrity.[9] TP53 mediates the cellular response to DNA damage through effects on gene transcription, DNA synthesis and repair, genomic plasticity, and apoptosis. Functional polymorphisms of the TP53 gene which influence the above activities of TP53 protein might be associated with human susceptibility to cancer.[10] The codon 72 polymorphism (rs1042522) is located in exon 4 of TP53 gene and involves a CCC → CGC transition leading to a proline (Pro) → arginine (Arg) amino acid substitution at position 72 (Pro72Arg), and the 72Arg allele shows more efficient in inducing apoptosis and lower ability in inducing cell cycle arrest and DNA repair.[10,11]

Several previous studies have explored the association between the p53 codon 72 polymorphism and POAG susceptibility; however, existing results are inconsistent. Therefore, we conducted this meta-analysis to obtain accurate and up-to-date estimates of the association between the TP53 codon 72 polymorphism and POAG.

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Materials and Methods

Search strategy

We performed a comprehensive search of the PubMed, Web of Science, and SID databases to identify potentially relevant studies on the association between p53 codon 72 Arg/Pro polymorphism and POAG risk up to January 2015. The following terms were used in the literature search: "POAG," "p53," "codon 72," "rs1042522," "Arg72Pro," "polymorphism," "variant," and "SNP." The search was restricted to humans with language exclusions. The references of retrieved publication, published reviews, letters, and comments were scanned for additional relevant studies. Additional studies were identified by a manual search of the references from the original or review articles on this topic.

Inclusion criteria

Studies included in our meta-analysis had to meet the following inclusion criteria: (1) evaluated the association between the TP53 codon 72 polymorphism and POAG susceptibility; (2) a case–control study; (3) provided the number of individual genotypes in both the case and control groups, or enabled the genotypes to be calculated from available published data; (4) published only in English; and (5) when multiple publications reported on the same or overlapping data, we chose the most recent or largest population. Studies were excluded if one of the following existed: (1) none-case–control studies; (2) studies that contained overlapping data; (3) not offering the source of cases and controls or other essential information; (4) reviews and repeated literature were also excluded; (5) no usable data reported.

Data extraction

Two authors independently extracted the following trial data from included studies: The following items were collected from each study: first author's surname, year of publication, ethnicity, countries of origin, total number of cases and controls, and genotype frequencies of cases and controls. Different descents were categorized as Caucasians, Asians, and Mixed populations which included more than one ethnic descent. For case–control studies, data were extracted separately for each group whenever possible.

Statistical analysis

Deviation from the Hardy–Weinberg equilibrium (HWE) among the controls was evaluated for each single study using online calculator named HWE calculator for 2 alleles (http://www.had2know.com). Dichotomous data were presented as odds ratio (OR) with 95% confidence interval (CI). Statistical heterogeneity was measured using the Q statistic test ($P < 0.10$ was considered statistically significant heterogeneity). An I^2 value of 25% indicates low heterogeneity, 50% indicates moderate heterogeneity and 75% indicates high heterogeneity. The heterogeneity was considered statistically significant at $I^2 > 50\%$ or $P < 0.10$. Either a random-effects model (DerSimonian–Laird method) or fixed-effects model (Mantel–Haenszel method) was used to calculate pooled effect estimates in the presence or absence of heterogeneity, respectively. To establish the effect of heterogeneity among the studies on the conclusions of this meta-analysis, subgroup analyses were conducted based on ethnicity. Several methods were used to assess the potential for publication bias. Visual inspection of funnel plot asymmetry was conducted. The Begg's rank correlation method and the Egger's weighted regression method were used to statistically assess publication bias. $P < 0.05$ was considered statistically significant. All the statistical tests were performed with Comprehensive Meta Analysis software (CMA) version 2.0 (Biostat, USA).

Results

Study characteristics

After comprehensive searching, a total of 21 articles were retrieved, but only 11 full-text publications[8,11-20] which catered to the inclusion criteria were finally included in our meta-analysis. The characteristics of all studies are summarized in Table 1. The 11 studies were published from 2002 to 2015 with 5 were carried out in Asian countries, 6 in Europe countries, and 8 in America. Of these 54 studies, the number of cases in the included studies for GSTM1 deletion varied from 58 to 523 patients. The genotype distribution in controls of the included studies all agreed with HWE. The genotype frequencies for p3 polymorphism of cases and controls are presented in Table 2 in detail.

Evaluation of heterogeneity

To analyze heterogeneity among the selected studies, Q-test and I^2 statistics were employed, and heterogeneity was noticed in all the five genetic models. Therefore, random-effects model was applied to synthesize the data [Table 2]. Then, we assessed the source of heterogeneity for dominant comparison (CC + CG vs. GG) by ethnicity. As a result, ethnicity ($\chi^2 = 14.41$; df = 2; $P = 0.001$) was found to contribute to substantial heterogeneity. In addition, subgroup analyses revealed that the heterogeneity was significantly reduced in the small sample size group and large sample size group in all genetic models, suggesting that the total sample size was the source of heterogeneity [Table 2 and Fig. 1].

Meta-analysis results

Table 2 lists the main results of the meta-analysis. The association of the p53 codon 72 polymorphism with POAG risk under different genetic models is shown in Table 2. The overall data comprising 2541 cases and 1844 controls exhibited significant increased POAG risk under the dominant (CC + CG vs. GG: OR = 7.678, 95% CI = 6.284–9.382, $P < 0.001$) [Fig. 1a], recessive (CC vs. CG + GG: OR = 1.432, 95% CI = 1.164–1.763, $P = 0.001$) [Fig. 1b], additive (CC vs. GG: OR = 1.534, 95% CI = 1.224–1.923, $P < 0.001$) [Fig. 1c], heterozygous genetic models (CG vs. GG: OR = 0.719, 95% CI = 0.579–0.892, $P = 0.003$) [Fig. 1d], except allelic model (C vs. G: OR = 0.961, 95% CI = 0.961–0.820, $P = 0.622$) [Fig. 1e].

Subgroup analyses of the different ethnic groups were performed. The results are shown in Table 2 and significant increased POSG risk was found in Caucasians under dominant (CC + CG vs. GG: OR = 12.568, 95% CI = 9.190–17.188, $P < 0.001$) and additive genetic models (CC vs. GG: OR = 1.496, 95% CI = 1.072–2.088, $P = 0.018$). Similarly, increased POAG risks were shown among Asians under dominant (CC + CG vs. GG: OR = 12.568, 95% CI = 9.190–17.188, $P < 0.001$), additive (CC vs. GG: OR = 1.496, 95% CI = 1.072–2.088, $P = 0.018$), recessive (CC vs. CG + GG: OR = 1.596, 95% CI = 1.218–2.090, $P < 0.001$), heterozygous genetic models (CG vs. GG: OR = 0.634, 95% CI = 0.476–0.844, $P = 0.002$), except allele model (C vs. G: OR = 0.975, 95% CI = 0.685–1.386, $P = 0.887$).

Table 1: Distribution of p53 codon 72 genotypes among primary open-angle glaucoma cases and controls included in the meta-analysis

Author	Country	Ethnicity	Case/control	Cases			Allele		Control			Allele	
				GG	GC	CC	G	C	GG	GC	CC	G	C
Lin et al., 2002[11]	Kashmir	Asian	58/59	12	26	20	50	66	25	26	8	76	42
Acharya et al. 2002[8]	China	Asian	67/112	23	30	14	76	58	30	57	25	117	107
Dimasi et al., 2005[12]	Poland	Caucasian	523/94	296	186	41	778	268	109	57	12	107	81
Mabuchi et al., 2009[13]	Algeria	Asian	425/189	177	197	51	551	43	83	83	23	249	129
Daugherty et al., 2009[14]	Italy	Caucasian	191/167	124	55	12	303	79	82	72	13	236	98
Saglar et al., 2009[15]	Poland	Caucasian	75/119	19	44	12	82	68	41	69	9	151	87
Silva et al., 2009[16]	Poland	Caucasian	208/58	24	78	2	126	82	18	40	0	76	40
Fan et al., 2010[17]	Taiwan	Asian	397/201	100	176	121	376	418	55	108	38	218	184
Blanco-Marchite et al., 2011[18]	Turkey	Caucasian	268/380	148	106	14	402	134	252	111	17	615	145
Wiggs et al., 2012[19]	The Netherlands	Caucasian	264/400	118	120	26	356	172	198	183	19	579	221
Neamatzadeh et al., 2015[20]	Iran	Asian	65/65	17	27	21	61	69	25	32	8	82	48

Table 2: Meta-analysis results for the p53 codon 72 polymorphism and primary open-angle glaucoma risk

Contrasts	Cases/controls	OR (95% CI)	P_{OR}	Q	Heterogeneity	
					I^2 (%)	P_H
Overall						
C versus G	2541/1844	0.961 (0.820-1.126)	0.622	86.001	91.8	<0.001
CC versus GG		1.534 (1.224-1.923)	<0.001	21.648	53.8	0.017
CG versus GG		0.719 (0.579-0.892)	0.003	30.551	67.2	0.001
CC + CG versus GG		7.678 (6.284-9.382)	0.001	117.515	92.3	<0.001
CC versus CG + GG		1.432 (1.164-1.763)	0.001	23.698	57.8	0.008
Ethnicity						
Caucasian						
C versus GC	1529/1218	0.957 (0.802-1.143)	0.631	81.475	93.8	<0.001
CC versus GG		1.496 (1.072-2.088)	0.018	8.404	40.5	0.135
CG versus GG		0.730 (0.520-1.024)	0.068	20.763	75.9	0.559
CC + CG versus GG		12.568 (9.190-17.188)	<0.001	23.159	82.7	<0.001
CC versus CG + GG		1.225 (0.886-1.695)	0.220	10.995	54.5	0.051
Asian						
C versus G	1012/626	0.975 (0.685-1.386)	0.887	4.518	77.8	0.034
CC versus GG		1.567 (1.152-2.130)	0.004	13.204	69.7	0.010
CG versus GG		0.634 (0.476-0.844)	0.002	8.058	50.3	0.089
CC + CG versus GG		5.453 (4.201-7.079)	<0.001	49.026	91.8	<0.001
CC versus CG + GG		1.596 (1.218-2.090)	0.001	11.196	64.2	0.024

P_{OR}: P values for analysis of the pooled ORs with corresponding 95% CIs, P_H: P values for heterogeneity analysis, ORs: Odds ratios, 95% CI: 95% confidence interval

In the dominant model in the overall population and by ethnicity subgroups, the highest elevated POAG risk was presented. The results indicated that individuals who carry variant G allele might have an increased POAG risk compared with those who bear wild-type C allele [Table 2].

Publication bias

Publication bias of the selected articles was assessed by the Begg's funnel plot and Egger's test. The shape of the funnel plot did not show obvious publication bias [Fig. 2]. Similarly, no evidence of publication bias was observed by Egger's test ($P = 0.173$ for allelic genetic model; $P = 0.299$ and for dominant genetic model; $P = 0.115$).

Discussion

In the present study, we systemically reviewed all available published studies and performed a meta-analysis to derive a more precise estimation of the association between p53 gene polymorphism and susceptibility to POAG. Our meta-analysis included 15 separate studies involving 2700 cases and 2365 controls. In Asians, we detected an association of the ε4 genotype with elevated risk for glaucoma, mainly for POAG. Thus, the Arg genotype may be associated with elevated risk for POAG in Asians.

The p53 gene is located on the short arm of chromosome 17, and its protein product is related to the regulation of the cell
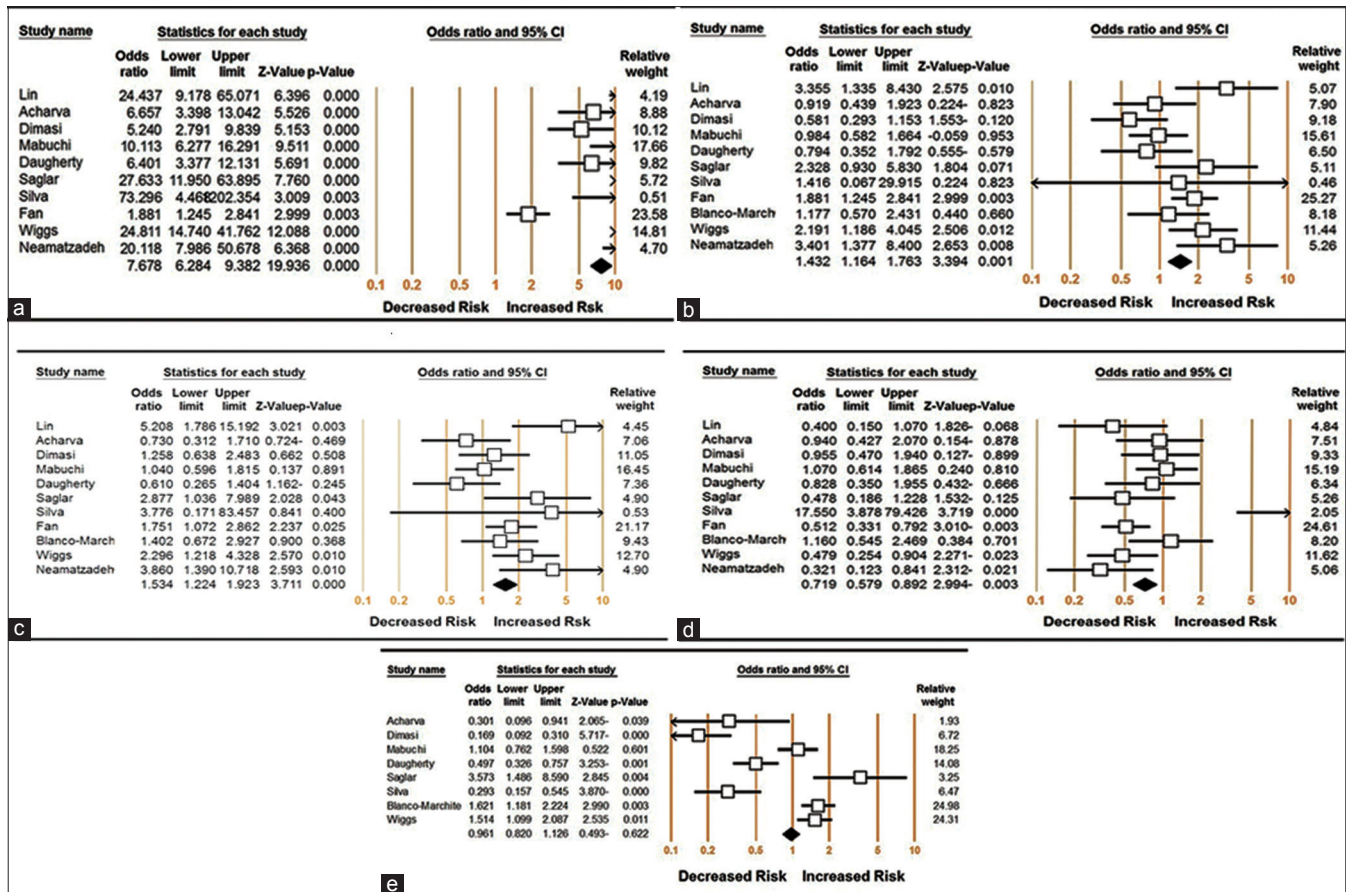
Figure 1: Meta-analysis of the odds ratio for p53 codon 72 polymorphism associated with primary open-angle glaucoma. (a) Dominant model: CC + CG versus GG; (b) recessive model: CC versus CG + GG; (c) additive model: CC versus GG; (d) heterozygous model: CG versus GG; and (e) allelic model: C versus G
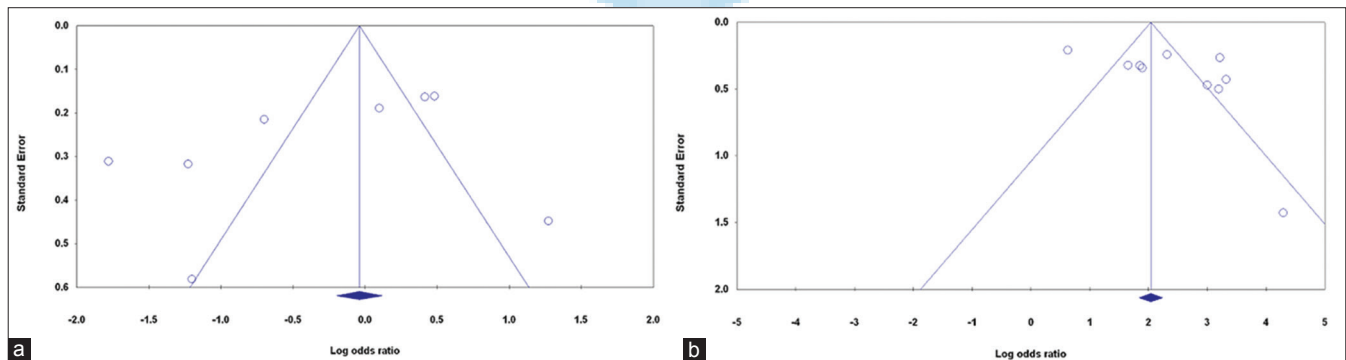

Figure 2: Begg's funnel plot of the meta-analysis of prostate cancer risk and p53 codon 72 polymorphism. (a) Allelic model: C versus G, and (b) dominant model: CC + CG versus GG

cycle.[1,2] It is well known that p53 are important components involved in the apoptosis pathway. A number of studies have investigated the genetic effects of p53 codon 72 polymorphism on POAG susceptibility with conflicting results.[21] Meta-analysis across sufficiently homogeneous studies can further enhance the sample size and power. Meta-analysis is, therefore, becoming a popular method for resolving discrepancies in genetic association studies.[22] Thus, to explain these contradictory results, as well as to decrease uncertainty about the effect size of estimated risk, a meta-analysis was conducted, examining

all available studies related to p53 codon 72 polymorphism and its associations with POAG.

In the present study, we systemically reviewed all available published studies and performed a meta-analysis to derive a more precise estimation of the association between p53 codon 72 polymorphism and susceptibility to POAG. Our meta-analysis included 11 separate studies involving 2700 cases and 2365 controls. The results have shown a significant association between p53 codon 72 and POAG except allele model. By ethnicity-pooled analysis, we detected an association of the

p53 gene genotype with elevated risk for POAG, in Asians and Caucasians. However, the number of studies and the number of subjects in the studies included in the meta-analysis were small, especially for the Asian population.

To the best of our knowledge, there is only a meta-analysis that assessed the association between p53 codon 72 polymorphism and POAG. The study of Guo *et al.* has 9 case–control studies with 1930 cases and 1463 controls, their conclusion indicate that it provided evidence that the p53 codon 72 polymorphism is an association with the risk of POAG. Guo *et al.* concluded that a significant association was found between the p53 codon 72 polymorphism and POAG risk when all the eligible studies were pooled into the meta-analysis; however, significant risk of POAG was observed in recessive model (OR = 1.31, 95% CI = 1.05–1.64, $P = 0.017$).[21] In subgroup analyses for ethnicity, they have found the association between codon 72 polymorphism and risk for POAG in Asian populations (recessive model: OR = 1.36, 95% CI = 1.03–1.80, $P = 0.026$) but not in Caucasian populations,[21] suggesting that the genetic background or environment they live in may influence the p53 codon 72 polymorphism on POAG susceptibility. The previous studies have identified that the ethnic differences may affect genetic predisposition to POAG.[8,16,17,23] However, the results of their meta-analysis should be interpreted with caution due to some limitations. However, in the stratified analysis by ethnicity, we have found significant increased risks in Asian and Caucasians for some genetic models.

Heterogeneity is a potential problem when interpreting the results of a meta-analysis, and finding the sources of heterogeneity is one of the most important goals of meta-analysis.[24] In the present meta-analysis, significant between-study moderate- to high-level heterogeneity in the pooled analyses of total eligible studies was observed in all genetic models [Table 2]. To find the sources of heterogeneity, we performed meta-regression and subgroup analyses. From the omitting studies and subgroups analysis, we found that ethnicity and source of control might not be the source of heterogeneity [Table 2].

Some potential limitations in our study should be considered. First, our meta-analysis was based on unadjusted estimates, and the confounding factors such as gender and age could not be controlled because most studies did not provide these data. Second, this meta-analysis is limited to language and database restrictions. The PubMed database is the only search source and included published studies were in English. Third, gene-gene and gene-environment interactions were not addressed in our meta-analysis. Fourth, the overall sample sizes of included literatures are quite small. Hence, we should have larger sample size, rigorous design approach, perfect retrieval strategy, and reasonable inclusion and exclusion criteria in the future studies.

Conclusion

This meta-analysis suggests that the p53 codon 72 polymorphism may be associated with increased risk of POAG, especially among Asians. However, it is necessary to conduct large sample studies and well-matched controls. Moreover, gene-gene and gene-environment interactions should also be considered in the analysis. Such studies taking these factors into account may eventually lead to our better, comprehensive understanding of the association between the p53 polymorphism and POAG risk.

Conflicts of interest

There are no conflicts of interest.

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