Association between the M98K variant of the OPTN gene and the risk for primary open angle glaucoma: an updated meta-analysis

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Background: The association between optineurin (OPTN) M98K variant and primary open angle glaucoma (POAG) has been widely investigated. However, the results remain controversial among published meta-analyses. Therefore, we conducted an updated meta-analysis to further explore the association between M98K and POAG and its subgroups.

Methods: PubMed, Embase, Web of Science, and China National Knowledge Infrastructure (CNKI) databases were searched to find all articles describing the relationships between the M98K variant and POAG, which were published from the inception to 31 December, 2019. The associations between M98K and overall POAG, normal tension glaucoma (NTG), high tension glaucoma (HTG), POAG in Asian and non-Asian populations, juvenile open angle glaucoma (JOAG) and adult-onset POAG were evaluated by calculating the pooled odds ratio (OR) and 95% confidence interval (CI). The Bonferroni correction was used to determine the statistically significant genetic models.

Results: A total of 34 eligible articles involving 7,310 POAG patients and 5,173 controls were identified in the present meta-analysis. The articles achieved an average of 6.21 stars for quality assessment by the Newcastle-Ottawa Scale (NOS). Evidence from the pooled results indicated significant association between M98K and overall POAG susceptibility under the dominant model (OR =1.30, 95% CI, 1.12–1.52; P<0.001). In the subgroup analyses, no significant associations were found between M98K and the risks of NTG, HTG, JOAG, adult-onset POAG, Asian POAG or non-Asian POAG.

Conclusions: The updated meta-analysis revealed that OPTN M98K was significantly associated with the susceptibility to overall POAG.

Keywords: M98K; meta; optineurin (OPTN); primary open angle glaucoma (POAG)

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Introduction

Primary open angle glaucoma (POAG), characterized by progressive neurodegeneration of retinal ganglion cells (RGCs) and their axons, is the leading cause of irreversible blindness worldwide (1). It is a heritable disease with the evidence from twin studies and familial clustering studies (2,3). There is a significant progress in the genetic basis of POAG. About 5% of POAG is known as a Mendedian disease and caused by a single gene (4). Others are attributed

to multiple genetic and environmental risk factors.

Optineurin (OPTN) is one of disease-causing genes of POAG, which is firstly investigated in a large British family with normal tension glaucoma (NTG) (5,6). Four mutations, Glu50 \rightarrow Lys (E50K), Arg545 \rightarrow Gln (R545Q), c.691_692insAG (Premature stop) and Met98→Lys (M98K), were identified in the original kindred (6). The rare, highpenetrance mutation, E50K, is the clearest disease-causing OPTN mutation for POAG (7). Glaucoma patients who had the E50K mutation were reported to have a younger age of onset, more advanced optic disc cupping, smaller neuroretinal rim area and higher rate of filtration surgery required (7). Among the above OPTN mutations, only M98K variant was present in normal controls (9/422), although the frequency was statistically lower than that in POAG patients (6). Multiple subsequent studies of different ethnicities were performed to evaluate the association between the risk allele (M98K) in the causative POAG gene (OPTN) and the risk of POAG, which produce conflicting results. Although three meta-analysis studies (8-10) have tried to clarify this association, the most recent meta-analysis included only 5 studies and new association studies were published after the other two meta-analyses published in 2006 (8) and 2010 (9). Importantly, the results among these meta-analyses differs, which makes an updated in depth analysis on this topic imperative to reach a definitive conclusion. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/aes-20-124).

Methods

Search strategy

In this study, we searched the PubMed, Embase, Web of Science, and China National Knowledge Infrastructure (CNKI) databases to find all articles describing the relationships between the M98K variant and POAG, which were published from the inception to 31 December, 2019. The following search terms were used as a text word: "Optineurin or OPTN or M98K or Met98Lys" and "primary open angle glaucoma or open angle glaucoma or POAG or normal pressure glaucoma or low tension glaucoma or normal tension glaucoma or high tension glaucoma". The detailed search strategy was provided as Appendix 1. The language was restricted to English and Chinese. Two independent reviewers (C.G. and X.Y.) screened the titles and abstracts of all relevant articles, manually examined the reference lists and relevant reviews for additional publications, and evaluated the full texts to identify eligible studies.

Eligibility criteria

Included studies were case-control studies in assessing the associations between OPTN (M98K) mutation and the risk of POAG and its subgroups, the age and intraocular pressure (IOP) at diagnosis in POAG patients. Studies without available data, case-only studies, reviews, conference abstracts or family-based studies were excluded. If more than one population with available data were included in a single study, each population was regarded as separate data in the analyses. We included the most comprehensive study when duplicate sequencing data existed in multiple studies.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of each case-control study with its 'star system' by two reviewers (C.G. and X.Y.), which is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control studies respectively (11). The disagreement between the two reviewers was solved by a senior reviewer (Z.F.).

Data extraction

Two reviewers (C.G. and X.Y.) extracted data into a customized table independently. Any discrepancy was resolved by consensus. The extracted information included first author, title, published year, country, ethnicity, age at diagnosis, IOP at diagnosis, genotypes distribution of M98K in POAG patients [NTG and high tension glaucoma (HTG) patients; Asian and non-Asian POAG patients; juvenile open angle glaucoma (JOAG) and adult-onset POAG] and controls, the total number of patients and controls.

Statistical analyses

Meta-analysis was conducted using Comprehensive Meta-Analysis software version 2.2.064 (Biostat Inc., NJ, USA). The statistical significance of the pooled odds ratio (OR) and 95% confidence interval (CI) was determined by Z-test. To reduce the type I error, the Bonferroni correction was used to determine the statistically significant genetic models. Because multiple comparisons were performed 35 times, the P value less than 0.05/35 (0.0014) was considered as statistical significance after Bonferroni correction. The heterogeneity across studies was assessed

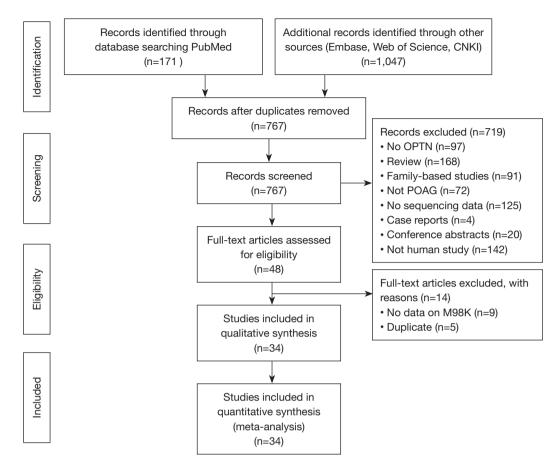


Figure 1 The flow chart of literature selection.

and qualified by the I^2 index, with I^2 of greater than 50% considered as large or extreme heterogeneity (12). Additionally, a Q-statistic test was performed. All metaanalyses and subgroup analyses were performed by the random-effects model. The contour-enhanced funnel plot with trim-and-fill method and Egger's tests were used to assess the potential publication bias. The Power and Sample Size Calculation software (13) was used to assess the expected statistical power of our meta-analysis in detecting the association between M98K and risk of POAG at a level of significance of 0.0014.

Results

Inclusion of studies

A total of 1,218 records were identified, yielding 767 studies after removal of duplicates. Following screening, 719 publications were excluded based on the title and abstract, and 48 full text articles were assessed for eligibility. After excluding 9 studies without data on M98K and 5 studies with duplicate data, a total of 34 publications including 39 populations with available data were included in the final analyses. Ayala-Hugo *et al.* (14) reported 4 populations, including Asian, African, Hispanic, and Caucasian subjects; Alward *et al.* (15) reported 2 populations, including Caucasian (Iowa and Australia) and Japanese samples; Melki *et al.* (16) reported 2 populations, including French and Moroccan. The flow chart of literature selection was shown in *Figure 1*. A total of 7,310 POAG patients and 5,173 controls were involved. The characteristics of subjects were summarized in *Table 1*. According to the NOS, our included studies achieved an average of 6.21 stars for quality assessment (*Table 2, Figure 2*).

Meta-analyses and subgroup analyses

In the analyses of association between M98K and risk of each POAG subgroup, including NTG, HTG, Asian POAG, non-Asian POAG, JOAG, and adult-onset POAG,

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Table 1 Characteristics of included participates in the meta-analysis

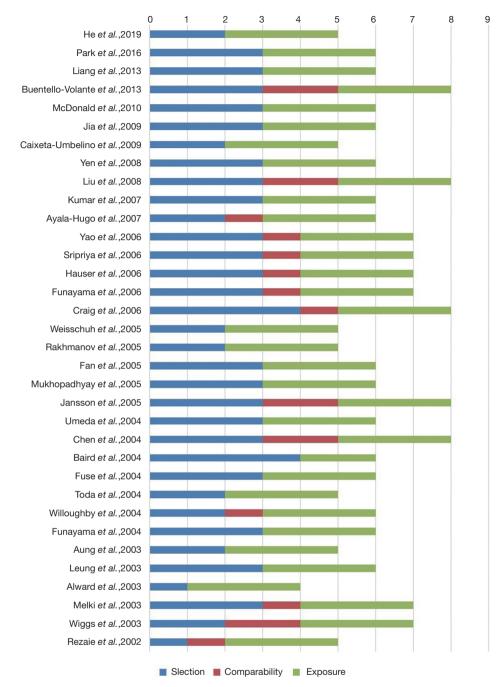
No.	Study	Year	Pagion	Populations	No. of participants		
NO.	Study	rear	Region	Populations	POAG	Controls	
	He et al. (17)	2019	Asia	Chinese	190	201	
2	Park e <i>t al.</i> (18)	2016	Asia	Korean	112	100	
3	Liang et al. (19)	2013	Asia	Chinese	100	60	
1	Buentello-Volante et al. (20)	2013	North America	Mexican	118	100	
5	McDonald et al. (21)	2010	North America	Mestizos	88	93	
6	Jia <i>et al.</i> (22)	2009	Asia	Chinese	176	200	
7	Caixeta-Umbelino et al. (23)	2009	South America	Brazilian	99	100	
3	Yen <i>et al.</i> (24)	2008	Asia	Chinese	51	51	
)	Liu <i>et al.</i> (25)	2008	Africa	Ghanaian	133	124	
10	Kumar <i>et al.</i> (26)	2007	Asia	Indian	251	96	
11	Ayala-Hugo et al. (14)	2007	Mixed	Mixed	314	371	
12	Yao et al. (27)	2006	Asia	Chinese	142	77	
13	Sripriya <i>et al.</i> (28)	2006	Asia	Indian	220	100	
14	Hauser <i>et al.</i> (29)	2006	North America	Mixed	153	100	
15	Funayama <i>et al.</i> (30)	2006	Asia	Japanese	528	240	
16	Craig et al. (8)	2006	Oceania	Australian	498	218	
17	Weisschuh <i>et al.</i> (31)	2005	Europe	German	112	100	
18	Rakhmanov et al. (32)	2005	Europe	Russian	170	100	
19	Fan <i>et al.</i> (33)	2005	Asia	Chinese	400	281	
20	Mukhopadhyay et al. (34)	2005	Asia	Indian	200	200	
21	Jansson <i>et al.</i> (35)	2005	Europe	Swede	200	200	
22	Umeda <i>et al.</i> (36)	2004	Asia	Japanese	83	58	
23	Chen <i>et al.</i> (37)	2004	Asia	Chinese	118	150	
24	Baird <i>et al.</i> (38)	2004	Oceania	Australian	27	94	
25	Fuse <i>et al.</i> (39)	2004	Asia	Japanese	154	100	
26	Toda <i>et al.</i> (40)	2004	Asia	Japanese	313	196	
27	Willoughby <i>et al.</i> (41)	2004	Mixed	Mixed	115	101	
28	Funayama <i>et al.</i> (42)	2004	Asia	Japanese	411	218	
29	Aung et al. (43)	2003	Europe	British	315	95	
30	Leung et al. (44)	2003	Asia	Chinese	119	126	
31	Alward et al. (15)	2003	Mixed	Mixed	897	251	
32	Melki <i>et al.</i> (16)	2003	Mixed	Mixed	293	170	
33	Wiggs <i>et al.</i> (45)	2003	North America	Mixed	86	80	
34	Rezaie <i>et al.</i> (6)	2002	_	Caucasian	124	422	

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Table 2 The assessment of quality of eligible studies using the Newcastle-Ottawa Scale (NOS)

NIa	Study	Selection				Compa	arability	Exposure			Tatalat
No.	Study	NOS1	NOS2	NOS3	NOS4	NOS5	NOS6	NOS7	NOS8	NOS9	Total sta
1	He et al. (17)	*	_	_	*	_	_	*	*	*	5
2	Park <i>et al.</i> (18)	*	*	-	*	-	-	*	*	*	6
3	Liang et al. (19)	*	*	-	*	-	-	*	*	*	6
4	Buentello-Volante et al. (20)	*	*	-	*	*	*	*	*	*	8
5	McDonald et al. (21)	*	*	-	*	-	-	*	*	*	6
6	Jia et al. (22)	*	*	-	*	-	-	*	*	*	6
7	Caixeta-Umbelino et al. (23)	*	-	-	*	-	-	*	*	*	5
8	Yen et al. (24)	*	*	-	*	-	-	*	*	*	6
9	Liu <i>et al.</i> (25)	*	*	-	*	*	*	*	*	*	8
10	Kumar <i>et al.</i> (26)	*	*	-	*	-	-	*	*	*	6
11	Ayala-Hugo <i>et al.</i> (14)	*	-	-	*	-	*	*	*	*	6
12	Yao et al. (27)	*	*	-	*	*	-	*	*	*	7
13	Sripriya et al. (28)	*	*	-	*	*	-	*	*	*	7
14	Hauser et al. (29)	*	*	-	*	*	-	*	*	*	7
15	Funayama et al. (30)	*	*	-	*	*	-	*	*	*	7
16	Craig et al. (8)	*	*	*	*	*	-	*	*	*	8
17	Weisschuh <i>et al.</i> (31)	*	*	-	-	-	-	*	*	*	5
18	Rakhmanov et al. (32)	*	*	-	-	-	-	*	*	*	5
19	Fan et al. (33)	*	*	-	*	-	-	*	*	*	6
20	Mukhopadhyay et al. (34)	*	*	-	*	-	-	*	*	*	6
21	Jansson <i>et al.</i> (35)	*	*	-	*	*	*	*	*	*	8
22	Umeda <i>et al.</i> (36)	*	*	-	*	-	-	*	*	*	6
23	Chen <i>et al.</i> (37)	*	*	-	*	*	*	*	*	*	8
24	Baird et al. (38)	*	*	*	*	-	-	*	*	-	6
25	Fuse <i>et al.</i> (39)	*	*	-	*	-	-	*	*	*	6
26	Toda <i>et al.</i> (40)	*	-	-	*	-	-	*	*	*	5
27	Willoughby <i>et al.</i> (41)	*	*	-	-	*	-	*	*	*	6
28	Funayama et al. (42)	*	*	-	*	-	-	*	*	*	6
29	Aung <i>et al.</i> (43)	*	*	-	-	-	-	*	*	*	5
30	Leung et al. (44)	*	*	-	*	-	-	*	*	*	6
31	Alward et al. (15)	*	-	-	-	-	-	*	*	*	4
32	Melki <i>et al.</i> (16)	*	*	*	-	*	-	*	*	*	7
33	Wiggs et al. (45)	*	*	-	-	*	*	*	*	*	7
34	Rezaie <i>et al.</i> (6)	*	_	_	_	*	_	*	*	*	5

NOS1, adequate definition of case; NOS2, representativeness of the cases; NOS3, selection of controls; NOS4, definition of controls; NNO5, cases and controls with comparable age; NNO6, cases and controls with comparability on other controlled factors (exception for ethnic); NNO7, ascertainment of exposure; NNO8, same method of ascertainment for cases and controls; NNO9, non-response rate. The stars indicate high quality items.





under the multiple genetic models, we performed the Bonferroni correction to reduce the type I error (*Table 3*).

We found significantly more OPTN M98K carriers in the overall POAG patients than those in the controls under the dominant model (OR =1.30, 95% CI, 1.12– 1.52, P<0.001; Power =0.958) (*Figure 3*). In the stratification analysis, M98K was not associated with NTG and HTG under any model. No association was observed between M98K and POAG risk in the non-Asian and the Asian population. Also, M98K was not associated with JOAG and adult-onset POAG under any model.

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Table 3 The associations between M98K and PAOG

Subgroups	No. of populations	Sample size (case/control)	OR (95% CI)	P value*	I ²	Q tests (P value)	Egger's tests (P value)
All							
A vs. T	21	3,864/2,826	1.24 (1.07–1.45)	0.005	21.89	0.178	0.026
AA vs. TT	14	2,962/2,115	1.65 (1.02–2.69)	0.043	0	0.933	0.302
TA vs. TT	21	3,864/2,826	1.19 (1.00–1.42)	0.045	23.31	0.163	0.078
TA vs. AA +TT	21	3,864/2,826	1.18 (0.99–1.41)	0.061	23.83	0.158	0.078
AA+TA vs. TT	39	7,310/5,173	1.30 (1.12–1.52)	<0.001	32.53	0.028	0.007
Asian							
A vs. T	15	3,199/2,208	1.24 (1.04–1.48)	0.016	32.81	0.106	0.014
AA vs. TT	11	2,596/1,790	1.73 (1.04–2.90)	0.036	0	0.912	0.098
TA vs. TT	15	3,199/2,208	1.17 (0.96–1.42)	0.111	31.99	0.113	0.053
TA vs. AA +TT	15	3,199/2,208	1.16 (0.95–1.40)	0.142	32.10	0.112	0.056
AA+TA vs. TT	19	3,820/2,660	1.29 (1.07–1.54)	0.007	33.78	0.076	0.006
Non-Asian							
A vs. T	5	550/517	1.18 (0.79–1.77)	0.423	0	0.590	0.860
AA vs. TT	2	251/224	1.56 (0.30–8.21)	0.600	0	0.431	-
TA vs. TT	5	550/517	1.19 (0.76–1.85)	0.449	0	0.876	0.522
TA vs. AA +TT	5	550/517	1.19 (0.76–1.85)	0.448	0	0.877	0.512
AA+TA vs. TT	17	3,136/2,232	1.33 (0.96–1.84)	0.084	37.79	0.058	0.196
NTG							
A vs. T	9	1,129/1,471	1.42 (1.07–1.90)	0.016	48.58	0.049	0.104
AA vs. TT	7	1,051/1,313	1.97 (0.96–4.04)	0.065	0	0.681	0.604
TA vs. TT	9	1,129/1,471	1.38 (1.03–1.84)	0.030	38.23	0.114	0.068
TA vs. AA +TT	9	1,129/1,471	1.36 (1.02–1.81)	0.033	36.58	0.126	0.057
AA+TA vs. TT	21	1,991/2,800	1.46 (1.14–1.86)	0.002	29.42	0.102	0.095
HTG							
A vs. T	14	1,953/1,905	1.16 (0.94–1.42)	0.178	29.50	0.142	0.023
AA vs. TT	10	1,529/1,587	1.41 (0.78–2.56)	0.251	0	0.988	0.613
TA vs. TT	14	1,953/1,905	1.11 (0.90–1.38)	0.320	18.19	0.255	0.065
TA vs. AA +TT	14	1,953/1,905	1.11 (0.90–1.36)	0.353	17.58	0.262	0.067
AA+TA vs. TT	24	3,557/3,045	1.12 (0.93–1.34)	0.233	17.79	0.217	0.004

Table 3 (Continued)

Table 3 (Continued)

Subgroups	No. of populations	Sample size (case/control)	OR (95% CI)	P value*	 ²	Q tests (P value)	Egger's tests (P value)
JOAG							
A vs. T	3	153/392	1.39 (0.83–2.30)	0.207	0	0.733	0.819
AA vs. TT	3	153/392	1.96 (0.50–7.67)	0.334	0	0.680	0.493
TA vs. TT	3	153/392	1.34 (0.74–2.44)	0.339	0	0.408	0.005
TA vs. AA +TT	3	153/392	1.30 (0.71–2.36)	0.397	0.40	0.366	0.037
AA+TA vs. TT	8	224/925	1.41 (0.89–2.23)	0.144	0	0.925	0.076
Adult-onset POA	AG						
A vs. T	4	742/499	2.84 (1.10–7.33)	0.031	53.97	0.089	0.022
AA vs. TT	3	659/441	2.47 (0.53–11.44)	0.248	0	0.718	0.685
TA vs. TT	4	742/499	3.18 (0.99–10.19)	0.052	60.61	0.055	0.175
TA vs. AA +TT	4	742/499	1.61 (1.09–2.38)	0.017	61.35	0.051	0.177
AA+TA vs. TT	12	1,777/1,241	1.45 (1.03–2.04)	0.034	21.28	0.234	0.027

All meta-analyses were performed by a random-effects model. *, P value less than 0.05/35 (0.0014) was considered as statistical significance after Bonferroni correction. OR, odds ratio; CI, confidence interval; NTG, normal tension glaucoma; HTG, high tension glaucoma; JOAG, juvenile open angle glaucoma; adult-onset POAG, adult-onset primary open angle glaucoma. A, A allele; T, T allele; AA, AA genotype; TT, TT genotype; TA, TA genotype.

	Study name	Subgroup within stud	ly	Statist	ics for e	ach study	1		Odd	s ratio and 95% Cl	
Park, 2016 Korean 0.93 0.46 1.89 -0.20 0.843 Liang, 2013 Chinese 1.25 0.54 2.89 0.52 0.601 Buentello-Volante, 2013Mexican 6.09 0.31 119.35 1.19 0.234 McDonald, 2010 Hispanic 1.06 0.30 3.80 0.09 0.928 Caixeta-Umbelino, 2008razilian 0.50 0.44 5.60 -0.66 0.574 Yen, 2008 Chinese 1.32 0.77 2.26 1.00 0.316 Kumar, 2007 Caicasian 1.12 0.77 2.06 0.08 0.937 Ayala-Lugo, 2007 African 0.97 0.47 2.00 -0.68 0.937 Ayala-Lugo, 2007 Caicasian 0.93 0.38 2.29 -0.16 0.876 Ayala-Lugo, 2007 Caicasian 0.93 0.38 2.29 -0.16 0.876 Ayala-Lugo, 2007 Chinese 0.63 0.35 1.13 -1.55 0.121 Yao, 2006 Chinese 0.63 0.35 1.13 -1.55 0.121 Sripriya, 2006 Indian 1.00 0.58 172.81 1.59 0.113 Hauser, 2006 Mixed 1.02 0.42 2.45 0.04 0.988 Rakhmanov, 2005 Russian 6.85 0.87 53.87 1.83 0.067 Craig, 2006 Australia 0.70 0.38 1.53 0.113 Hauser, 2006 Linese 1.18 0.84 1.64 0.95 0.341 Mixehopadhya, 2005 Russian 6.85 0.87 53.87 1.83 0.067 Fan, 2005 Chinese 1.18 0.84 1.56 0.010 Jansson, 2005 Swedish 0.90 0.36 2.25 -0.23 0.814 Fuse, 2004 Japanese 1.22 0.74 2.02 0.77 0.443 Bird, 2004 Caucasian 1.82 1.07 10.57 2.07 0.038 Funayama, 2005 Indian 2.12 1.00 4.51 1.56 0.050 Jansson, 2005 Swedish 0.90 0.36 2.25 -0.23 0.814 Fuse, 2004 Japanese 1.22 0.74 2.02 0.77 0.443 Hikhopadhya, 2005 Indian 2.12 1.00 4.51 1.56 0.050 Jansson, 2005 Swedish 0.90 0.36 2.25 -0.23 0.814 Fuse, 2004 Japanese 1.22 0.74 2.02 0.77 0.443 Hikhopadhya, 2005 Indian 2.12 1.00 4.51 1.56 0.121 Hundra, 2004 Japanese 1.22 0.74 2.02 0.77 0.443 Hikhopadhya, 2005 Indian 2.12 1.00 4.51 1.56 0.121 Hundra, 2004 Japanese 1.24 0.81 1.57 0.17 0.032 Chen, 2004 Caucasian 1.16 0.57 2.35 0.010 Hode, 2004 Japanese 1.24 0.51 1.55 0.121 Hundra, 2004 Japanese 1.24 0.580 2.241 0.016 Huki, 200						Z-Value	p-Value				
Liang, 2013 Chinese 1.25 0.54 2.89 0.52 0.601 Buentello-Volante, 2013Mexican 6.09 0.31 119.35 1.19 0.234 McDonaid, 2010 Hispanic 1.06 0.30 3.80 0.09 0.928 Jia, 2009 Chinese 0.89 0.54 1.45 -0.48 0.630 Caixeta-Umbelino, 2008Fazillan 0.50 0.04 5.60 -0.574 Yen, 2008 Chinese 1.32 0.57 3.08 0.65 0.519 Liu, 2008 Ghanaian 1.32 0.77 2.26 1.00 0.316 Ayala-Lugo, 2007 Arican 0.97 0.47 2.00 -0.88 0.937 Ayala-Lugo, 2007 Arian 0.97 0.47 2.00 -0.88 0.937 Ayala-Lugo, 2007 Asian 4.55 0.72 2.86 0.100 Ayala-Lugo, 2007 Asian 4.55 0.72 2.86 0.100 Ayala-Lugo, 2007 Asian 0.93 0.38 2.29 -0.16 0.876 Ayala-Lugo, 2007 Hispanic 4.90 0.28 85.05 1.09 0.275 Shpriya, 2006 Chinese 0.63 0.35 1.13 -1.55 0.121 Shpriya, 2006 Indian 10.03 0.58 172.81 1.59 0.113 Shpriya, 2006 Australia 0.70 0.38 1.32 -1.10 0.272 Weisschul, 2005 German 0.89 0.30 2.62 -0.22 0.826 Rakhmanov, 2005 Swedish 0.90 0.36 2.25 -0.23 0.814 Buird, 2004 Guacasian 2.43 0.38 1.53 0.94 0.346 Fuayama, 2005 Indian 2.12 100 4.51 1.96 0.050 Jamsson, 2005 Swedish 0.90 0.36 2.25 -0.23 0.814 Buird, 2004 Guacasian 2.43 0.38 1.53 0.94 0.346 Fuayama, 2004 Japanese 1.28 0.77 7.07 0.433 Willoughby, 2004 Mixed 3.36 1.70 1.57 2.07 0.038 Fuayama, 2004 Japanese 1.24 0.81 1.91 0.98 0.328 Umeda, 2004 Japanese 1.24 0.81 1.91 0.98 0.328 Umeda, 2004 Japanese 1.24 0.81 1.55 0.121 Aiward, 2003 Chinese 1.64 0.88 3.08 1.55 0.121 Aiward, 2003 Chinese 1.24 0.51 1.91 0.98 0.328 Umeda, 2004 Japanese 1.24 0.51 1.91 0.98 0.328 Umeda, 2004 Japanese 1.24 0.51 0.70 0.482 Aiward, 2003 Chinese 1.23 0.69 2.16 0.70 0.482 Aiward, 2003 Chinese 1.23 0.69 2.16 0.70 0.482 Aiward, 2003 Chinese 1.23 0.69 2.16 0.70 0.482 Aiward, 2003 Chinese 1.23 0.58 0.241 0.016 Mekli, 2003 Mixed 0.92 0.33 2.59 0.15 0.879 Rezaie, 2002 Caucasian 1.16 0.57 2.35 0.41 0.6	He, 2019	Chinese	1.02	0.65		0.10	0.920		1		1
Buentello-Volante, 2013Mexican 6.09 0.31 119.35 1.19 0.234 McDonald, 2010 Hispanic 1.06 0.30 3.80 0.09 0.928 Jia, 2009 Chinese 0.88 0.54 1.45 0.48 0.630 Caixeta-Umbelino, 2009Frazilian 0.50 0.04 5.60 -0.56 0.574 Yen, 2008 Ghanaian 1.32 0.57 3.08 0.65 0.519 Liu, 2008 Ghanaian 1.10 0.45 2.69 0.21 0.833 Ayala-Lugo, 2007 African 0.97 0.47 2.00 -0.08 0.937 Ayala-Lugo, 2007 African 0.93 0.38 2.29 -0.16 0.876 Ayala-Lugo, 2007 Hispanic 4.90 0.28 85.05 1.09 0.275 Yao, 2006 Chinese 0.63 0.35 1.13 -1.55 0.121 Mayala-Lugo, 2007 Hispanic 4.90 0.28 85.05 1.09 0.275 Yao, 2006 Chinese 0.63 0.35 1.42 0.167 Craig, 2006 Australia 0.70 0.38 1.32 -1.10 0.272 Weisschuh, 2005 Russian 6.85 0.87 53.87 1.83 0.067 Fan, 2006 Chinese 1.18 0.84 1.64 0.95 0.341 Mukhopadhyay, 2005 Indian 2.12 1.00 4.51 1.96 0.500 Chinese 1.18 0.84 1.64 0.95 0.341 Mukhopadhyay, 2005 Indian 2.12 0.077 0.443 Willoughby, 2004 Japanese 3.68 1.36 9.97 2.56 0.010 Toda, 2004 Japanese 3.68 1.36 9.97 2.56 0.010 Toda, 2004 Japanese 3.68 1.36 9.97 2.56 0.010 Toda, 2004 Japanese 1.22 0.77 0.038 Lurayama, 2004 Japanese 1.24 0.187 1.33 0.84 Umeda, 2004 Japanese 1.24 0.77 0.328 Umeda, 2004 Japanese 1.24 0.77 0.443 Willoughby, 2035 Mixed 3.36 1.07 10.57 2.077 0.443 Willoughby, 2034 Mixed 3.36 1.77 1.33 0.183 Leung, 203 Gaucasian 1.16 0.57 2.35 0.411 0.685 Alward, 203 Gaucasian 1.16 0.57 2.35 0.414 0.685 Alward, 203 Gaucasian 1.16 0.57 2.33 0.44 0.968 Mixed 0.92 0.33 2.59 -0.15 0.879 Rezaie, 2002 Caucasian 6.31 2.69 14.82 4.23 0.0001	Park, 2016	Korean	0.93	0.46	1.89	-0.20	0.843				
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Jia, 2009 Chinese 0.89 0.54 1.45 0.48 0.630 Caixeta-Umbelino, 2009Brazilian 0.50 0.04 5.60 0.574 Yen, 2008 Chinese 1.32 0.77 2.26 1.00 0.316 Kumar, 2007 Indian 1.10 0.45 2.69 0.21 0.833 Ayala-Lugo, 2007 African 0.97 0.47 2.00 -0.08 0.937 Ayala-Lugo, 2007 Asian 4.55 0.72 28.60 1.62 0.106 Ayala-Lugo, 2007 Hispanic 4.90 0.28 85.05 1.09 0.275 Yao, 2006 Chinese 0.63 0.35 17.28 1.59 0.113 Hauser, 2006 Mixed 1.02 0.42 2.45 0.044 0.968 Frunayama, 2006 Japanese 1.55 0.87 5.387 1.83 0.067 Fan, 2005 Chinese 1.18 0.84 1.64 0.95 0.341 Mukhopadhya, 2005 Keishan 2.12 1.00 4.51 1.59 0.131 Hauser, 2006 Chinese 1.18 0.84 1.64 0.95 0.341 Mukhopadhya, 2005 Swedish 0.90 0.36 2.25 -0.22 0.826 Fan, 2005 Chinese 1.18 0.84 1.64 0.95 0.341 Mukhopadhya, 2005 Swedish 0.90 0.36 2.25 -0.23 0.814 Baird, 2004 Japanese 3.86 1.36 9.72 5.56 0.010 Toda, 2004 Japanese 1.22 0.74 2.02 0.77 0.443 Willoughby, 2004 Japanese 1.24 0.67 7.87 1.33 0.183 Leung, 2004 Japanese 9.63 1.22 7.6.31 2.15 0.0322 Chen, 2004 Japanese 9.63 1.22 7.6.31 2.15 0.0328 Umeda, 2004 Japanese 9.6.3 1.22 7.6.31 2.4.5 0.040 0.665 Alward, 2003 Grittish 2.30 0.69 7.67 7.7 1.33 0.183 Leung, 2003 Chinese 1.24 0.38 4.59 0.44 0.0665 Alward, 2003 Grucesian 1.16 0.57 2.35 0.41 0.016 Melki, 2003 Mixed 0.92 0.33 4.59 0.44 0.0663 Wiggs, 2003 Mixed 0.92 0.	Buentello-Volante, 20	13Mexican	6.09	0.31	119.35	1.19	0.234		-		+-
Caixeta-Umbelino, 200 Brazilian 0.50 0.04 5.60 -0.56 0.574 Yen, 2008 Ghanaian 1.32 0.57 3.08 0.65 0.519 Liu, 2008 Ghanaian 1.32 0.77 2.26 1.00 0.316 Kumar, 2007 Indian 1.10 0.45 2.69 0.21 0.833 Ayala-Lugo, 2007 Asian 4.55 0.72 28.60 1.62 0.106 Ayala-Lugo, 2007 Asian 0.93 0.38 2.29 -0.16 0.876 Ayala-Lugo, 2007 Hispanic 4.90 0.28 85.05 1.09 0.275 Yao, 2006 Chinese 0.63 0.35 1.13 -1.55 0.121 Sripriya, 2006 Indian 10.03 0.58 172.81 1.59 0.113 Hauser, 2006 Mixed 1.02 0.42 2.45 0.04 0.968 Funayama, 2006 Japanese 1.35 0.89 2.03 1.42 0.157 Craig, 2006 Australia 0.70 0.38 1.52 -1.10 0.272 Weissohuh, 2005 Russian 6.85 0.87 53.87 1.83 0.067 Fan, 2005 Chinese 1.18 0.84 1.64 0.95 0.341 Wukhopadhyay, 2005 Indian 2.12 1.00 4.51 1.96 0.050 Hansson, 2005 Swedish 0.90 0.36 2.25 -0.23 0.814 Baird, 2004 Gaucasian 2.43 0.38 1.53 0.94 0.346 Cruay, 2005 Swedish 0.90 0.36 2.25 -0.23 0.814 Baird, 2004 Japanese 3.68 1.36 9.97 2.56 0.010 Toda, 2004 Japanese 1.22 0.77 0.038 Lugo, 2004 Japanese 1.22 0.77 0.038 Lugo, 2004 Japanese 1.22 0.77 0.038 Lugo, 2004 Japanese 1.23 0.69 2.16 0.70 0.482 Jmeda, 2004 Japanese 1.23 0.67 7.87 1.33 0.183 Leung, 2003 British 2.30 0.67 7.87 1.33 0.183 Leung, 2003 Chinese 1.18 0.57 2.35 0.41 0.663 Jward, 2003 Chinese 1.23 0.67 7.87 1.33 0.183 Leung, 2003 Chinese 1.23 0.67 7.87 1.33 0.183 Leung, 2003 Chinese 1.23 0.69 2.41 0.016 Welki, 2003 Mired 0.92 0.33 2.59 0.41 0.663 Wiggs, 2003 Mired 0.92 0.33 2.59 0.41 0.663 Wiggs, 2003 Mired 0.92 0.33 0.20 0.44 0.968 Wiggs, 2003 Mired 0.92 0.33 0.25 0.41 0.663 Wiggs, 2003 Mired 0.92 0.33 0.25 0.41 0.016 Welki, 2003 Mired 0.92 0.33 0.25 0.41 0.663 Wiggs, 2003 Mired 0.92 0.33 0.25 0.45 0.587 Wiggs, 2003 Mired 0.92 0.33 0.25 0.4	McDonald, 2010	Hispanic	1.06	0.30	3.80	0.09	0.928				
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Figure 3 Forest plot of the association between M98K mutation and primary open angle glaucoma susceptibility under the dominant model.

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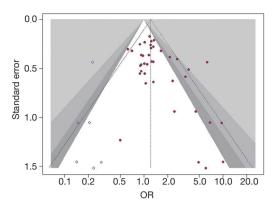


Figure 4 Assessment of the influence of publication bias in overall primary open angle glaucoma group under the dominant model by the counter-enhanced funnel plot with trim-and-fill method.

	p.M98K
Homo sapiens	IQSKEAKERLMALSHENEKLK
Macaca mulatta	TQSKEAKERLMALSHENEKLK
Macaca fascicularis	TQSKEAKERLMALSHENEKLK
Callithrix jacchus	TQSKEAKERLMALSQENEKLK
Pan troglodytes	IQSKEAKERLMALSHENEKLK
Gorilla gorilla gorilla	IQSKEAKERLMALSHENEKLK

Figure 5 Evolutionary conservation of primary open angle glaucoma M98K mutation across different species.

Association between M98K and IOP/age at diagnosis in POAG patients

No significant association was observed between M98K and IOP at diagnosis in POAG patients (SMD =-0.19, 95% CI, -0.46 to 0.07; P=0.156). Also, M98K was not associated with age at diagnosis in POAG patients (SMD =0.17, 95% CI, -0.15 to 0.49; P=0.294).

Publication bias and sensitivity analysis

For the significant association in our study (*Table 3*), the Egger tests suggested statistically significant publication biases existed in the associations between M98K and overall POAG risk under the dominant model (P=0.007).

The counter-enhanced funnel plot with trim-and-fill method was used to assess the influence of publication bias in the pooled effects (*Figure 4*). The association between M98K and overall POAG risk under the dominant model (OR: 1.22, 95% CI, 1.02–1.46; P=0.029) was still statistically significant after adding 6 studies.

Conclusions

This is an updated meta-analysis to investigate the association between M98K polymorphism and risk for POAG. Our results indicate that M98K increases risks of overall POAG under the dominant model.

The three reported meta-analyses on the M98K in the risk of POAG had controversial results, with positive associations by Chen *et al.* (10) and Craig *et al.* (8) while negative association by Cheng *et al.* (9). The difference in included populations may explain this inconsistency. The latest meta-analysis only included 5 studies (10), and the other two published in 2010 (9) and 2006 (8) included 23 and 19 studies respectively. In this comprehensive study, a total of 34 publications including 39 populations were included, which made us possible to make a more definitive conclusion.

Being in accordance with the dominant inherited mode of OPTN in the POAG pedigree (5,6), M98K was found to be positively associated with overall POAG under the dominant model. Hubens et al. (46) recently reported that OPTN was intensively expressed in the retina, including RGCs, in the healthy mouse eves. There is some evidence that OPTN might play a neuro-protective role by reducing RGCs susceptibility to apoptosis through negatively regulating TNF- α -induced NF- κ B activation (47,48). The M98K, evolutionarily conservative in various species (Figure 5), was reported to induce cell death when expressed in RGC-5 (49) and 661W (50) cells, which may indicate the M98K could directly induce the death of RGCs. In this study, we found that the M98K is associate with NTG at a nominal level of significance, but not with HTG patients, in which the myocilin (MYOC) mutations may be the common causes. Besides, the age at diagnosis showed no significant association with M98K mutation in POAG patients, the mean age at diagnosis was 61.07 (95% CI, 57.00-65.14) years in POAG patients with M98K pooled from 4 studies (8,32,36,42).

Some concerns remain in this study, though. Firstly, the effects estimated here were modest although several significant associations were observed, suggesting the possible mild role of this risk allele in POAG patients. Secondly, since publication bias existed, we performed trimand-fill method to evaluate the influence of these biases. As a result, the association remained statistical significant, although the association should be further studied with a large sample size. Thirdly, only articles published in English and Chinese were included, which may cause language bias.

In summary, our updated meta-analysis provided the

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most comprehensive role of M98K in the susceptibility of POAG patients. This common variant, M98K, could contribute to POAG susceptibility.

Acknowledgments

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/aes-20-124). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1 The search strategy for databases

PubMed (Search data: 2020-12-15)

	Search Query	Results
#1	Optineurin or OPTN or M98K or Met98Lys [All Fields]	1,216
#2	OPTN protein, human [Mesh Terms]	409
#3	#1 or #2	1,216
#4	Primary Open Angle Glaucoma or open angle glaucoma or POAG or normal pressure glaucoma or low tension glaucoma or Normal tension glaucoma or high tension glaucoma [All Fields]	22,546
#5	Glaucoma, Open-Angle or Low Tension Glaucoma [MeSH Terms]	19,279
#6	#4 or #5	22,546
#7	#3 and #6	175
#8	#7 AND (("1966/01/01"[Date - Publication]: "2019/12/31"[Date - Publication]))	171

Embase (Search data: 2020-12-15)

	Search Query	Results
#1	optineurin OR optn OR m98k OR met98lys	3,033
#2	'optineurin'/exp	732
#3	#1 OR #2	3,033
#4	'primary open angle glaucoma' OR 'open angle glaucoma' OR poag OR 'normal pressure glaucoma' OR 'low tension glaucoma' OR 'normal tension glaucoma' OR 'high tension glaucoma'	23,700
#5	'open angle glaucoma'/exp	19,451
#6	#4 OR #5	23,700
#7	#3 AND #6	253
#8	#7 AND [<1966-2019]/py	242

Web of Science (Search data: 2020-12-15)

	Search Query	Results
#1	optineurin OR optn OR m98k OR met98lys [Topic]	2,043
#2	ʻprimary open angle glaucoma' OR ʻopen angle glaucoma' OR poag OR ʻnormal pressure glaucoma' OR ʻlow tension glaucoma' OR ʻnormal tension glaucoma' OR ʻhigh tension glaucoma'	34,324
#3	#1 AND #2	369
#4	#3 AND [excluding] PUBLICATION YEARS: (2020)	359

CNKI (Search data: 2020-12-15)

	Search Query	Results
#1	optineurin OR optn OR m98k OR met98lys OR 视神经病变诱导反应蛋白 [全文] 同义词扩展	5,936
#2	'primary open angle glaucoma' OR 'open angle glaucoma' OR poag OR 'normal pressure glaucoma' OR 'low tension glaucoma' OR 'normal tension glaucoma' OR 'high tension glaucoma' OR 开角型青光眼 OR 原发性开角型青光眼	29,782
#3	#1 AND #2	471
#4	#3 AND [excluding] PUBLICATION YEARS: (2020)	446