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→Lys (E50K), Arg545→Gln (R545Q), c.691_692insAG (Premature stop) and Met98→Lys (M98K), were identified in the original kindred (6). The rare, high-penetrance 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

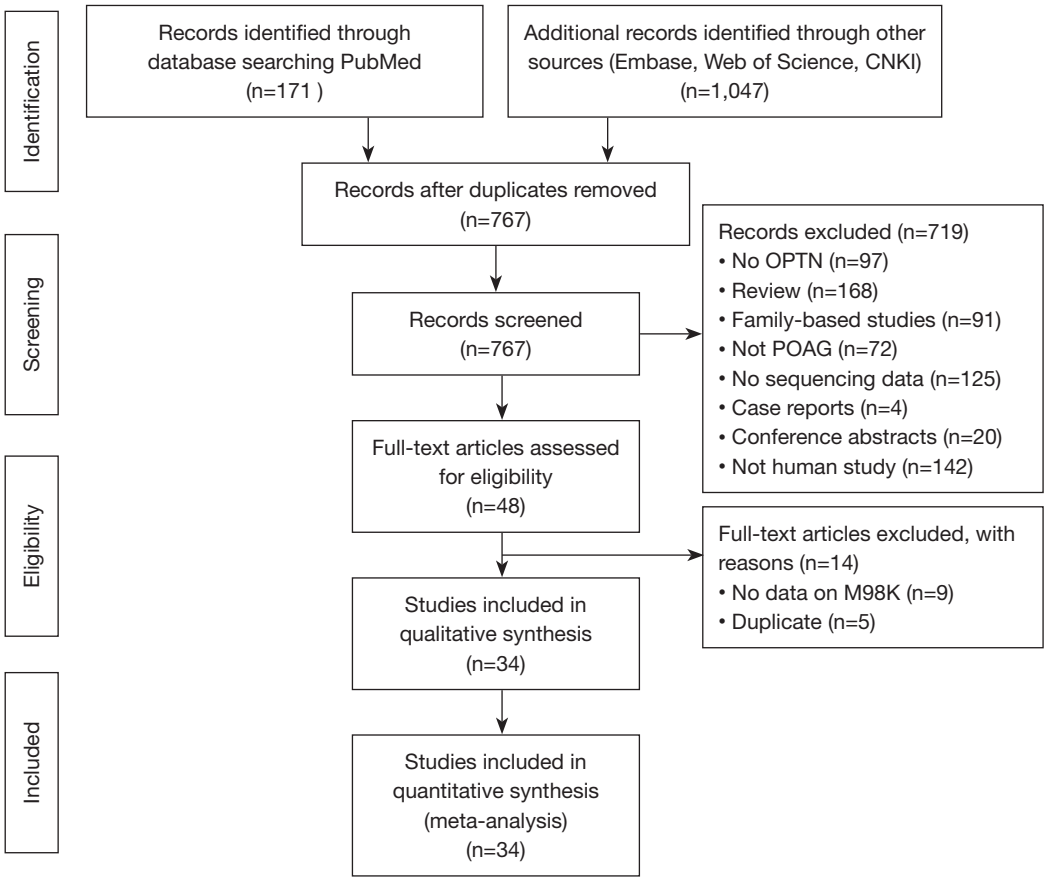

Figure 1 The flow chart of literature selection.

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 meta-analyses 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,

Table 1 Characteristics of included participates in the meta-analysis

No.	Study	Year	Region	Populations	No. of participants	
					POAG	Controls
1	He *et al.* (17)	2019	Asia	Chinese	190	201
2	Park *et al.* (18)	2016	Asia	Korean	112	100
3	Liang *et al.* (19)	2013	Asia	Chinese	100	60
4	Buentello-Volante *et al.* (20)	2013	North America	Mexican	118	100
5	McDonald *et al.* (21)	2010	North America	Mestizos	88	93
6	Jia *et al.* (22)	2009	Asia	Chinese	176	200
7	Caixeta-Umbelino *et al.* (23)	2009	South America	Brazilian	99	100
8	Yen *et al.* (24)	2008	Asia	Chinese	51	51
9	Liu *et al.* (25)	2008	Africa	Ghanaian	133	124
10	Kumar *et al.* (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 *et al.* (28)	2006	Asia	Indian	220	100
14	Hauser *et al.* (29)	2006	North America	Mixed	153	100
15	Funayama *et al.* (30)	2006	Asia	Japanese	528	240
16	Craig *et al.* (8)	2006	Oceania	Australian	498	218
17	Weisschuh *et al.* (31)	2005	Europe	German	112	100
18	Rakhmanov *et al.* (32)	2005	Europe	Russian	170	100
19	Fan *et al.* (33)	2005	Asia	Chinese	400	281
20	Mukhopadhyay *et al.* (34)	2005	Asia	Indian	200	200
21	Jansson *et al.* (35)	2005	Europe	Swede	200	200
22	Umeda *et al.* (36)	2004	Asia	Japanese	83	58
23	Chen *et al.* (37)	2004	Asia	Chinese	118	150
24	Baird *et al.* (38)	2004	Oceania	Australian	27	94
25	Fuse *et al.* (39)	2004	Asia	Japanese	154	100
26	Toda *et al.* (40)	2004	Asia	Japanese	313	196
27	Willoughby *et al.* (41)	2004	Mixed	Mixed	115	101
28	Funayama *et al.* (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 *et al.* (16)	2003	Mixed	Mixed	293	170
33	Wiggs *et al.* (45)	2003	North America	Mixed	86	80
34	Rezaie *et al.* (6)	2002	–	Caucasian	124	422

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

No.	Study	Selection				Comparability		Exposure			Total star
		NOS1	NOS2	NOS3	NOS4	NOS5	NOS6	NOS7	NOS8	NOS9	
1	He *et al.* (17)	★	–	–	★	–	–	★	★	★	5
2	Park *et al.* (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 *et al.* (25)	★	★	–	★	★	★	★	★	★	8
10	Kumar *et al.* (26)	★	★	–	★	–	–	★	★	★	6
11	Ayala-Hugo *et al.* (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 *et al.* (31)	★	★	–	–	–	–	★	★	★	5
18	Rakhmanov *et al.* (32)	★	★	–	–	–	–	★	★	★	5
19	Fan *et al.* (33)	★	★	–	★	–	–	★	★	★	6
20	Mukhopadhyay *et al.* (34)	★	★	–	★	–	–	★	★	★	6
21	Jansson *et al.* (35)	★	★	–	★	★	★	★	★	★	8
22	Umeda *et al.* (36)	★	★	–	★	–	–	★	★	★	6
23	Chen *et al.* (37)	★	★	–	★	★	★	★	★	★	8
24	Baird *et al.* (38)	★	★	★	★	–	–	★	★	–	6
25	Fuse *et al.* (39)	★	★	–	★	–	–	★	★	★	6
26	Toda *et al.* (40)	★	–	–	★	–	–	★	★	★	5
27	Willoughby *et al.* (41)	★	★	–	–	★	–	★	★	★	6
28	Funayama *et al.* (42)	★	★	–	★	–	–	★	★	★	6
29	Aung *et al.* (43)	★	★	–	–	–	–	★	★	★	5
30	Leung *et al.* (44)	★	★	–	★	–	–	★	★	★	6
31	Alward *et al.* (15)	★	–	–	–	–	–	★	★	★	4
32	Melki *et al.* (16)	★	★	★	–	★	–	★	★	★	7
33	Wiggs *et al.* (45)	★	★	–	–	★	★	★	★	★	7
34	Rezaie *et al.* (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.

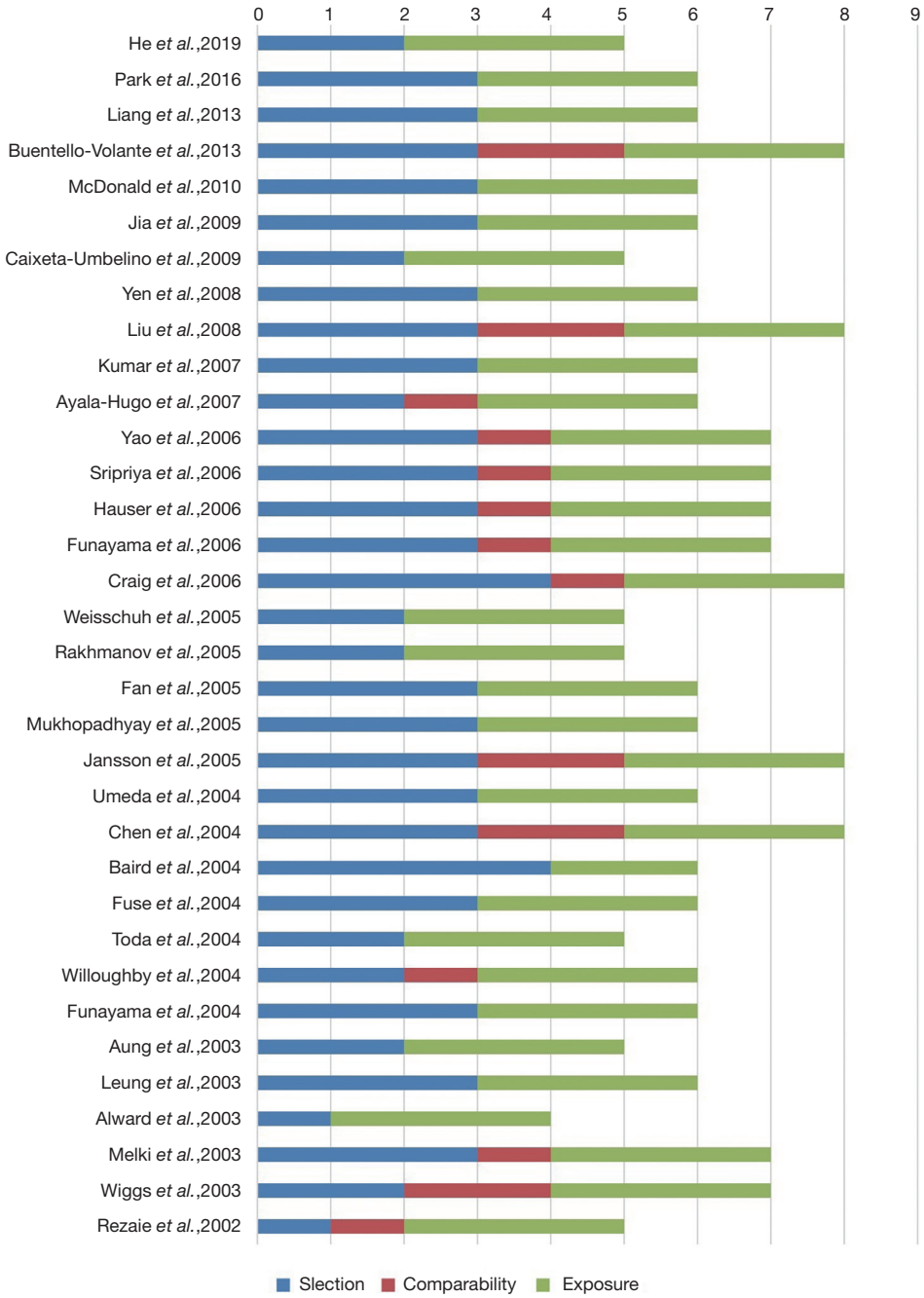

Figure 2 Newcastle-Ottawa Quality Assessment Scale Chart for each study.

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.

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*	I^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 POAG							
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.

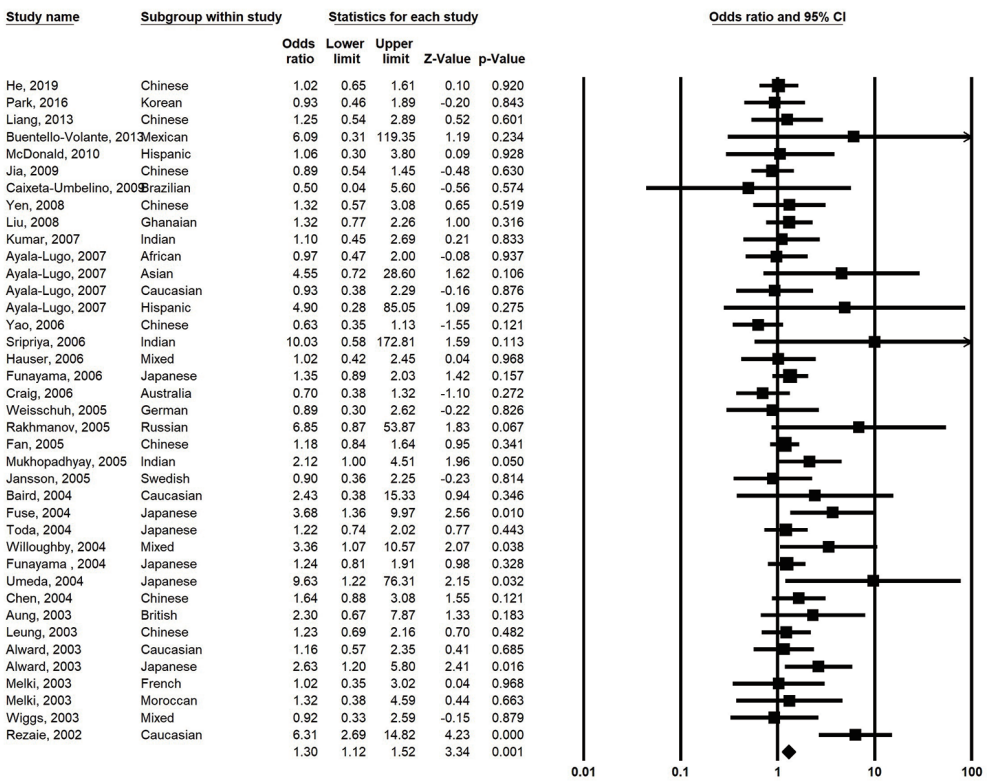

Figure 3 Forest plot of the association between M98K mutation and primary open angle glaucoma susceptibility under the dominant model.

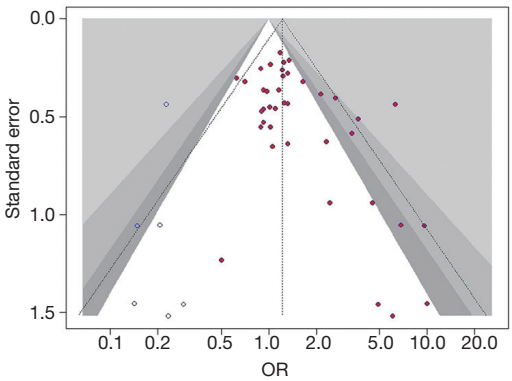

Figure 4 Assessment of the influence of publication bias in overall primary open angle glaucoma group under the dominant model by the counter-enhanced funnel plot with trim-and-fill method.

	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 eyes. 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-κB 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 trim-and-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

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

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Supplementary

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	‘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’	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

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