Association of Gene Polymorphisms With Primary Open Angle Glaucoma: A Systematic Review and Meta-Analysis

Min Chen,[1,2] Xiaoning Yu,[1,2] Jia Xu,[1,2] Jian Ma,[1,2] Xinyi Chen,[1,2] Binbin Chen,[1,2] Yuxiang Gu,[1,2] and Kaijun Wang[1,2]

[1]Eye Center, the 2nd Affiliated Hospital, Medical College of Zhejiang University, Hangzhou, China
[2]Zhejiang Provincial Key Lab of Ophthalmology, Hangzhou, China

Correspondence: Kaijun Wang, The 2nd Affiliated Hospital, Medical College of Zhejiang University, No. 88 Jiefang Road, Hangzhou 310009, China;
ze_wkj@zju.edu.cn.

MC and XY contributed equally to the work presented here and should therefore be regarded as equivalent authors.

Submitted: October 7, 2018
Accepted: January 16, 2019

Citation: Chen M, Yu X, Xu J, et al. Association of gene polymorphisms with primary open angle glaucoma: a systematic review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2019;60:1105–1121. https://doi.org/10.1167/iovs.18-25922

Purpose. To confirm the association of all reported common polymorphisms with POAG.

Methods. We searched in PubMed and Web of Science (up to January 10, 2018) for genetic studies of POAG. All case control studies investigating the association between single-nucleotide polymorphisms (SNPs) and POAG risk were included. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by fixed- or random-effect model.

Results. This meta-analysis included 108 case control studies involving 35,389 POAG patients and 51,742 controls. The pooled results showed a significant association between 20 SNPs in 12 genes (148Asp/Glu in *APE1* gene; rs449647 in *APOE* gene; rs1052990 and rs4236601 in *CAV1/CAV2* gene; rs1799750 in *MMP* gene; c.603T3A (Met98Lys) in *OPTN* gene; rs7081455 in *PLXDC2* gene; rs1279683 in *SLC23A2* gene; 372 T/C in *TIMP1* gene; rs1927911, rs2149356, rs4986791, rs7037117, and rs10759930 in *TLR4* gene; rs4656461 in *TMCO1* gene; 399Arg/Gln in *XRCC1* gene; and rs540782, rs547984, and rs693421 in *ZP4* gene) with POAG.

Conclusions. Based on the current meta-analysis, we indicate 20 SNPs in 12 genes (*APE1*, *APOE*, *CAV1/CAV2*, *MMP*, *OPTN*, *PLXDC2*, *SLC23A2*, *TIMP1*, *TLR4*, *TMCO1*, *XRCC1*, *ZP4*) as predictive risk factors for POAG. More studies with large sample sizes and various ethnicities are warranted in the future to provide more powerful evidence.

Keywords: genetics, polymorphism, POAG, meta-analysis

Glaucoma is the leading cause of irreversible blindness and affects more than 70 million people in the world.[1–3] It has been estimated that over 11.1 million people will be bilaterally blind from primary glaucoma by 2020.[4] POAG is the most common type of glaucoma, accounting for 74% of all glaucoma cases.[4]

POAG is characterized by progressive loss of retinal ganglion cells (RGCs), damage of the optic nerve, and subsequent irreversible visual field loss.[5] So far, the pathogenesis of POAG is not entirely clear. Epidemiologic studies suggest various risk factors, including age, elevated IOP, vascular factors, systemic disease, diabetes, myopia, family history, and cigarette smoking.[6] Genetic factors are also thought to be a potential risk to POAG patients.[7] So far, more than 20 candidate chromosomal loci have been linked to POAG.[8] Among them, genes causing monogenic forms of POAG include myocilin (*MYOC*), optineurin (*OPTN*), and WD repeat-domain 36 (*WDR36*).[7] Besides, genome-wide association studies (GWASs) have identified several susceptibility loci, such as *CAV1/CAV2*,[9] *CDKN2B-AS1* gene,[10,11] *SIX6* gene,[12] *NTM* and *CNTNAP4* genes,[13] and so on.

In recent years, the relationship between genetic polymorphisms and glaucoma has attracted much concern. Several studies have identified many genetic variants that might contribute to POAG.[14,15] However, the association of individual genes, including allele frequency, odds ratio (OR), and statistical significance, vary across different study cohorts, due to clinical heterogeneity, different ethnic populations, and sample sizes. Therefore, we conducted a systematic review and meta-analysis to summarize the effects of all reported gene polymorphisms and clarify their possible association with POAG.

Materials and Methods

This meta-analysis complies with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement[16] (Supplementary Files S1).

Literature Search

A systematic literature search in PubMed and Web of Science was conducted to identify all published genetic studies on the association of polymorphisms with POAG, covering publications up to January 10, 2018. The key words used for the literature search were as follows: ("single nucleotide polymorphisms" OR "gene" OR "SNPs") AND ("open angle" OR "open-angle"). Titles and abstracts were screened to identify potentially relevant studies by two investigators (CM and YXN) independently. Hand searching of reviews was performed to obtain additional studies. All related articles published in English-language journals were retrieved for analysis (Supplementary Files S2).

Inclusion and Exclusion Criteria

Literature selection had to meet the following criteria: (1) unrelated case control of cohort studies investigating the

relationship between a certain single-nucleotide polymorphisms (SNP) and POAG; (2) allele or genotype counts or frequency of common SNPs in both the case and control groups available from the articles; and (3) sufficient information for estimating OR or relevant risk (RR) with corresponding 95% confidence interval (CI). The exclusion criteria were as follows: (1) case report or case series; (2) meeting abstract, editorial comment, letters, or review papers; (3) animal studies; and (4) family or pedigree studies. For studies that were published by the same group on the same gene and makers, only the most recent or complete study was used in this meta-analysis.

Literature Review and Data Extraction

Two reviewers (CM and YXN) independently reviewed and extracted data from the eligible studies. Disagreements were resolved by discussion between all authors until consensus was reached. The following information was extracted from each article: first author, year of publication, region, ethnicity of study subjects, sex composition, mean age, sample size, subtypes of POAG, genotyping method and genotype frequency, and Hardy-Weinberg equilibrium result in controls, and so on. When the allelic counts were not reported in some articles, they were calculated from the genotype data or estimated by using the allelic frequencies and sample sizes if genotype counts were not given. If the allele and/or genotype data in high-tension glaucoma (HTG) and normal-tension glaucoma (NTG) were reported separately, the data were combined into one group as POAG.

Quality Assessment

The methodologic quality of eligible studies was evaluated independently by two authors (CM and YXN), according to the Newcastle-Ottawa scale (NOS) for genetic association studies.[17] NOS quality scores ranged between 0 and 9 stars. Studies with a score of 5 stars or greater were considered high quality (Supplementary Files S3).

Statistical Analysis

Meta-analysis for each polymorphism was performed if it was reported in two or more studies. The strength of association between SNPs and POAG was estimated by OR/RR values with corresponding 95% CI. The pooled OR/RRs were analyzed for the allele model (T versus C), homozygote model (CC versus TT), heterozygote model (TC versus CC), dominant model (TT + TC versus CC), and recessive model (TT versus CT + CC), respectively. Statistical analyses were performed by using the Stata version 12.0 software (Stata Corporation, College Station, TX, USA). A pooled P value of less than 0.05 was considered to have significant genetic association.

The I^2 index score was applied to evaluate the potential heterogeneity among the individual studies, with I^2 score greater than 50% regarded as having a high degree of heterogeneity.[18] In addition, a Q-statistic test was performed, and P less than 0.01 was considered to have significant heterogeneity. The summary OR and 95% CI for each polymorphism were pooled by using the fixed-effects model (Mantel-Haenszel) when no significant heterogeneity was observed among studies. Otherwise, the random-effects model (DerSimonian and Laird) was applied.[19] Sensitivity analysis was performed to evaluate the stability of individual studies. Potential publication bias was evaluated by Begg's funnel plot test.[20]

Results

Literature Search

The process of literature selection is presented in Figure 1. Initially, we identified a total of 3805 articles; 3642 were identified from electronic databases by using the search strategy, and hand searching identified 163 additional records from reference lists of included studies. Three thousand four hundred seventy-eight studies remained after removal of 327 duplicates, which underwent a careful screening of title and abstract. Among them, 3329 articles were excluded because 1687 were about irrelevant topics, 155 were not original studies, 363 were reviews and meta-analyses, 394 were functional studies, 62 were family or pedigree studies, and 668 were animal studies. We retrieved the full text of the remaining 149 studies for review. Forty-one articles were further excluded for the following reasons: seven were not case control studies[21–27]; 27 articles did not provide genotype or allele data[28–54]; and seven articles did not provide proper OR/RR values.[13,55–60] Thus, 108 studies were finally included in this meta-analysis.[10,12,61–167]

Characteristics of Included Studies

The main characteristics of the included studies are summarized in Table 1. This meta-analysis involved 108 case control studies, with a total of 35,398 POAG cases and 51,742 controls. The publication years of the included studies ranged from 2002 to 2018. The distributions of genotypes of all SNPs in the control groups were consistent with the Hardy-Weinberg equilibrium in all studies. All studies had adequate quality because the NOS scores in each study were above 5 stars and the mean score was 7.3. The quality of these studies is summarized in Supplementary Files S3.

Meta-Analysis of the Genetic Association With POAG

Significant Association Between SNPs and POAG. Twenty SNPs in 12 genes reported in candidate studies showed significant association with POAG in this meta-analysis (Table 2).

For SNP 148Asp/Glu in the *APE1* gene, two studies (562 POAG cases and 644 controls) were involved.[74,90] Significant association was found between this SNP and POAG risk in homozygote (OR 5.91, 95% CI: 1.24–28.17; $P = 0.85$, $I^2 = 0.00$) and recessive models (OR 5.26, 95% CI: 1.12–24.82; $P = 0.85$, $I^2 = 0.00$), but not in allelic, heterozygote, or dominant models (Table 2, Supplementary Files S4).

For SNP rs449647 in the *APOE* gene, five studies (1937 cases and 1958 controls) were included for calculation.[78,79,138,144,148] Significant association was found in the overall populations in allelic (OR 1.33, 95% CI: 1.13–1.57; $P = 0.54$, $I^2 = 0.00$), homozygote (OR 1.61, 95% CI: 1.05–2.45; $P = 0.53$, $I^2 = 0.00$), heterozygote (OR 1.32, 95% CI: 1.08–1.62; $P = 0.95$, $I^2 = 0.00$), and dominant comparisons (OR 1.37, 95% CI: 1.12–1.66; $P = 0.80$, $I^2 = 0.00$), but not in the recessive model (Table 2, Supplementary Files S5).

Two SNPs in the *CAV1/CAV2* gene showed significant association with POAG in allelic models (rs1052990, OR 1.17, 95% CI: 1.04–1.31; $P = 0.00$, $I^2 = 87.30$; rs4236601, OR 1.24, 95% CI: 1.16–1.32; $P = 0.06$, $I^2 = 51.10$). No significant association was found in SNP rs4236601 in homozygote, heterozygote, dominant, or recessive models (Table 2, Supplementary Files S6).[65,72,77,82,84,85,115]

For SNP rs1799750 in the *MMP* gene, four studies (885 POAG cases and 875 controls) were involved.[94,95,104,121] The

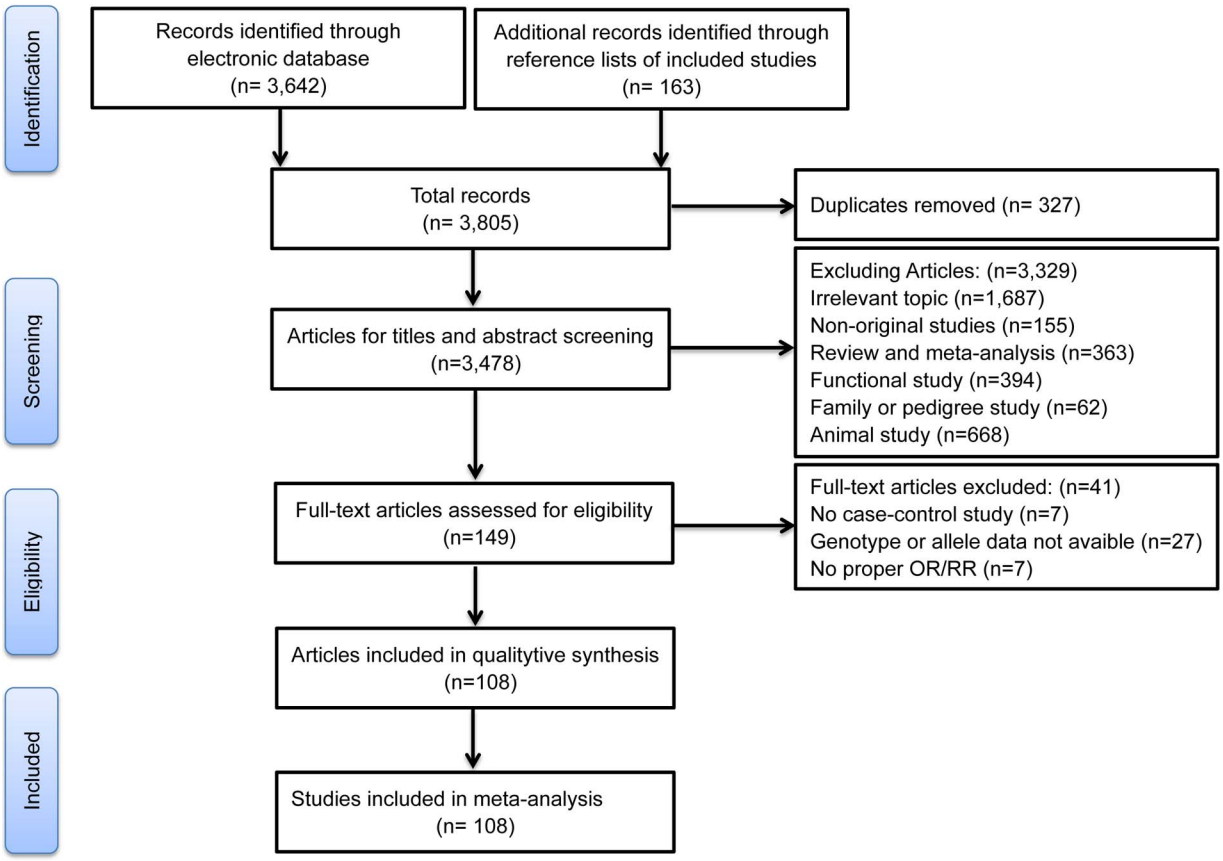

Figure 1. Flow chart of the study selection procedure.

pooled results showed that rs1799750 was significantly correlated with POAG in recessive model (OR 1.64, 95% CI: 1.05–2.56; $P = 0.01$, $I^2 = 73.90$). No evidence of association was observed in rs3918242 in the *MMP* gene[94,95] (Table 2, Supplementary Files S7).

For SNP c.603T3A (Met98Lys) in the *OPTN* gene, five studies (1339 POAG cases and 939 controls) were included for calculation.[123,137,144,145,152] Significant association was found in the overall populations in homozygote (OR 52.58, 95% CI: 1.12–5.97; $P = 0.41$, $I^2 = 0.00$) and recessive models (OR 2.50, 95% CI: 1.09–5.77; $P = 0.55$, $I^2 = 0.00$). No evidence of association was found in c.412G3A (Thr34Thr) in the *OPTN* gene in all genetic models (Table 2, Supplementary Files S8).

SNP rs7081455 in the *PLXDC2* gene was reported in three studies, involving a total of 1428 POAG cases and 1222 controls.[64,101,128] Significant association was found in the overall populations in the allelic model (OR 1.46, 95% CI: 1.28–1.68; $P = 0.697$, $I^2 = 0.00$, Table 2, Supplementary Files S9).

SNP rs1279683 in the *SLC23A2* gene was reported in two studies, involving a total of 400 POAG cases and 400 controls.[97,117] Significant association was found in the overall populations in the allelic model (OR 1.43, 95% CI: 1.10–1.87; $P = 0.04$, $I^2 = 76.20$, Table 2, Supplementary Files S10).

SNP 372 T/C in the *TIMP1* gene was reported in two studies, involving a total of 451 POAG cases and 509 controls.[94,104] Significant association was found in the overall populations in the recessive model (OR 1.50, 95% CI: 1.12–2.01; $P = 0.69$, $I^2 = 0.00$, Table 2, Supplementary Files S11).

Nine SNPs in the *TLR4* gene were included in this meta-analysis and five of them conferred significant risk of POAG.[66,70,101,107,114,134,153] Rs1927911 (4 studies, 669 POAG patients and 830 controls) was found to have significant association with POAG in allelic (OR 1.28, 95% CI: 1.03–1.57; $P = 0.07$, $I^2 = 57.20$), homozygote (OR 1.43, 95% CI: 1.00–2.05; $P = 0.20$, $I^2 = 34.70$), heterozygote (OR 1.46, 95% CI: 1.06–1.99; $P = 0.06$, $I^2 = 58.90$), and dominant models (OR 1.45, 95% CI: 1.07–1.97; $P = 0.05$, $I^2 = 62.00$), but not in the recessive model.[66,70,114,134] Rs2149356 (4 studies, 669 POAG patients and 830 controls) was found to have significant association with POAG in allelic (OR 1.35, 95% CI: 1.04–1.76; $P = 0.01$, $I^2 = 73.00$), homozygote (OR 1.61, 95% CI: 1.07–2.43; $P = 0.11$, $I^2 = 50.70$), heterozygote (OR 1.53, 95% CI: 1.01–2.32; $P = 0.01$, $I^2 = 76.10$), dominant (OR 1.56, 95% CI: 1.04–2.33; $P = 0.00$, $I^2 = 77.90$), and recessive comparisons (OR 1.33, 95% CI: 1.03–1.73; $P = 0.51$, $I^2 = 0.00$).[66,70,114,134] For rs4986791 (2 studies, 272 POAG patients and 204 controls), significant association was found in the overall population in allelic (OR 2.54, 95% CI: 1.21–5.32; $P = 0.42$, $I^2 = 0.00$) and heterozygote models (OR 2.31, 95% CI: 1.06–5.00; $P = 0.35$, $I^2 = 0.00$).[66,70] For rs7037117 (4 studies, 769 POAG patients and 961 controls), significant association was found only in homozygote comparison (OR 1.50, 95% CI: 1.01–2.24; $P = 0.62$, $I^2 = 0.00$), but not in allelic, heterozygote, dominant, and recessive models.[70,101,114,134] For rs10759930 (4 studies, 666 POAG patients and 937 controls), significant association was found in allelic (OR 1.34, 95% CI: 1.06–1.70; $P = 0.02$, $I^2 = 69.90$), homozygote (OR 1.64, 95% CI: 1.10–2.43; $P = 0.10$, $I^2 = 52.40$), heterozygote (OR 1.55, 95% CI: 1.28–1.88; $P = 0.01$, $I^2 = 72.80$), dominant (OR 1.58, 95% CI: 1.08–2.29; $P = 0.01$, $I^2 = 75.70$), and recessive comparisons (OR 1.29, 95% CI: 1.01–1.65; $P = 0.58$, $I^2 = 0.00$).[70,107,114,134] However, poor association was found in rs1927914, rs7045953, rs11536889, and rs12377632 in the *TLR4* gene[66,70,114,134] (Table 2, Supplementary Files S12).

Table 1. Characteristics of the Studies Included in the Meta-Analysis

				Sample Size		Age, y		Female/Male		Genotypes for Cases			Genotypes for Controls		
No.	First Author	Year	Ethnicity	Case	Control	Case	Control	Case	Control	TT	TC	CC	TT	TC	CC
1	Gong[61]	2018	Chinese	416	997	51.28 ± 8.94	54.7 ± 16.5	126/290	389/608	0	31	385	0	60	937
2	Azad[155]	2017	Saudi Arab	90	95	60.7 ± 12.3	57.1 ± 13.5	35/55	26/69	25	45	25	18	52	20
3	Kondkar[62]	2017	Saudi Arab	92	94	NA	NA	36/56	NA	14	33	45	21	44	29
4	Kondkar[154]	2017	Saudi Arab	92	95	60.7 ± 12.3	57.2 ± 13.5	36/56	26/69	24	46	25	16	54	22
5	Kondkar[63]	2017	Saudi Arab	92	95	60.5 ± 12.2	57.1 ± 13.6	36/56	26/69	10	45	37	19	41	35
6	Mabuchi[64]	2017	Japanese	417	244	63.4 ± 14.3	67.7 ± 11.2	202/215	154/90	NA	NA	NA	NA	NA	NA
7	Nunes[65]	2017	Brazilian	310	247	67 ± 13	69 ± 8	162/148	145/102	26	97	124	38	121	151
8	Navarro-Partida[66]	2017	Mexican	187	109	66.94 ± 13.3	63.28 ± 7.93	93/94	69/40	17	87	83	11	34	64
9	Navarro-Partida[153]	2017	Mexican	189	109	64.49 ± 14.3	63.28 ± 7.93	95/94	69/40	1	20	166	0	3	105
10	Tikunova[164]	2017	Russia	252	191	70.53 ± 8.43	69.24 ± 10.14	127/125	98/93	0	39	208	6	36	139
11	Yoshikawa[67]	2017	Japanese	740	2723	70.1 ± 11.9	52.5 ± 14.1	400/340	1845/878	37	239	460	184	1039	1500
12	Abu-Amero[68]	2017	Saudi Arab	85	95	60.9 ± 12.7	58.7 ± 10.4	32/53	38/57	1	14	70	1	8	86
13	Abu-Amero[157]	2016	Saudi Arab	87	94	61.7 ± 12.6	56.3 ± 12.3	33/54	25/69	2	32	53	5	31	58
14	Al-Shahrani[149]	2016	Saudi Arab	144	280	60 ± 12.2	56 ± 11.6	63/81	135/145	0	56	88	0	70	210
15	Hamid[165]	2016	Egyptian	60	26	47.3 ± 12.7	45.2 ± 12.3	22/38	10/16	14	18	26	2	5	19
16	Kimura[69]	2016	Japanese	247	276	56.2 ± 14.2	54.7 ± 13.9	131/116	185/91	12	92	143	18	107	151
17	Mousa[70]	2016	Saudi Arab	85	95	60.9 ± 12.7	58.7 ± 10.4	32/53	38/57	92	267	190	25	85	106
18	Ng[71]	2016	Australian	2241	3176	60.6 ± 14.3	55.3 ± 8.7	1180/1061	1383/1793	NA	NA	NA	NA	NA	NA
19	Rong[72]	2016	Chinese	454	436	62 ± 15	74 ± 8	120/334	252/184	NA	NA	NA	NA	NA	NA
20	Sang[73]	2016	Chinese	866	266	55.1 ± 17.0	67.6 ± 11.3	287/579	152/114	47	275	544	23	103	140
21	Cuchra[74]	2015	Polish	412	454	73 ± 9	71 ± 12	275/148	260/194	13	136	263	16	132	297
22	Chen[75]	2015	Chinese	1157	934	48.81 ± 16.28	53.37 ± 14.83	373/784	558/376	NA	NA	NA	NA	NA	NA
23	Gong[76]	2015	Chinese	416	997	54.7	51.3	NA	NA	3	87	326	10	214	771
24	Kim[77]	2015	Korean	229	932	56.1 ± 15.9	57.6 ± 13.2	72/157	465/467	0	8	221	0	11	920
25	Nowak[79]	2015	Polish	183	209	74 ± 10	64 ± 16	114/69	120/89	15	64	104	10	59	140
26	Nowak[79]	2015	Polish	363	406	73 ± 10	64 ± 16	265/98	232/174	31	127	205	25	124	257
27	Neamatzadeh[160]	2015	Iranian	65	65	40.16 ± 17.51	35.64 ± 13.61	NA	NA	21	27	17	8	32	25
28	Zanon-Moreno[80]	2015	Spanish	232	241	70.5	65.8	126/106	131/110	51	114	76	75	106	51
29	Anastasopoulos[81]	2014	Greece	65	92	72.6 ± 6.3	68.8 ± 4.7	34/31	54/38	2	21	43	1	31	61
30	Burdon[82]	2014	Australian	67	1919	68.9 ± 7.9	63.8 ± 8.3	49/16	1094/825	NA	NA	NA	NA	NA	NA
31	Emam[83]	2014	Egyptian	160	110	48.9 ± 7.0	63.8 ± 6.3	84/76	54/56	38	59	63	12	38	60
32	Loomis[84]	2014	American	3108	3430	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
33	Micheal[85]	2014	Pakistani	268	233	54.6 ± 1.4	54.1 ± 1.3	129/139	118/115	30	127	111	25	98	110
34	Nowak[86]	2014	Polish	186	188	73 ± 10	64 ± 16	115/71	90/98	1	15	170	0	21	167
35	Abu-Amero[156]	2013	Saudi Arab	225	403	65.1 ± 17.6	60.7 ± 11.7	98/127	282/121	4	52	169	11	103	289
36	Abu-Amero[87]	2013	Saudi Arab	226	403	61.8 ± 12.7	60.7 ± 11.7	98/128	282/121	61	115	50	110	202	91
37	Bachernegg[88]	2013	Caucasian	366	357	74.1 ± 10.4	73.7 ± 8.0	219/147	189/168	11	127	228	12	129	216
38	Buentello-Volante[89]	2013	Mexican	118	100	67.9 ± 10.7	71 ± 9.3	85/33	62/38	23	53	42	17	49	34
39	Cuchra[90]	2013	Polish	150	190	72.3 ± 7.34	67 ± 14	96/64	120/70	3	111	36	1	129	60
40	Chiras[91]	2013	Greek	52	107	69.4 ± 8.8	74.4 ± 8.2	25/27	60/47	0	16	27	4	45	48
41	Kato[92]	2013	Japanese	292	352	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
42	Kasım[93]	2013	Turkish	100	100	67.7 ± 9.3	66 ± 5.7	54/46	67/33	6	30	64	3	26	71
43	Markiewicz[94]	2013	Polish	255	256	70 ± 15	67 ± 16	165/90	NA	6	83	166	5	56	195
44	Micheal[95]	2013	Pakistani	112	118	52.6 ± 1.4	50.1 ± 1.3	34/78	60/58	2	40	70	7	37	74
45	Szaflik[96]	2013	Polish	170	193	70 ± 14	67 ± 14	107/63	73/120	4	56	110	7	68	115

Table 1. Continued

No.	First Author	Year	Ethnicity	Sample Size		Age, y		Female/Male		Genotypes for Cases			Genotypes for Controls		
				Case	Control	Case	Control	Case	Control	TT	TC	CC	TT	TC	CC
46	Zanon-Moreno[97]	2013	Spanish	250	250	70.1 ± 8.7	70.0 ± 8.6	144/106	144/106	NA	NA	NA	NA	NA	NA
47	Abu-Amero[98]	2012	Saudi Arab	96	308	63.7 ± 14.7	69.3 ± 12.4	33/63	37/64	8	32	56	4	40	57
48	Balasubbu[99]	2012	Indian	220	220	56.80 ± 11.74	56.80 ± 11.74	NA	NA	16	83	120	18	82	120
49	Bozkurt[100]	2012	Turkish	86	193	65.1 ± 10.2	66.2 ± 7.8	51/35	119/74	0	7	79	0	13	180
50	Chen[101]	2012	Chinese	184	230	59.7 ± 16.6	73.5 ± 7.5	64/120	124/106	22	91	70	28	101	100
51	Cao[102]	2012	Afro-Caribbean	272	165	67.6 ± 11.8	62.1 ± 12.4	150/122	52/113	20	92	159	15	77	73
52	Dimasi[103]	2012	Australian	876	883	73.5 ± 11.8	80.5 ± 5.7	489/407	462/421	NA	NA	NA	NA	NA	NA
53	Majsterek[104]	2012	Polish	196	253	70 ± 14	67 ± 16	130/66	181/72	59	74	63	49	113	91
54	Nilforoushan[105]	2012	Iranian	73	90	67.8	67.5	19/54	25/65	6	28	39	4	33	53
55	Osman[12]	2012	Japanese	1394	6599	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
56	Magalhaes da Silva[106]	2012	Brazilian	90	127	53.0 ± 9.38	51.75 ± 10.95	61/29	63/64	8	39	42	11	38	74
57	Takano[107]	2012	Japanese	184	216	65/119	100/116	64.6 ± 14.3	69.7 ± 11.3	32	103	49	28	85	103
58	Wang[108]	2012	Chinese	234	230	67	67	112/122	108/122	16	70	148	26	84	120
59	Burdon[10]	2011	Australian	892	4582	72 ± 13.0	64.9 ± 12.4	456/436	2172/2410	NA	NA	NA	NA	NA	NA
60	Chen[109]	2011	Chinese	142	289	NA	NA	38/104	147/142	NA	NA	NA	NA	NA	NA
61	Fan[110]	2011	Caucasian	539	336	61.4 ± 11.2	65.2 ± 10.7	276/263	183/153	93	174	120	54	132	118
62	Kang[112]	2011	American	527	1539	NA	NA	373/154	1078/461	NA	NA	NA	NA	NA	NA
63	Kim[151]	2011	Korean	188	918	NA	NA	NA	NA	29	76	81	120	422	120
64	Kang[111]	2011	American	374	1085	NA	NA	64.1	64	NA	NA	NA	NA	NA	NA
65	Mossböck[113]	2011	Caucasian	330	251	73.5 ± 10.0	74.2 ± 7.2	196/134	126/125	33	161	136	19	112	120
66	Suh[114]	2011	Korean	147	308	NA	NA	NA	NA	23	71	53	61	190	129
67	Wiggs[115]	2011	Caucasians	1000	1183	63.6	65.5	589/411	715/468	NA	NA	NA	NA	NA	NA
68	Yousaf[116]	2011	Pakistani	160	193	41.3 ± 13.7	39.7 ± 11.9	80/80	92/101	17	73	70	30	65	98
69	Zanon-Moreno[117]	2011	Mediterranean	150	150	68 ± 9	68 ± 8	89/61	89/61	58	62	30	42	82	26
70	Burdon[158]	2010	Australian	860	897	74.8	80.5	447/413	475/422	53	278	478	48	298	509
71	Fan[118]	2010	Chinese	355	201	NA	NA	NA	NA	8	69	274	4	40	157
72	Liu[119]	2010	African-American	382	275	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
73	Mabuchi[120]	2010	Japanese	425	191	NA	NA	NA	NA	51	198	176	16	101	74
74	Mossböck[121]	2010	Caucasian	322	248	74.1 ± 10.6	74.4 ± 7.1	188/134	126/122	68	165	89	57	131	60
75	Yu-Wai-Man[122]	2010	English	137	75	71.6 ± 8.0	79.3 ± 4.4	NA	NA	5	42	90	3	13	59
76	Caixeta-Umbelino[123]	2009	Brazilian	99	100	63.6 ± 12.9	69.5 ± 6.5	46/53	62/38	9	28	62	6	17	77
77	Daugherty[161]	2009	Caucasian	191	167	67.5 ± 12.5	60.3 ± 12.0	92/99	105/62	12	55	124	13	72	82
78	Fourgeux[124]	2009	French	150	118	69.5 ± 1	70.9 ± 1.1	79/71	67/51	5	53	92	3	58	57
79	Jiao[125]	2009	Afro-Caribbean	249	128	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
80	Lemmela[126]	2009	Finnish	71	404	NA	NA	NA	NA	2	25	41	14	87	224
81	Micheal[127]	2009	Pakistani	173	143	50.4 ± 1.1	49.1 ± 1.3	69/104	40/103	1	49	123	1	41	101
82	Mabuchi[162]	2009	Japanese	425	189	NA	65.5 ± 11.4	NA	119/70	51	197	177	23	83	83
83	Nakano[128]	2009	Japanese	827	748	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
84	Chakrabarti[130]	2008	Indian	112	105	NA	NA	NA	NA	6	26	80	11	32	62
85	Gong[131]	2008	Chinese	293	250	66.8 ± 12.9	74.1 ± 6.8	117/176	127/123	6	50	237	5	52	193
86	Mabuchi[132]	2008	Japanese	213	191	62.9 ± 14.8	65.7 ± 11.4	NA	NA	6	52	155	8	40	143
87	Michael[133]	2008	Pakistani	90	70	57.9 ± 14.3	50.98 ± 8.1	32/58	23/47	0	20	70	0	13	57
88	Sbibuya[134]	2008	Japanese	250	318	NA	NA	NA	NA	41	122	87	42	135	141
89	Liu[159]	2007	Multiethnic	939	462	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
90	Zetterberg[129]	2007	Swedish	243	187	70.7 ± 9.1	65.8 ± 6.9	155/88	136/51	20	97	126	23	75	89

Table 1. Continued

No.	First Author	Year	Ethnicity	Sample Size		Age, y		Female/Male		Genotypes for Cases			Genotypes for Controls		
				Case	Control	Case	Control	Case	Control	TT	TC	CC	TT	TC	CC
91	How[135]	2007	Chinese	194	79	NA	67.7 ± 4.7	55/138	47/32	42	96	56	13	42	24
92	Wang[136]	2007	Taiwanese	231	245	NA	NA	NA	NA	53	108	70	59	125	61
93	Funayama[137]	2006	Japanese	492	240	NA	NA	NA	NA	16	143	333	3	60	177
94	Lam[138]	2006	Chinese	800	600	NA	NA	NA	NA	4	25	371	1	13	286
95	Mabuchi[139]	2006	Japanese	133	106	61.8 ± 15.4	65.5 ± 10.5	NA	NA	27	55	51	19	39	48
96	Mossböck[141]	2006	Australian	204	211	73.1 ± 10.3	73.1 ± 9.7	129/75	131/80	14	71	119	20	86	105
97	Mossböck[140]	2006	Australian	114	228	72.3 ± 9.5	72.7 ± 9.6	NA	NA	0	7	107	0	23	205
98	Mabuchi[142]	2006	Japanese	385	185	NA	65.3 ± 11.5	NA	NA	0	11	274	0	3	182
99	Yao[143]	2006	West Indies	109	48	NA	NA	NA	NA	0	4	105	0	2	46
100	Fan[144]	2005	Chinese	400	281	NA	NA	150/250	101/180	4	25	371	1	13	267
101	Jünemann[150]	2004	Germany	76	71	68.6 ± 9.8	68.1 ± 11.8	43/33	36/35	7	37	32	2	24	45
102	Funayama[145]	2004	Japanese	194	218	NA	NA	NA	NA	8	61	125	2	50	166
103	Woo[146]	2004	Korean	65	101	47.0 ± 10.3	49.0 ± 9.2	39/36	53/48	0	3	62	0	0	101
104	Fuse[152]	2004	Japanese	89	100	63.6 ± 14.4	68.0 ± 7.7	40/49	38/62	1	14	74	0	5	95
105	Powell[147]	2003	United Kingdom	61	168	NA	NA	NA	NA	4	16	41	4	53	111
106	Lin[166]	2003	Chinese	60	103	55	50	30/30	48/55	19	13	28	7	30	66
107	Copin[148]	2002	French	191	102	NA	NA	NA	NA	4	58	129	4	28	70
108	Lin[163]	2002	Chinese	58	59	55	50	29/29	30/29	20	26	12	8	26	25

NA, not available.

SNP rs4656461 in the *TMCO1* gene has been reported in four studies; involving a total of 2384 POAG cases and 7668 controls.[10,75,82,85] Significant association was found in the overall populations in the allelic comparison (OR 1.46, 95% CI: 1.32–1.62; $P = 0.00$, $I^2 = 87.50$, Table 2, Supplementary Files S13).

SNP 399Arg/Gln in the *XRCC1* gene was reported in three studies involving a total of 742 POAG cases and 840 controls. Significant association was found in the overall populations in allelic (OR 1.23, 95% CI: 1.07–1.43; $P = 0.39$, $I^2 = 0.00$), heterozygote (OR 1.70, 95% CI: 1.21–2.38; $P = 0.13$, $I^2 = 50.70$), and dominant models (OR 1.58, 95% CI: 1.08–2.29; $P = 0.19$, $I^2 = 39.30$), although no significant association was found in 194Arg/Trp in the *XRCC1* gene under allelic, heterozygote, and dominant models (Table 2, Supplementary Files S14).

Three SNPs in the *ZP4* gene showed significant association with POAG. For rs540782 (2 studies, 919 POAG cases and 843 controls), significant association was found in the allelic model (OR 1.31, 95% CI: 1.15–1.50; $P = 0.39$, $I^2 = 0.00$).[128,154] For rs547984 (3 studies, 1334 POAG cases and 1087 controls), significant association was found in the overall populations in the allelic model (OR 1.25, 95% CI: 1.10–1.42; $P = 0.32$, $I^2 = 11.40$).[64,128,155] For rs693421 (2 studies, 1011 POAG cases and 978 controls), significant association was found in the overall populations in the allelic model (OR 1.26, 95% CI: 1.11–1.43; $P = 0.05$, $I^2 = 75.20$)[101,128] (Table 2, Supplementary Files S15).

Stratified Analysis of Candidate SNPs Associated With POAG

Stratified analysis for candidate SNPs associated with POAG was further performed if it was reported in two or more studies. Subgroup analysis stratified by HTG and NTG showed that *APOE* rs449647 had significant association with HTG in allele (OR 1.89, 95% CI: 1.20–2.96, $P = 0.006$), heterozygote (OR 1.74, 95% CI: 1.06–2.86, $P = 0.030$), and dominant models (OR 1.83, 95% CI: 1.14–2.96, $P = 0.013$), but not with NTG in any of the genetic models. *PLXDC2* rs7081455 also indicated significant association with HTG in allele model (OR 1.41, 95% CI: 1.09–1.81, $P = 0.008$). *OPTN* c.603T>A (Met98Lys) showed significant association with NTG in allele (OR 1.53, 95% CI: 1.21–1.94, $P = 0.000$), homozygote (OR 2.82, 95% CI: 1.14–6.93, $P = 0.024$), heterozygote (OR 1.48, 95% CI: 1.13–1.93, $P = 0.004$), dominant (OR 1.55, 95% CI: 1.19–2.01, $P = 0.001$), and recessive models (OR 2.55, 95% CI: 1.05–6.22, $P = 0.039$). For the *TLR4* gene, only rs10759930 indicated significant association with NTG in homozygote (OR 1.43, 95% CI: 1.06–1.94, $P = 0.020$) and heterozygote models (OR 1.27, 95% CI: 1.02–1.59, $P = 0.031$, Supplementary Files S16).

In the stratification analyses by ethnicity, four SNPs in three genes indicated significant association with POAG in Asians, including rs449647 in the *APOE* gene, c.603T>A (Met98Lys) in the *OPTN* gene, rs1927911 and rs2149356 in the *TLR4* gene, and rs547984 in the *ZP4* gene. Besides, *APOE* rs449647, *CAV1/CAV2* rs4236601, and *MMP* rs1799750 showed significant association with POAG in Caucasians. Only rs4656461 in the *TMCO1* gene showed significant association with POAG in Australian (Supplementary Files S16).

Lack of Association Between SNPs and POAG

Twenty-seven SNPs in 19 genes showed no significant association with POAG in this meta-analysis, including rs1900004 and rs7916697 in the *ATOH7* gene,[75,85,102,109,110] rs1001179 in the *CAT* gene,[61,15] rs1063192, and rs4977756 in the *CDKN2B* gene,[10,12,67,69,71,75,82,85,102,103,110,157] rs12994401 in the *cbromosome2p* gene,[88,99,101,119,120,125,151] rs1800440 in the *CYP1B1* gene,[89,118,158] rs754203 in the *CYP46A1*

Table 2. Significant Association of Gene Polymorphisms With POAG

No.	Gene	SNP	No. of Cohorts	Ethnicity	Genetic Model	Pooled Sample Size		FEM or REM		Heterogeneity		Begg's Test	
						Case	Control	OR (95% CI)	*P*	*P* (Q)	I^2 (%)	Z	*P*
1	*APE1*	148Asp/Glu	2	Caucasian	T vs. C	562	644	1.08 (0.91–1.28)	0.372	0.40	0.00	0.00	1.00
			2		CC vs. TT	562	644	**5.91 (1.24–28.17)**	**0.026**	0.85	0.00	0.00	1.00
			2		TC vs. CC	562	644	1.08 (0.85–1.37)	0.546	0.18	43.80	0.00	1.00
			2		TT + TC vs. CC	562	644	1.09 (0.90–1.31)	0.391	0.19	41.60	0.00	1.00
			2		TT vs. TC + CC	562	644	**5.26 (1.12–24.82)**	**0.036**	0.71	0.00	0.00	1.00
2	*APOE*	rs449647	5	Caucasian	T vs. C	1937	1958	**1.33 (1.13–1.57)**	**0.001**	0.54	0.00	0.24	0.81
			5	Asian	CC vs. TT	1937	1958	**1.61 (1.05–2.45)**	**0.027**	0.53	0.00	−0.24	1.00
			5		TC vs. CC	1937	1958	**1.32 (1.08–1.62)**	**0.008**	0.95	0.00	−0.24	1.00
			5		TT + TC vs. CC	1937	1958	**1.37 (1.12–1.66)**	**0.002**	0.80	0.00	−0.24	1.00
			5		TT vs. TC + CC	1937	1958	1.47 (0.97–2.23)	0.066	0.55	0.00	0.73	0.46
3	*CAV1/CAV2*	rs1052990	3	Asian, Caucasian	T vs. C	1746	1791	**1.17 (1.04–1.31)**	**0.008**	0.00	87.30	0.00	1.00
		rs4236601	7	Multiple ancestries*	T vs. C	5436	8380	**1.24 (1.16–1.32)**	**0.000**	0.06	51.10	0.30	0.76
			3		CC vs. TT	807	1412	1.41 (0.45–4.37)	0.555	0.03	78.40	0.00	1.00
			3		TC vs. CC	807	1412	1.40 (0.87–2.25)	0.171	0.05	65.90	1.04	0.30
			3		TT + TC vs. CC	807	1412	1.43 (0.85–2.42)	0.176	0.02	73.40	1.04	0.30
			3		TT vs. TC + CC	807	1412	1.31 (0.49–3.52)	0.592	0.06	72.90	0.00	1.00
4	*MMP*	rs1799750	4	Caucasian	T vs. C	885	875	1.33 (0.97–1.81)	0.074	0.00	80.50	1.02	0.31
			4	Asian	CC vs. TT	885	875	1.65 (0.96–2.83)	0.069	0.01	76.40	0.34	0.73
			4		TC vs. CC	885	875	0.99 (0.66–1.48)	0.966	0.03	67.80	1.02	0.31
			4		TT + TC vs. CC	885	875	1.21 (0.82–1.80)	0.342	0.01	72.60	1.02	0.31
			4		TT vs. TC + CC	885	875	**1.64 (1.05–2.56)**	**0.030**	0.01	73.90	0.34	0.73
		rs3918242	2	Caucasian	T vs. C	367	374	1.20 (0.69–2.06)	0.520	0.054	73.00	0.00	1.00
			2	Asian	CC vs. TT	367	374	0.72 (0.16–3.23)	0.665	0.13	56.2	0.00	1.00
			2		TC vs. CC	367	374	1.48 (0.99–2.21)	0.058	0.23	31.8	0.00	1.00
			2		TT + TC vs. CC	367	374	1.36 (0.81–2.28)	0.242	0.12	59.7	0.00	1.00
			2		TT vs. TC + CC	367	374	0.65 (0.16–2.64)	0.549	0.16	50.1	0.00	1.00
5	*OPTN*	c.603T>A(Met98Lys)	5	Asian	T vs. C	1339	939	1.44 (0.91–2.27)	0.116	0.01	70.80	0.73	0.46
			5	Latino	CC vs. TT	1339	939	**2.58 (1.12–5.97)**	**0.027**	0.41	0.00	0.30	0.73
			5		TC vs. CC	1339	939	1,34 (0.84–2.14)	0.220	0.02	65.80	0.24	0.81
			5		TT + TC vs. CC	1339	939	1.41 (0.87–2.31)	0.163	0.01	69.50	0.24	0.81
			5		TT vs. TC + CC	1339	939	**2.50 (1.09–5.77)**	**0.031**	0.55	0.00	0.34	0.73
		c.412G>A(Thr34Thr)	4	Latino	T vs. C	1185	839	1.26 (0.79–2.02)	0.325	0.001	82.5	−0.34	1.00
			4	Asian	CC vs. TT	1185	839	1.77 (0.66–4.75)	0.256	0.05	62.0	1.70	0.09
			4		TC vs. CC	1185	839	1.23 (0.76–1.98)	0.398	0.01	75.2	0.34	0.73
			4		TT + TC vs. CC	1185	839	1.27 (0.76–2.12)	0.357	0.00	80.3	−0.34	1.00
			4		TT vs. TC + CC	1185	839	1.65 (0.70–3.88)	0.254	0.11	50.5	1.70	0.09
6	*PLXDC2*	rs7081455	3	Asian	T vs. C	1428	1,222	**1.46 (1.28–1.68)**	**0.000**	0.70	0.00	1.04	0.30
7	*SLC23A2*	rs1279683	2	Caucasian	T vs. C	400	400	**1.43 (1.10–1.87)**	**0.007**	0.04	76.20	0.00	1.00
8	*TIMP1*	372 T/C	2		T vs. C	451	509	1.11 (0.93–1.33)	0.260	0.80	0.00	0.00	1.00
			2		CC vs. TT	451	509	1.26 (0.91–1.76)	0.166	0.80	0.00	0.00	1.00
			2		TC vs. CC	451	509	**0.72 (0.53–0.96)**	**0.027**	0.80	0.00	0.00	1.00
			2		TT + TC vs. CC	451	509	0.90 (0.69–1.17)	0.427	1.00	0.00	0.00	1.00
			2		TT vs. TC + CC	451	509	**1.50 (1.12–2.01)**	**0.007**	0.69	0.00	0.00	1.00

Table 2. Continued

No.	Gene	SNP	No. of Cohorts	Ethnicity	Genetic Model	Pooled Sample Size		FEM or REM		Heterogeneity		Begg's Test	
						Case	Control	OR (95% CI)	*P*	*P* (Q)	I^2 (%)	Z	*P*
9	*TLR4*	rs1927911	4	Latino	T vs. C	669	830	**1.28 (1.03–1.57)**	**0.023**	0.07	57.20	0.34	0.73
			4	Asian	CC vs. TT	669	830	**1.43 (1.00–2.05)**	**0.007**	0.20	34.70	1.02	0.31
			4		TC vs. CC	669	830	**1.47 (1.20–1.78)**	**0.000**	0.06	58.90	0.34	0.73
			4		TT + TC vs. CC	669	830	**1.45 (1.07–1.97)**	**0.017**	0.05	62.00	0.34	0.73
			4		TT vs. TC + CC	669	830	1.22 (0.94–1.59)	0.147	0.51	0.00	0.34	0.73
		rs2149356	4	Latino	T vs. C	669	830	**1.35 (1.04–1.76)**	**0.024**	0.01	73.00	−0.34	1.00
			4	Asian	CC vs. TT	669	830	**1.61 (1.07–2.43)**	**0.023**	0.11	50.70	0.34	0.73
			4		TC vs. CC	669	830	**1.53 (1.01–2.32)**	**0.043**	0.01	76.10	−0.34	1.00
			4		TT + TC vs. CC	669	830	**1.56 (1.04–2.33)**	**0.031**	0.00	77.90	−0.34	1.00
			4		TT vs. TC + CC	669	830	**1.33 (1.03–1.73)**	**0.031**	0.51	0.00	0.34	0.73
		rs4986791	2	Latino	T vs. C	272	204	**2.54 (1.21–5.32)**	**0.014**	0.42	0.00	0.00	1.00
			2	Asian	TC vs. CC	272	204	**2.31 (1.06–5.00)**	**0.034**	0.35	0.00	0.00	1.00
		rs7037117	4	Asian	T vs. C	769	961	1.21 (0.96–1.52)	0.112	0.07	56.80	1.02	0.31
			4		CC vs. TT	769	961	**1.50 (1.01–2.24)**	**0.045**	0.62	0.00	1.70	0.09
			4		TC vs. CC	769	961	1.14 (0.76–1.71)	0.523	0.00	77.30	1.70	0.09
			4		TT + TC vs. CC	769	961	1.20 (0.84–1.70)	0.311	0.01	72.30	1.02	0.31
			4		TT vs. TC + CC	769	961	1.44 (0.97–2.13)	0.071	0.59	0.00	1.70	0.09
		rs10759930	4	Asian	T vs. C	666	937	**1.34 (1.06–1.70)**	**0.014**	0.02	69.90	−0.34	1.00
			4		CC vs. TT	666	937	**1.64 (1.10–2.43)**	**0.014**	0.10	52.40	−0.34	1.00
			4		TC vs. CC	666	937	**1.55 (1.28–1.88)**	**0.021**	0.01	72.80	−0.34	1.00
			4		TT + TC vs. CC	666	937	**1.58 (1.08–2.29)**	**0.017**	0.01	75.70	−0.34	1.00
			4		TT vs. TC + CC	666	937	**1.29 (1.01–1.65)**	**0.039**	0.58	0.00	1.02	0.31
		rs1927914	2	Asian	T vs. C	397	626	1.14 (0.79–1.63)	0.479	0.049	74.2	0.00	1.00
			2		CC vs. TT	397	626	1.27 (0.66–2.45)	0.470	0.089	65.3	0.00	1.00
			2		TC vs. CC	397	626	1.18 (0.72–1.92)	0.508	0.081	67.2	0.00	1.00
			2		TT + TC vs. CC	397	626	1.20 (0.71–2.03)	0.502	0.046	74.8	0.00	1.00
			2		TT vs. TC + CC	397	626	1.18 (0.83–1.66)	0.403	0.277	15.3	0.00	1.00
		rs7045953	2	Asian	T vs. C	397	626	1.05 (0.65–1.66)	0.846	0.148	52.1	0.00	1.00
			2		CC vs. TT	397	626	1.48 (0.42–5.22)	0.540	0.233	29.8	0.00	1.00
			2		TC vs. CC	397	626	1.01 (0.67–1.54)	0.896	0.233	29.8	0.00	1.00
			2		TT + TC vs. CC	397	626	1.04 (0.75–1.46)	0.800	0.181	44.2	0.00	1.00
			2		TT vs. TC + CC	397	626	1.51 (0.43–5.33)	0.524	0.248	25.2	0.00	1.00
		rs11536889	4	Latino	T vs. C	669	830	1.03 (0.88–1.20)	0.705	0.336	11.3	0.34	0.73
			4	Asian	CC vs. TT	669	830	0.82 (0.54–1.25)	0.355	0.375	3.6	0.34	0.73
			4		TC vs. CC	669	830	1.15 (0.95–1.40)	0.159	0.542	0	0.34	0.73
			4		TT + TC vs. CC	669	830	1.10 (0.91–1.33)	0.316	0.392	0	0.34	0.73
			4		TT vs. TC + CC	669	830	0.77 (0.51–1.17)	0.227	0.481	0	0.34	0.73
		rs12377632	4	Latino	T vs. C	669	830	1.06 (0.77–1.46)	0.729	0.001	82.7	1.70	0.09
			4	Asian	CC vs. TT	669	830	1.06 (0.59–1.93)	0.841	0.004	77.7	1.70	0.09
			4		TC vs. CC	669	830	1.18 (0.80–1.73)	0.410	0.014	71.9	1.02	0.31
			4		TT + TC vs. CC	669	830	1.14 (0.74–1.75)	0.561	0.002	80.1	1.70	0.09
			4		TT vs. TC + CC	669	830	1.00 (0.66–1.51)	0.987	0.05	61.7	1.70	0.09
10	*TMCO1*	rs4656461	4	Asian, Australian	T vs. C	2384	7668	**1.46 (1.32–1.62)**	**0.000**	0.00	87.50	0.34	0.73

Investigative Ophthalmology & Visual Science

Table 2. Continued

No.	Gene	SNP	No. of Cohorts	Ethnicity	Genetic Model	Pooled Sample Size		FEM or REM		Heterogeneity		Begg's Test	
						Case	Control	OR (95% CI)	*P*	*P* (Q)	I^2 (%)	Z	*P*
11	*XRCC1*	399Arg/Gln	3	Caucasian	T vs. C	742	840	**1.23 (1.07–1.43)**	**0.004**	0.39	0.00	0.00	1.00
			3	Asian	CC vs. TT	742	840	1.31 (0.89–1.92)	0.165	0.21	36.30	0.00	1.00
			3		TC vs. CC	742	840	**1.70 (1.21–2.38)**	**0.002**	0.13	50.70	1.04	0.30
			3		TT + TC vs. CC	742	840	**1.56 (1.18–2.06)**	**0.002**	0.19	39.30	1.04	0.30
			3		TT vs. TC + CC	742	840	1.02 (0.79–1.33)	0.852	0.25	27.90	1.04	0.30
		194Arg/Trp	2	Caucasian	T vs. C	582	647	0.89 (0.63–1.27)	0.518	0.379	0	0.00	1.00
			2		TC vs. CC	582	647	0.88 (0.61–1.27)	0.514	0.369	0	0.00	1.00
			2		TT + TC vs. CC	582	647	0.88 (0.61–1.27)	0.506	0.369	0	0.00	1.00
12	*ZP4*	rs540782	2	Asian	T vs. C	919	843	**1.31 (1.15–1.50)**	**0.000**	0.39	0.00	0.00	1.00
		rs547984	3	Asian	T vs. C	1334	1087	**1.25 (1.10–1.42)**	**0.001**	0.32	11.40	0.00	1.00
		rs693421	2	Asian	T vs. C	1011	978	**1.26 (1.11–1.43)**	**0.000**	0.05	75.20	0.00	1.00

FEM, fixed-effect model; REM, random-effect model.

* Multiple ancestries included ≥3 ethnic groups from Caucasian or Asian (Chinese, Korean, Japanese, Saudi Arabian, or Pakistani) or Australian or Latino (Mexican or Brazilian).

Bold value: OR (95% CI) > 1 and $P < 0.05$.

gene,[101,113,124] rs3764028 in the *GRIN2B* gene,[78,86] -511C/T in the *IL-1b* gene,[94,135,136] rs3825942, rs1048661, and rs2165241 in the *LOXL1* gene,[27,76,80,81,91,93,98,126,130–132] rs1801133 in the *MTHFR* gene,[89,105,118,127,129,133,141,149,150] 324Gln/His in the *MUTYH* gene,[74,96] rs2070744 in the *NOS3* gene,[83,106,111,112,118] 326Ser/Cys in the *OGG1* gene,[74,96] rs166850 and rs10451941 in the *OPA1* gene,[89,118,122,142–144,146,147,159] rs1042522 in the *p53* gene,[86,118,160–163] rs10483727 and rs33912345 in the *SIX1/SIX6* gene,[12,62,67,75,82,85,103,110] rs7961953 in the *TMTC2* gene,[64,105] -863C/A, -238G/A, and rs1800629 in the *TNF-a* gene,[89,100,118,140,164–167] and rs1042522 in the *TP53* gene[86,118] (Supplementary Files S17).

Sensitivity Analysis

To examine the stability of pooled results, sensitivity analysis was conducted by sequentially excluding individual studies and calculating the pooled ORs for the remaining studies. The outcomes did not alter the significance of pooled OR estimates, which indicated that our results were stable and reliable (data not shown).

Publication Bias

Begg's test did not detect evidence of publication bias in the overall analyses for 20 SNPs in 12 genes, which show significant association with POAG in candidate studies (Begg's test, $Z < 1.96$, $P > 0.05$, Table 2, Supplementary File S16).

Discussion

This is the first meta-analysis that summarized all reported gene SNPs and relevant phenotypes associated with POAG. We confirmed significant associations of 20 SNPs in 12 genes with POAG risk. Meanwhile, 27 SNPs in 19 genes were revealed to have no significant association with POAG. Possible functions and hypothetical involvement in POAG of candidate gene SNPs were summarized in Figure 2 and Table 3.

Outflow Pathway–Related Genes

Matrix metalloproteinases (MMPs) are endopeptidases involved in the proteolysis of extracellular matrix (ECM) proteins.[168] Decreased activity of MMPs in the aqueous humor might result in abnormal accumulation of matrix in POAG patients.[169] It was reported that the rs1799750 of the *MMP1* gene may be a risk factor associated with POAG in a Polish[94,104] and a Pakistani population.[95] Three hundred seventy-two T/C polymorphisms in tissue inhibitors for metalloproteinases (TIMPs) encoding genes have also been identified in POAG patients.[94] Plexin domain containing 2 (PLXDC2) is a cell-surface transmembrane protein, which was identified as a receptor for pigment epithelium–derived factor (PEDF).[170] The PLXDC2 genetic variant may lead to a different responsiveness to PEDF and increased IOP. Mabuchi et al.[64] found that there was a significant difference in the rs7081455 in *PLXDC2* gene allele frequencies between POAG patients and control subjects in a Japanese population.

The three genes may be associated with outflow pathway and increased IOP. Our meta-analysis found significant association with POAG in rs1799750 of the *MMP1* gene (recessive model), 372 T/C of the *TIMP1* gene (recessive model), and rs7081455 of the *PLXDC2* gene (allelic model).

Oxidative Stress–Related Genes

Oxidative stress is one of the risk factors for POAG.[171] Cells developed special mechanisms to remove DNA damage and

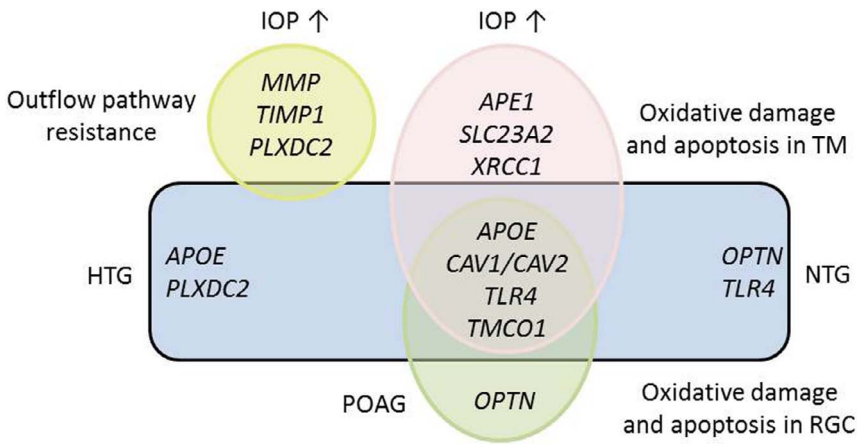

Figure 2. Possible functions and hypothetical involvement in POAG of candidate gene SNPs.

base exaction repair (BER) is the most important pathway.[172] APE1 is a crucial enzyme that participates in the BER pathway. The 148 Asp/Glu polymorphism of *APE1* gene may have a relationship with hypersensitivity to ionizing radiation and play a protective role in POAG progression.[173] *OPTN* is the second gene identified by genetic linkage analysis, which may be responsible for approximately 1.5% of NTG cases.[174] It was reported that OPTN protects cells from oxidative stress and inhibits cytochrome c release from mitochondria.[175] Vitamin C is an important water-soluble antioxidant.[176] The *SLC23A2* gene encodes the vitamin C co-transporter gene, which plays an important role in vitamin C transmembrane transport. It was reported that rs1279683 polymorphism of the *SLC23A2* gene was associated with lower plasma vitamin C concentrations and higher risk of POAG.[97,117] XRCC1 protein was encoded by the x-ray repair cross-complementing group1 (*XRCC1*) gene, which can coordinate the various components of the BER mechanism. Genetic polymorphism of *XRCC1* can change the structure of this protein and result in impaired DNA repair capacity.[177] It has been reported that the 399Arg/Gln genotype of the *XRCC1* gene was associated with an increased risk of POAG.[74,96]

The overall results of our study showed significant association with POAG in 148Asp/Glu of the *APE1* gene (homozygote and recessive models), c.412G3A (Thr34Thr) of the *OPTN* gene (homozygote model), rs1279683 of the *SLC23A2* gene (allelic model), and 399Arg/Gln of the *XRCC1* gene (allelic, heterozygote, and dominant model).

Apoptosis and Neurodegeneration–Related Genes

Apolipoprotein E (APOE) belongs to the class of lipoproteins that regulate the metabolism of lipids in the body. Many studies have shown that apolipoprotein E is associated with the neurodegenerative diseases, such as Alzheimer disease and glaucoma.[178] APOE (-219G) is associated with increased optic nerve damage, and APOE (-491T) interacts with an SNP in the MYOC promoter (-1000G), which is associated with the increased IOP in POAG.[148] CAV1 and CAV2 code for caveolin protein family members caveolin 1 and caveolin 2.[179] These proteins inhibit endothelial nitric oxide synthase activity within the caveolae. This interaction may alter nitric oxide generation and change trabecular meshwork function, both of which have been implicated in POAG pathogenesis.[180] The *TMCO1* gene encodes a transmembrane protein, which may localize to the Golgi apparatus and endoplasmic reticulum or mitochondria in different cell types, and with a proposed role in apoptosis.[10] The toll-like receptor 4 (*TLR4*) gene encodes for a transmembrane pathogen recognition receptor involved in the detection of lipopolysaccharides of gram-negative bacteria and other exogenous or endogenous ligands.[181] *TLR4* signaling has been implicated in the pathogenesis of IOP-induced RGC death. Upregulation of the *TLR4* gene may lead to enhanced neurodegeneration, which has been demonstrated in glaucomatous animals.[182] Recently, multiple SNPs (rs10759930, rs1927914, and rs7037117, rs10759930, rs1927914, rs1927911, rs12377632, and rs2149356) in the *TLR4* gene have been reported with POAG.[134]

In this meta-analysis, pooled results showed that rs449647 of the *APOE* gene showed significant association with POAG in allelic, homozygote, heterozygote, and dominant comparison; rs1052990 and rs4236601 of the *CAV1/CAV2* gene showed significant association with POAG in the allelic model; SNP rs4656461 of the *TMCO1* gene showed significant association with POAG in allelic model, and five SNPs (rs1927911, rs2149356, rs4986791, rs7037117, and rs10759930) of the *TLR4* gene confer an increased risk of POAG.

Other POAG-Associated Genes

The zona pellucida glycoprotein 4 (*ZP4*) gene is involved in functions related to fertilization and preimplantation development. SNPs and/or mutations in this gene were reported in association with ovarian diseases.[183] Reported association of ZP4 SNPs with POAG was controversial. In 2009, Nakano et al.[128] reported that three candidate SNPs (rs547984, rs540782, rs693421, and rs2499601) in the *ZP4* gene were modestly associated with the pathogenesis of POAG. Subsequent studies have failed to replicate this association between rs540782 and POAG in Indian,[184] Afro-Caribbean,[102] Japanese,[185] and Saudi[154] populations. Rs547984 in the *ZP4* gene also lacked association with POAG in a Saudi cohort.[155] In our meta-analysis, three SNPs (rs540782, rs547984, and rs693421) in the *ZP4* gene proved to have significant association with POAG in the allelic model.

Strengths and Limitations

Our meta-analysis has several strengths. As far as we know, this is the first meta-analysis that summarized all reported gene SNPs and relevant phenotypes associated with POAG. The results were robust due to the large number of cases and controls. Quality assessment, sensitivity analysis, and Begg's test were used to assess the potential biases, and failed to detect a significant bias in any of the genetic models, which demonstrated the credibility of the present meta-analysis.

Table 3. Candidate POAG Associated Genes, Possible Functions, and Hypothetical Involvement in POAG

Gene	Name	SNP	OR (95% CI)	Significance	Possible Function	Hypothetical Involvement in POAG
MMP	Matrix metallopeptidase	rs1799750	1.64 (1.05–2.56)	0.030	Proteolysis of extracellular matrix proteins	Abnormal accumulation of matrix in TM of POAG patients
TIMP1	Tissue inhibitors for metalloproteinase 1	372 T/C	1.50 (1.12–2.01)	0.007	Inhibition of matrix metalloproteinase expression	Imbalance between MMP and their tissue inhibitors in the aqueous humor and accumulation of matrix in TM of POAG patients
PLXDC2	Plexin domain containing 2	rs7081455	1.46 (1.28–1.68)	0.000	A receptor for PEDF	Through a different responsiveness to PEDF, and decrease the conventional outflow facility of the aqueous humor
APE1	Apyrimidinic endonuclease 1	148Asp/Glu	5.26 (1.12–24.82)	0.036	Participates in the base exaction repair pathway	May have a relationship with oxidative DNA lesions in TM of POAG patients
OPTN	Optineurin	c.603T3A(Met98Lys)	2.58 (1.12–5.97)	0.031	Protein binding	Through oxidative stress/the mitochondrial caspase-dependent cell death
SLC23A2	Solute carrier family 23 member 2	SLC23A2	1.43 (1.10–1.87)	0.007	Nucleobase transmembrane transporter activity	May be through lowering the plasma level of vitamin C Low level of vitamin C was found in POAG patients carrying mutation in this gene
XRCC1	X-ray repair cross-complementing group1	399Arg/Gln	1.23 (1.07–1.43)	0.004	Coordinate the various components of the base exaction repair mechanism	May change the structure of protein and result in impaired DNA repair capacity
APOE	Apolipoprotein E	rs449647	1.33 (1.13–1.57)	0.001	Protein binding, receptor binding	Role in oxidative stress and disrupted cellular homeostasis in CB, TM, LC, and RGC
CAV1/CAV2	Caveolin protein family member	rs1052990	1.17 (1.04–1.31)	0.008	Receptor binding, structural molecule activity	Dysfunction of cellular signaling and transport leading to the damage in tissues
	Caveolin 1 and caveolin 2	rs4236601	1.24 (1.16–1.32)	0.000		
TMCO1	Transmembrane and coiled-coil domains 1	rs4656461	1.46 (1.32–1.62)	0.000	Encoding transmembrane protein	Association with oxidative stress and apoptosis
TLR4	Toll-like receptor 4	rs1927911	1.28 (1.03–1.57)	0.007	Receptor binding, pathogen recognition, and innate immunity	Involved in oxidative stress and decreased cellular viability in CB, TM, LC, and RGC
		rs2149356	1.35 (1.04–1.76)	0.024		
		rs4986791	2.54 (1.21–5.32)	0.014		
		rs7037117	1.50 (1.01–2.24)	0.045		
		rs10759930	1.34 (1.06–1.70)	0.014		
ZP4	Zona pellucida glycoprotein 4	rs540782	1.31 (1.15–1.50)	0.000	Signal transducer activity, fertilization, and preimplantation development	Unknown
		rs547984	1.25 (1.10–1.42)	0.001		
		rs693421	1.26 (1.11–1.43)	0.000		

CB, ciliary body; TM, trabecular meshwork; LC, lamina cribrosa; CCT, central corneal thickness.

However, some limitations should be mentioned in this meta-analysis. First, adjusted factors, such as age, sex, and genotyping procedure, did not apply in the pooled results assessment. Second, the possibility of publication bias may exist because studies without statistically significant results would not be published. Only articles published in English-language journals were included, which might lead to language bias and the omission of inconclusive or negative studies in non-English articles. Third, Begg's funnel plot test may not play a perfect role in the present meta-analysis owing to an insufficient number of studies.

Conclusions

This systematic review and meta-analysis provided an overview of all reported gene SNPs in POAG. Our results highlighted 20 SNPs in 12 genes (*APE1*, *APOE*, *CAV1/CAV2*, *MMP*, *OPTN*, *PLXDC2*, *SLC23A2*, *TIMP1*, *TLR4*, *TMCO1*, *XRCC1*, *ZP4*) as predictive risk factors for POAG. Further efforts should be made to generate a better understanding of the potential pathways and mechanisms. Well-designed and large-scale studies in various populations should be carried out in the future to provide more powerful evidence.

Acknowledgments

Supported by the National Natural Science Foundation of China (No. 81700829 and 81800869; Beijing, China) and the Zhejiang Provincial Natural Science Foundation of China (No. LY19H120006 and LY17H120002; Hangzhou, Zhejiang, China).

Disclosure: **M. Chen**, None; **X. Yu**, None; **J. Xu**, None; **J. Ma**, None; **X. Chen**, None; **B. Chen**, None; **Y. Gu**, None; **K. Wang**, None

References

1. Kapetanakis VV, Chan MP, Foster PJ, et al. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. *Br J Ophthalmol*. 2016;100:86–93.
2. Bourne RR, Taylor HR, Flaxman SR, et al. Number of people blind or visually impaired by glaucoma worldwide and in world regions 1990 - 2010: a meta-analysis. *PLoS One*. 2016; 11:e0162229.
3. Quigley HA. Glaucoma. *Lancet*. 2011;377:1367–1377.
4. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262–267.
5. Kwon YH, Fingert JH, Kuehn MH, et al. Primary open-angle glaucoma. *N Engl J Med*. 2009;360:1113–1124.
6. Worley A, Grimmer-Somers K. Risk factors for glaucoma: what do they really mean? *Aust J Prim Health*. 2011;17:233–239.
7. Liu Y, Allingham RR. Major review: molecular genetics of primary open-angle glaucoma. *Exp Eye Res*. 2017;160:62–84.
8. Takamoto M, Araie M. Genetics of primary open angle glaucoma. *Jpn J Ophthalmol*. 2014;58:1–15.
9. Gu X, Reagan AM, McClellan ME, et al. Caveolins and caveolae in ocular physiology and pathophysiology. *Prog Retin Eye Res*. 2017;56:84–106.
10. Burdon KP, Macgregor S, Hewitt AW, et al. Genome-wide association study identifies susceptibility loci for open angle glaucoma at TMCO1 and CDKN2B-AS1. *Nat Genet*. 2011;43: 574–578.
11. Nakano M, Ikeda Y, Tokuda Y, et al. Common variants in CDKN2B-AS1 associated with optic-nerve vulnerability of glaucoma identified by genome-wide association studies in Japanese. *PloS One*. 2012;7:e33389.
12. Osman W, Low SK, Takahashi A, et al. A genome-wide association study in the Japanese population confirms 9p21 and 14q23 as susceptibility loci for primary open angle glaucoma. *Hum Mol Genet*. 2012;21:2836–2842.
13. Ulmer M, Li J, Yaspan BL, et al. Genome-wide analysis of central corneal thickness in primary open-angle glaucoma cases in the NEIGHBOR and GLAUGEN consortia. *Invest Ophthalmol Vis Sci*. 2012;53:4468–4474.
14. Suh W, Won HH, Kee C. The association of single-nucleotide polymorphisms in the MMP-9 gene with normal tension glaucoma and primary open-angle glaucoma. *Curr Eye Res*. 2018;43:534–538.
15. Li J, Feng Y, Sung MS, et al. Association of interleukin-1 gene clusters polymorphisms with primary open-angle glaucoma: a meta-analysis. *BMC Ophthalmol*. 2017;17:218.
16. Panic N, Leoncini E, de Belvis G, et al. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS One*. 2013;8:e83138.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.
18. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
20. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315: 629–634.
21. Fang Kho P, Lea RA, Benton MC, et al. Expression QTL analysis of glaucoma endophenotypes in the Norfolk Island isolate provides evidence that immune-related genes are associated with optic disc size. *J Hum Genet*. 2018;63:83–87.
22. Narooie-Nejad M, Rasouli A, Mousavi M, et al. Study of MYOC gene mutation in POAG patients in Zahedan, Iran. *Clin Lab*. 2017;63:1283–1291.
23. Kosior-Jarecka E, Lukasik U, Wrobel-Dudzinska D, et al. Risk factors for normal and high-tension glaucoma in Poland in connection with polymorphisms of the endothelial nitric oxide synthase gene. *PloS One*. 2016;11:e0147540.
24. Trikha S, Saffari E, Nongpiur M, et al. A genetic variant in TGFBR3-CDC7 is associated with visual field progression in primary open-angle glaucoma patients from Singapore. *Ophthalmology*. 2015;122:2416–2422.
25. Pasquale LR, Loomis SJ, Kang JH, et al. CDKN2B-AS1 genotype-glaucoma feature correlations in primary open-angle glaucoma patients from the United States. *Am J Ophthalmol*. 2013;155:342–353 e345.
26. Kumar V, Singh S, Ahmed RS, et al. Frequency of common CYP1B1 polymorphic variations in Delhi population of Northern India. *Environ Toxicol Pharmacol*. 2009;28:392–396.
27. Tanito M, Minami M, Akahori M, et al. LOXL1 variants in elderly Japanese patients with exfoliation syndrome/glaucoma, primary open-angle glaucoma, normal tension glaucoma, and cataract. *Mol Vis*. 2008;14:1898–1905.
28. Liu Y, Bailey JC, Helwa I, et al. A common variant in MIR182 is associated with primary open-angle glaucoma in the NEIGHBORHOOD consortium. *Invest Ophthalmol Vis Sci*. 2016;57:3974–3981.
29. Collins DW, Gudiseva HV, Trachtman B, et al. Association of primary open-angle glaucoma with mitochondrial variants and haplogroups common in African Americans. *Mol Vis*. 2016;22:454–471.

30. Vishal M, Sharma A, Kaurani L, et al. Genetic association and stress mediated down-regulation in trabecular meshwork implicates MPP7 as a novel candidate gene in primary open angle glaucoma. *BMC Med Genomics*. 2016;9:15.
31. Liu XL, Jia QJ, Wang LN, et al. Roles of CYP2C19 gene polymorphisms in susceptibility to POAG and individual differences in drug treatment response. *Med Sci Monit*. 2016;22:310–315.
32. Dewundara SS, Wiggs JL, Sullivan DA, et al. Is estrogen a therapeutic target for glaucoma? *Semin Ophthalmol*. 2016; 31:140–146.
33. Gharahkhani P, Burdon KP, Hewitt AW, et al. Accurate imputation-based screening of Gln368Ter myocilin variant in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2015;56:5087–5093.
34. Philomenadin FS, Asokan R, N V, et al. Genetic association of SNPs near ATOH7, CARD10, CDKN2B, CDC7 and SIX1/SIX6 with the endophenotypes of primary open angle glaucoma in Indian population. *PLoS One*. 2015;10:e0119703.
35. Gong B, Qu C, Li X, et al. Mutation spectrum of CYP1B1 in Chinese patients with primary open-angle glaucoma. *Br J Ophthalmol*. 2015;99:425–430.
36. Jakobsson C, Kheir V, Munier FL, et al. Molecular analysis of NOTCH2 in patients with primary open-angle glaucoma. *Klin Monbl Augenheilkd*. 2015;232:427–431.
37. Barbosa AM, Frare AB, Costa NB, et al. GSTM1 polymorphism in patients with primary open-angle glaucoma. *Genet Mol Res*. 2012;11:3256–3262.
38. Wolf C, Gramer E, Muller-Myhsok B, et al. Mitochondrial haplogroup U is associated with a reduced risk to develop exfoliation glaucoma in the German population. *BMC Genet*. 2010;11:8.
39. Rakhmanov VV, Nikitina N, Zakharova FM, et al. Mutations and polymorphisms in the genes for myocilin and optineur in as the risk factors of primary open-angle glaucoma [in Russian]. *Genetika*. 2005;41:1567–1574.
40. de Voogd S, Wolfs RC, Jansonius NM, et al. Estrogen receptors alpha and beta and the risk of open-angle glaucoma: the Rotterdam Study. *Arch Ophthalmol*. 2008; 126:110–114.
41. Fingert JH, Alward WL, Kwon YH, et al. No association between variations in the WDR36 gene and primary open-angle glaucoma. *Arch Ophthalmol*. 2007;125:434–436.
42. Unal M, Guven M, Devranoglu K, et al. Glutathione S transferase M1 and T1 genetic polymorphisms are related to the risk of primary open-angle glaucoma: a study in a Turkish population. *Br J Ophthalmol*. 2007;91:527–530.
43. Guven M, Unal M, Sarici A, et al. Glutathione-S-transferase M1 and T1 genetic polymorphisms and the risk of cataract development: a study in the Turkish population. *Curr Eye Res*. 2007;32:447–454.
44. Ressiniotis T, Griffiths PG, Birch M, et al. Apolipoprotein E promoter polymorphisms do not have a major influence on the risk of developing primary open angle glaucoma. *Mol Vis*. 2004;10:805–807.
45. Fan BJ, Leung YF, Wang N, et al. Genetic and environmental risk factors for primary open-angle glaucoma. *Chin Med J (Engl)*. 2004;117:706–710.
46. Toda Y, Tang S, Kashiwagi K, et al. Mutations in the optineurin gene in Japanese patients with primary open-angle glaucoma and normal tension glaucoma. *Am J Med Genet A*. 2004;125A:1–4.
47. Alward WL, Kwon YH, Kawase K, et al. Evaluation of optineurin sequence variations in 1,048 patients with open-angle glaucoma. *Am J Ophthalmol*. 2003;136:904–910.
48. Fan BJ, Leung YF, Pang CP, et al. Single nucleotide polymorphisms of the myocilin gene in primary open-angle glaucoma patients [in Chinese]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2004;21:70–73.
49. Tang S, Toda Y, Kashiwagi K, et al. The association between Japanese primary open-angle glaucoma and normal tension glaucoma patients and the optineurin gene. *Hum Genet*. 2003;113:276–279.
50. Jansson M, Rada A, Tomic L, et al. Analysis of the glutathione S-transferase M1 gene using pyrosequencing and multiplex PCR–no evidence of association to glaucoma. *Exp Eye Res*. 2003;77:239–243.
51. Sjostrand A, Tomic L, Larsson LI, et al. No evidence of association between GT/CA-repeat polymorphism in the GLC1A gene promoter and primary open-angle or exfoliation glaucoma. *Acta Ophthalmol Scand*. 2002;80:384–386.
52. Wang N, Peng Z, Fan B, et al. Case control study on the risk factors of primary open angle glaucoma in China [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2002;23: 293–296.
53. Aung T, Ocaka L, Ebenezer ND, et al. Investigating the association between OPA1 polymorphisms and glaucoma: comparison between normal tension and high tension primary open angle glaucoma. *Hum Genet*. 2002;110:513–514.
54. Juronen E, Tasa G, Veromann S, et al. Polymorphic glutathione S-transferase M1 is a risk factor of primary open-angle glaucoma among Estonians. *Exp Eye Res*. 2000; 71:447–452.
55. Wiggs JL, Hauser MA, Abdrabou W, et al. The NEIGHBOR consortium primary open-angle glaucoma genome-wide association study: rationale, study design, and clinical variables. *J Glaucoma*. 2013;22:517–525.
56. Banerjee D, Banerjee A, Mookherjee S, et al. Mitochondrial genome analysis of primary open angle glaucoma patients. *PloS One*. 2013;8:e70760.
57. Chen Y, Lin Y, Vithana EN, et al. Common variants near ABCA1 and in PMM2 are associated with primary open-angle glaucoma. *Nat Genet*. 2014;46:1115–1119.
58. Hysi PG, Cheng CY, Springelkamp H, et al. Genome-wide analysis of multi-ancestry cohorts identifies new loci influencing intraocular pressure and susceptibility to glaucoma. *Nat Genet*. 2014;46:1126–1130.
59. Park S, Jamshidi Y, Vaideanu D, et al. Common TGFbeta2, BMP4, and FOXC1 variants are not associated with primary open-angle glaucoma. *Mol Vis*. 2012;18:1526–1539.
60. Motushchuk AE, Komarova T, Grudinina NA, et al. Genetic variants of CYP1B1 and WDR36 in the patients with primary congenital glaucoma and primary open angle glaucoma from Saint-Petersburg [in Russian]. *Genetika*. 2009;45:1659–1667.
61. Gong B, Shi Y, Qu C, et al. Association of catalase polymorphisms with primary open-angle glaucoma in a Chinese population. *Ophthalmic Genet*. 2018;39:35–40.
62. Kondkar AA, Azad TA, Almobarak FA, et al. Polymorphism rs10483727 in the SIX1/SIX6 gene locus is a risk factor for primary open angle glaucoma in a Saudi cohort. *Genet Test Mol Biomarkers*. 2018;22:74–78.
63. Kondkar AA, Azad TA, Almobarak FA, et al. Polymorphism rs11656696 in GAS7 is not associated with primary open angle glaucoma in a Saudi Cohort. *Genet Test Mol Biomarkers*. 2017;21:754–758.
64. Mabuchi F, Mabuchi N, Takamoto M, et al. Genetic variant near PLXDC2 influences the risk of primary open-angle glaucoma by increasing intraocular pressure in the Japanese population. *J Glaucoma*. 2017;26:963–966.
65. Nunes HF, Ananina G, Costa VP, et al. Investigation of CAV1/CAV2 rs4236601 and CDKN2B-AS1 rs2157719 in primary open-angle glaucoma patients from Brazil. *Ophthalmic Genet*. 2018;39:194–199.

Investigative Ophthalmology & Visual Science

66. Navarro-Partida J, Alvarado Castillo B, Martinez-Rizo AB, et al. Association of single-nucleotide polymorphisms in non-coding regions of the TLR4 gene with primary open angle glaucoma in a Mexican population. *Ophthalmic Genet*. 2017;38:325–329.
67. Yoshikawa M, Nakanishi H, Yamashiro K, et al. Association of glaucoma-susceptible genes to regional circumpapillary retinal nerve fiber layer thickness and visual field defects. *Invest Ophthalmol Vis Sci*. 2017;58:2510–2519.
68. Abu-Amero KK, Kondkar AA, Mousa A, et al. Analysis of toll-like receptor rs4986790 polymorphism in Saudi patients with primary open angle glaucoma. *Ophthalmic Genet*. 2017;38:133–137.
69. Kimura Y, Akagi T, Miyake M, et al. Association between the CDKN2B-AS1 gene and primary open angle glaucoma with high myopia in Japanese patients. *Ophthalmic Genet*. 2016; 37:242–244.
70. Mousa A, Kondkar AA, Al-Obeidan SA, et al. Lack of association between polymorphism rs4986791 in TLR4 and primary open-angle glaucoma in a Saudi cohort. *Genet Test Mol Biomarkers*. 2016;20:556–559.
71. Ng SK, Burdon KP, Fitzgerald JT, et al. Genetic association at the 9p21 glaucoma locus contributes to sex bias in normal-tension glaucoma. *Invest Ophthalmol Vis Sci*. 2016;57: 3416–3421.
72. Rong SS, Chen LJ, Leung CK, et al. Ethnic specific association of the CAV1/CAV2 locus with primary open-angle glaucoma. *Sci Rep*. 2016;6:27837.
73. Sang J, Jia L, Zhao B, et al. Association of three single nucleotide polymorphisms at the SIX1-SIX6 locus with primary open angle glaucoma in the Chinese population. *Sci China Life Sci*. 2016;59:694–699.
74. Cuchra M, Markiewicz L, Mucha B, et al. The role of base excision repair in the development of primary open angle glaucoma in the Polish population. *Mutat Res*. 2015;778:26–40.
75. Chen Y, Hughes G, Chen X, et al. Genetic variants associated with different risks for high tension glaucoma and normal tension glaucoma in a Chinese population. *Invest Ophthalmol Vis Sci*. 2015;56:2595–2600.
76. Gong B, Li X, Li N, et al. Association between LOXL1 gene polymorphisms and primary open angle glaucoma in Sichuan population [in Chinese]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2015;32:89–93.
77. Kim S, Kim K, Heo DW, et al. Expression-associated polymorphisms of CAV1-CAV2 affect intraocular pressure and high-tension glaucoma risk. *Mol Vis*. 2015;21:548–554.
78. Nowak A, Majsterek I, Przybylowska-Sygut K, et al. Analysis of the expression and polymorphism of APOE, HSP, BDNF, and GRIN2B genes associated with the neurodegeneration process in the pathogenesis of primary open angle glaucoma. *Biomed Res Int*. 2015;2015:258281.
79. Nowak A, Przybylowska-Sygut K, Gacek M, et al. Neurodegenerative genes polymorphisms of the -491A/T APOE, the -877T/C APP and the risk of primary open-angle glaucoma in the Polish population. *Ophthalmic Genet*. 2015;36:105–112.
80. Zanon-Moreno V, Zanon-Moreno L, Ortega-Azorin C, et al. Genetic polymorphism related to exfoliative glaucoma is also associated with primary open-angle glaucoma risk. *Clin Exp Ophthalmol*. 2015;43:26–30.
81. Anastasopoulos E, Coleman AL, Wilson MR, et al. Association of LOXL1 polymorphisms with pseudoexfoliation, glaucoma, intraocular pressure, and systemic diseases in a Greek population. The Thessaloniki eye study. *Invest Ophthalmol Vis Sci*. 2014;55:4238–4243.
82. Burdon KP, Mitchell P, Lee A, et al. Association of open-angle glaucoma loci with incident glaucoma in the Blue Mountains Eye Study. *Am J Ophthalmol*. 2015;159:31–36 e31.
83. Emam WA, Zidan HE, Abdulhalim BE, et al. Endothelial nitric oxide synthase polymorphisms and susceptibility to high-tension primary open-angle glaucoma in an Egyptian cohort. *Mol Vis*. 2014;20:804–811.
84. Loomis SJ, Kang JH, Weinreb RN, et al. Association of CAV1/CAV2 genomic variants with primary open-angle glaucoma overall and by gender and pattern of visual field loss. *Ophthalmology*. 2014;121:508–516.
85. Micheal S, Ayub H, Khan MI, et al. Association of known common genetic variants with primary open angle, primary angle closure, and pseudoexfoliation glaucoma in Pakistani cohorts. *Mol Vis*. 2014;20:1471–1479.
86. Nowak A, Przybylowska-Sygut K, Szymanek K, et al. The relationship of TP53 and GRIN2B gene polymorphisms with risk of occurrence and progression of primary open-angle glaucoma in a Polish population. *Pol J Pathol*. 2014;65:313–321.
87. Abu-Amero KK, Kondkar AA, Mousa A, et al. Association of Mn-SOD mutation (c.47T > C) with various POAG clinical indices. *Ophthalmic Genet*. 2014;35:85–90.
88. Bachernegg A, El-Shabrawi Y, Weger M, et al. Role of rs1533428 and rs12994401 in patients with primary open angle glaucoma in an European population. *Ophthalmic Genet*. 2013;34:48–51.
89. Buentello-Volante B, Elizondo-Olascoaga C, Miranda-Duarte A, et al. Association study of multiple gene polymorphisms with the risk of adult-onset primary open-angle glaucoma in a Mexican population. *Exp Eye Res*. 2013;107:59–64.
90. Cuchra M, Szaflik JP, Przybylowska-Sygut K, et al. The role of the 148 Asp/Glu polymorphism of the APE1 gene in the development and progression of primary open angle glaucoma development in the Polish population. *Pol J Pathol*. 2013;64:296–302.
91. Chiras D, Tzika K, Kokotas H, et al. Development of novel LOXL1 genotyping method and evaluation of LOXL1, APOE and MTHFR polymorphisms in exfoliation syndrome/glaucoma in a Greek population. *Mol Vis*. 2013;19:1006–1016.
92. Kato T, Meguro A, Nomura E, et al. Association study of genetic variants on chromosome 7q31 with susceptibility to normal tension glaucoma in a Japanese population. *Eye*. 2013;27:979–983.
93. Kasim B, Irkec M, Alikasifoglu M, et al. Association of LOXL1 gene polymorphisms with exfoliation syndrome/glaucoma and primary open angle glaucoma in a Turkish population. *Mol Vis*. 2013;19:114–120.
94. Markiewicz L, Majsterek I, Przybylowska K, et al. Gene polymorphisms of the MMP1, MMP9, MMP12, IL-1beta and TIMP1 and the risk of primary open-angle glaucoma. *Acta Ophthalmol*. 2013;91:e516–e523.
95. Micheal S, Yousaf S, Khan MI, et al. Polymorphisms in matrix metalloproteinases MMP1 and MMP9 are associated with primary open-angle and angle closure glaucoma in a Pakistani population. *Mol Vis*. 2013;19:441–447.
96. Szaflik JP, Cuchra M, Przybylowska-Sygut K, et al. Association of the 399Arg/Gln XRCC1, the 194 Arg/Trp XRCC1, the 326Ser/Cys OGG1, and the 324Gln/His MUTYH gene polymorphisms with clinical parameters and the risk for development of primary open-angle glaucoma. *Mutat Res*. 2013;753:12–22.
97. Zanon-Moreno V, Asensio-Marquez EM, Ciancotti-Oliver L, et al. Effects of polymorphisms in vitamin E-, vitamin C-, and glutathione peroxidase-related genes on serum biomarkers and associations with glaucoma. *Mol Vis*. 2013;19:231–242.
98. Abu-Amero KK, Osman EA, Azad MT, et al. Lack of association between LOXL1 gene polymorphisms and primary open angle glaucoma in the Saudi Arabian population. *Ophthalmic Genet*. 2012;33:130–133.

Investigative Ophthalmology & Visual Science

99. Balasubbu S, Krishnadas SR, Jiao X, et al. Evaluation of SNPs on chromosome 2p with primary open angle glaucoma in the South Indian cohort. *Invest Ophthalmol Vis Sci*. 2012; 53:1861–1864.
100. Bozkurt B, Mesci L, Irkec M, et al. Association of tumour necrosis factor-alpha -308 G/A polymorphism with primary open-angle glaucoma. *Clin Exp Ophthalmol*. 2012;40:e156–e162.
101. Chen LJ, Tam PO, Leung DY, et al. SNP rs1533428 at 2p16.3 as a marker for late-onset primary open-angle glaucoma. *Mol Vis*. 2012;18:1629–1639.
102. Cao D, Jiao X, Liu X, et al. CDKN2B polymorphism is associated with primary open-angle glaucoma (POAG) in the Afro-Caribbean population of Barbados, West Indies. *PLoS One*. 2012;7:e39278.
103. Dimasi DP, Burdon KP, Hewitt AW, et al. Genetic investigation into the endophenotypic status of central corneal thickness and optic disc parameters in relation to open-angle glaucoma. *Am J Ophthalmol*. 2012;154:833–842.
104. Majsterek I, Markiewicz L, Przybylowska K, et al. Association of MMP1-1607 1G/2G and TIMP1 372 T/C gene polymorphisms with risk of primary open angle glaucoma in a Polish population. *Med Sci Monit*. 2011;17:CR417–CR421.
105. Nilforoushan N, Aghapour S, Raoofian R, et al. Lack of association between the C677T single nucleotide polymorphism of the MTHFR gene and glaucoma in Iranian patients. *Acta Med Iran*. 2012;50:208–212.
106. Magalhaes da Silva T, Rocha AV, Lacchini R, et al. Association of polymorphisms of endothelial nitric oxide synthase (eNOS) gene with the risk of primary open angle glaucoma in a Brazilian population. *Gene*. 2012;502:142–146.
107. Takano Y, Shi D, Shimizu A, et al. Association of toll-like receptor 4 gene polymorphisms in Japanese subjects with primary open-angle, normal-tension, and exfoliation glaucoma. *Am J Ophthalmol*. 2012;154:825–832.
108. Wang CY, Shen YC, Wei LC, et al. Polymorphism in the TNF-alpha(-863) locus associated with reduced risk of primary open angle glaucoma. *Mol Vis*. 2012;18:779–785.
109. Chen JH, Wang D, Huang C, et al. Interactive effects of ATOH7 and RFTN1 in association with adult-onset primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2012;53: 779–785.
110. Fan BJ, Wang DY, Pasquale LR, et al. Genetic variants associated with optic nerve vertical cup-to-disc ratio are risk factors for primary open angle glaucoma in a US Caucasian population. *Invest Ophthalmol Vis Sci*. 2011;52:1788–1792.
111. Kang JH, Wiggs JL, Haines J, et al. Reproductive factors and NOS3 variant interactions in primary open-angle glaucoma. *Mol Vis*. 2011;17:2544–2551.
112. Kang JH, Wiggs JL, Rosner BA, et al. Endothelial nitric oxide synthase gene variants and primary open-angle glaucoma: interactions with hypertension, alcohol intake, and cigarette smoking. *Arch Ophthalmol*. 2011;129:773–780.
113. Mossböck G, Weger M, Faschinger C, et al. Role of cholesterol 24S-hydroxylase gene polymorphism (rs754203) in primary open angle glaucoma. *Mol Vis*. 2011;17:616–620.
114. Suh W, Kim S, Ki CS, et al. Toll-like receptor 4 gene polymorphisms do not associate with normal tension glaucoma in a Korean population. *Mol Vis*. 2011;17:2343–2348.
115. Wiggs JL, Kang JH, Yaspan BL, et al. Common variants near CAV1 and CAV2 are associated with primary open-angle glaucoma in Caucasians from the USA. *Hum Mol Genet*. 2011;20:4707–4713.
116. Yousaf S, Khan MI, Micheal S, et al. XRCC1 and XPD DNA repair gene polymorphisms: a potential risk factor for glaucoma in the Pakistani population. *Mol Vis*. 2011;17: 1153–1163.
117. Zanon-Moreno V, Ciancotti-Olivares L, Asencio J, et al. Association between a SLC23A2 gene variation, plasma vitamin C levels, and risk of glaucoma in a Mediterranean population. *Mol Vis*. 2011;17:2997–3004.
118. Fan BJ, Liu K, Wang DY, et al. Association of polymorphisms of tumor necrosis factor and tumor protein p53 with primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2010;51:4110–4116.
119. Liu Y, Qin X, Schmidt S, et al. Association between chromosome 2p16.3 variants and glaucoma in populations of African descent. *Proc Natl Acad Sci U S A*. 2010;107:E61; author reply E62.
120. Mabuchi F, Sakurada Y, Kashiwagi K, et al. Lack of association of common variants on chromosome 2p with primary open-angle glaucoma in the Japanese population. *Proc Natl Acad Sci U S A*. 2010;107:E90–E91.
121. Mossbock G, Weger M, Faschinger C, et al. Role of functional single nucleotide polymorphisms of MMP1, MMP2, and MMP9 in open angle glaucomas. *Mol Vis*. 2010;16:1764–1770.
122. Yu-Wai-Man P, Stewart JD, Hudson G, et al. OPA1 increases the risk of normal but not high tension glaucoma. *J Med Genet*. 2010;47:120–125.
123. Caixeta-Umbelino C, de Vasconcellos JP, Costa VP, et al. Lack of association between optineurin gene variants T34T, E50K, M98K, 691_692insAG and R545Q and primary open angle glaucoma in Brazilian patients. *Ophthalmic Genet*. 2009;30: 13–18.
124. Fourgeux C, Martine L, Bjorkhem I, et al. Primary open-angle glaucoma: association with cholesterol 24S-hydroxylase (CYP46A1) gene polymorphism and plasma 24-hydroxycholesterol levels. *Invest Ophthalmol Vis Sci*. 2009;50:5712–5717.
125. Jiao X, Yang Z, Yang X, et al. Common variants on chromosome 2 and risk of primary open-angle glaucoma in the Afro-Caribbean population of Barbados. *Proc Natl Acad Sci U S A*. 2009;106:17105–17110.
126. Lemmela S, Forsman E, Onkamo P, et al. Association of LOXL1 gene with Finnish exfoliation syndrome patients. *J Hum Genet*. 2009;54:289–297.
127. Micheal S, Qamar R, Akhtar F, et al. MTHFR gene C677T and A1298C polymorphisms and homocysteine levels in primary open angle and primary closed angle glaucoma. *Mol Vis*. 2009;15:2268–2278.
128. Nakano M, Ikeda Y, Taniguchi T, et al. Three susceptible loci associated with primary open-angle glaucoma identified by genome-wide association study in a Japanese population. *Proc Natl Acad Sci U S A*. 2009;106:12838–12842.
129. Zetterberg M, Tasa G, Palmer MS, et al. Methylenetetrahydrofolate reductase genetic polymorphisms in patients with primary open-angle glaucoma. *Ophthalmic Genet*. 2007;28: 47–50.
130. Chakrabarti S, Rao KN, Kaur I, et al. The LOXL1 gene variations are not associated with primary open-angle and primary angle-closure glaucomas. *Invest Ophthalmol Vis Sci*. 2008;49:2343–2347.
131. Gong WF, Chiang SW, Chen LJ, et al. Evaluation of LOXL1 polymorphisms in primary open-angle glaucoma in southern and northern Chinese. *Mol Vis*. 2008;14:2381–2389.
132. Mabuchi F, Sakurada Y, Kashiwagi K, et al. Lysyl oxidase-like 1 gene polymorphisms in Japanese patients with primary open angle glaucoma and exfoliation syndrome. *Mol Vis*. 2008;14:1303–1308.
133. Michael S, Qamar R, Akhtar F, et al. C677T polymorphism in the methylenetetrahydrofolate reductase gene is associated with primary closed angle glaucoma. *Mol Vis*. 2008;14:661–665.

Investigative Ophthalmology & Visual Science

134. Shibuya E, Meguro A, Ota M, et al. Association of toll-like receptor 4 gene polymorphisms with normal tension glaucoma. *Invest Ophthalmol Vis Sci*. 2008;49:4453–4457.
135. How AC, Aung T, Chew X, et al. Lack of association between interleukin-1 gene cluster polymorphisms and glaucoma in Chinese subjects. *Invest Ophthalmol Vis Sci*. 2007;48:2123–2126.
136. Wang CY, Shen YC, Su CH, et al. Investigation of the association between interleukin-1beta polymorphism and normal tension glaucoma. *Mol Vis*. 2007;13:719–723.
137. Funayama T, Mashima Y, Ohtake Y, et al. SNPs and interaction analyses of noelin 2, myocilin, and optineurin genes in Japanese patients with open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2006;47:5368–5375.
138. Lam CY, Fan BJ, Wang DY, et al. Association of apolipoprotein E polymorphisms with normal tension glaucoma in a Chinese population. *J Glaucoma*. 2006;15:218–222.
139. Mabuchi F, Tang S, Kashiwagi K, et al. Methylenetetrahydrofolate reductase gene polymorphisms c.677C/T and c.1298A/C are not associated with open angle glaucoma. *Mol Vis*. 2006;12:735–739.
140. Mossböck G, Weger M, Moray M, et al. TNF-alpha promoter polymorphisms and primary open-angle glaucoma. *Eye*. 2006;20:1040–1043.
141. Mossböck G, Weger M, Faschinger C, et al. Methylenetetrahydrofolatereductase (MTHFR) 677C>T polymorphism and open angle glaucoma. *Mol Vis*. 2006;12:356–359.
142. Mabuchi F, Tang S, Kashiwagi K, et al. The OPA1 gene polymorphism is associated with normal tension and high tension glaucoma. *Am J Ophthalmol*. 2007;143:125–130.
143. Yao W, Jiao X, Hejtmancik JF, et al. Evaluation of the association between OPA1 polymorphisms and primary open-angle glaucoma in Barbados families. *Mol Vis*. 2006;12:649–654.
144. Fan BJ, Wang DY, Fan DS, et al. SNPs and interaction analyses of myocilin, optineurin, and apolipoprotein E in primary open angle glaucoma patients. *Mol Vis*. 2005;11:625–631.
145. Funayama T, Ishikawa K, Ohtake Y, et al. Variants in optineurin gene and their association with tumor necrosis factor-alpha polymorphisms in Japanese patients with glaucoma. *Invest Ophthalmol Vis Sci*. 2004;45:4359–4367.
146. Woo SJ, Kim DM, Kim JY, et al. Investigation of the association between OPA1 polymorphisms and normal-tension glaucoma in Korea. *J Glaucoma*. 2004;13:492–495.
147. Powell BL, Toomes C, Scott S, et al. Polymorphisms in OPA1 are associated with normal tension glaucoma. *Mol Vis*. 2003;9:460–464.
148. Copin B, Brezin AP, Valtot F, et al. Apolipoprotein E-promoter single-nucleotide polymorphisms affect the phenotype of primary open-angle glaucoma and demonstrate interaction with the myocilin gene. *Am J Hum Genet*. 2002;70:1575–1581.
149. Al-Shahrani H, Al-Dabbagh N, Al-Dohayan N, et al. Association of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism with primary glaucoma in Saudi population. *BMC Ophthalmol*. 2016;16:156.
150. Jünemann AG, von Ahsen N, Reulbach U, et al. C677T variant in the methylentetrahydrofolate reductase gene is a genetic risk factor for primary open-angle glaucoma. *Am J Ophthalmol*. 2005;139:721–723.
151. Kim K, Yun YJ, Kim S, et al. Analysis of an extended chromosome locus 2p14-21 for replication of the 2p16.3 association with glaucoma susceptibility. *Mol Vis*. 2011;17:1136–1143.
152. Fuse N, Takahashi K, Akiyama H, et al. Molecular genetic analysis of optineurin gene for primary open-angle and normal tension glaucoma in the Japanese population. *J Glaucoma*. 2004;13:299–303.
153. Navarro-Partida J, Martinez-Rizo AB, Ramirez-Barrera P, et al. Association of toll-like receptor 4 single-nucleotide polymorphisms Asp299Gly and Thr399Ile with the risk of primary open angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2017;255:995–1001.
154. Kondkar AA, Edward NB, Kalantan H, et al. Lack of association between polymorphism rs540782 and primary open angle glaucoma in Saudi patients. *J Negat Results Biomed*. 2017;16:3.
155. Azad TA, Edward NB, Kondkar AA, et al. Polymorphism rs547984 on human chromosome 1q43 is not associated with primary open angle glaucoma in a Saudi cohort. *J Negat Results Biomed*. 2017;16:12.
156. Abu-Amero KK, Kondkar AA, Mousa A, et al. Analysis of catalase SNP rs1001179 in Saudi patients with primary open angle glaucoma. *Ophthalmic Genet*. 2013;34:223–228.
157. Abu-Amero KK, Kondkar AA, Mousa A, et al. Analysis of cyclin-dependent kinase inhibitor-2B rs1063192 polymorphism in Saudi patients with primary open-angle glaucoma. *Genet Test Mol Biomarkers*. 2016;20:637–641.
158. Burdon KP, Hewitt AW, Mackey DA, et al. Tag SNPs detect association of the CYP1B1 gene with primary open angle glaucoma. *Mol Vis*. 2010;16:2286–2293.
159. Liu Y, Schmidt S, Qin X, et al. No association between OPA1 polymorphisms and primary open-angle glaucoma in three different populations. *Mol Vis*. 2007;13:2137–2141.
160. Neamatzadeh H, Soleimanizad R, Atefi A, et al. Association between p53 codon 72 (Arg72Pro) polymorphism and primary open-angle glaucoma in Iranian patients. *Iran Biomed J*. 2015;19:51–56.
161. Daugherty CL, Curtis H, Realini T, et al. Primary open angle glaucoma in a Caucasian population is associated with the p53 codon 72 polymorphism. *Mol Vis*. 2009;15:1939–1944.
162. Mabuchi F, Sakurada Y, Kashiwagi K, et al. Lack of association between p53 gene polymorphisms and primary open angle glaucoma in the Japanese population. *Mol Vis*. 2009;15:1045–1049.
163. Lin HJ, Chen WC, Tsai FJ, et al. Distributions of p53 codon 72 polymorphism in primary open angle glaucoma. *Br J Ophthalmol*. 2002;86:767–770.
164. Tikunova E, Ovtcharova V, Reshetnikov E, et al. Genes of tumor necrosis factors and their receptors and the primary open angle glaucoma in the population of Central Russia. *Int J Ophthalmol*. 2017;10:1490–1494.
165. Hamid MA, Moemen L, Labib H, et al. Risk of open angle glaucoma due to tumor necrosis factor alpha gene polymorphisms. *Electron Physician*. 2016;8:1978–1983.
166. Lin HJ, Tsai FJ, Chen WC, et al. Association of tumour necrosis factor alpha -308 gene polymorphism with primary open-angle glaucoma in Chinese. *Eye*. 2003;17:31–34.
167. Razeghinejad MR, Rahat F, Kamali-Sarvestani E. Association of TNFA -308 G/A and TNFRI +36 A/G gene polymorphisms with glaucoma. *Ophthalmic Res*. 2009;42:118–124.
168. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. *Annu Rev Cell Dev Biol*. 2001;17:463–516.
169. Schlotzer-Schrehardt U, Lommatzsch J, Kuchle M, et al. Matrix metalloproteinases and their inhibitors in aqueous humor of patients with pseudoexfoliation syndrome/glaucoma and primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2003;44:1117–1125.
170. Cheng G, Zhong M, Kawaguchi R, et al. Identification of PLXDC1 and PLXDC2 as the transmembrane receptors for the multifunctional factor PEDF. *Elife*. 2014;3:e05401.
171. Izzotti A, Bagnis A, Sacca SC. The role of oxidative stress in glaucoma. *Mutat Res*. 2006;612:105–114.

Investigative Ophthalmology & Visual Science

172. Weissman L, de Souza-Pinto NC, Stevnsner T, et al. DNA repair, mitochondria, and neurodegeneration. *Neuroscience*. 2007;145:1318–1329.

173. Gu D, Wang M, Wang S, et al. The DNA repair gene APE1 T1349G polymorphism and risk of gastric cancer in a Chinese population. *PLoS One*. 2011;6:e28971.

174. McDonald KK, Abramson K, Beltran MA, et al. Myocilin and optineurin coding variants in Hispanics of Mexican descent with POAG. *J Hum Genet*. 2010;55:697–700.

175. De Marco N, Buono M, Troise F, et al. Optineurin increases cell survival and translocates to the nucleus in a Rab8-dependent manner upon an apoptotic stimulus. *J Biol Chem*. 2006;281:16147–16156.

176. Yuki K, Murat D, Kimura I, et al. Reduced-serum vitamin C and increased uric acid levels in normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:243–248.

177. Hu Z, Ma H, Chen F, et al. XRCC1 polymorphisms and cancer risk: a meta-analysis of 38 case-control studies. *Cancer Epidemiol Biomarkers Prev*. 2005;14:1810–1818.

178. Drory VE, Birnbaum M, Korczyn AD, et al. Association of APOE epsilon4 allele with survival in amyotrophic lateral sclerosis. *J Neurol Sci*. 2001;190:17–20.

179. Mineo C, Shaul PW. Regulation of eNOS in caveolae. *Adv Exp Med Biol*. 2012;729:51–62.

180. Ellis DZ, Dismuke WM, Chokshi BM. Characterization of soluble guanylate cyclase in NO-induced increases in aqueous humor outflow facility and in the trabecular meshwork. *Invest Ophthalmol Vis Sci*. 2009;50:1808–1813.

181. Rallabhandi P, Bell J, Boukhvalova MS, et al. Analysis of TLR4 polymorphic variants: new insights into TLR4/MD-2/CD14 stoichiometry, structure, and signaling. *J Immunol*. 2006; 177:322–332.

182. Astafurov K, Elhawy E, Ren L, et al. Oral microbiome link to neurodegeneration in glaucoma. *PLoS One*. 2014;9:e104416.

183. Meczekalski B, Nawrot R, Nowak W, et al. Study on the zona pellucida 4 (ZP4) gene sequence and its expression in the ovaries of patients with polycystic ovary syndrome. *J Endocrinol Invest*. 2015;38:791–797.

184. Rao KN, Kaur I, Chakrabarti S. Lack of association of three primary open-angle glaucoma-susceptible loci with primary glaucomas in an Indian population. *Proc Natl Acad Sci U S A*. 2009;106:E125–E126; author reply E127.

185. Takamoto M, Kaburaki T, Mabuchi A, et al. Common variants on chromosome 9p21 are associated with normal tension glaucoma. *PLoS One*. 2012;7:e40107.

Investigative Ophthalmology & Visual Science