An Updated Review on the Genetics of Primary Open Angle Glaucoma

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Abstract: Epidemiological studies suggest that by 2020 the prevalence of primary open angle glaucoma (POAG) is estimated to increase to 76.0 million, and to 111.8 million by 2040 globally due to the population aging. The prevalence of POAG is the highest among those of African descent, followed by Asians, and the lowest in Europeans. POAG is a genetically complex trait with a substantial fraction exhibiting a significant heritability. Less than 10% of POAG cases in the general population are caused by specific gene mutations and the remaining cases are polygenic. Quantitative traits related to POAG pathogenesis such as intra-ocular pressure (IOP), vertical cup/disc ratio (VCDR), optic disc area, and central corneal thickness (CCT) are highly heritable, and likely to be influenced at least in part by genes and show substantial variation in human populations. Recent genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) at different loci including CAV1/CAV2, TMCO1, CDKN2B-AS1, CDC7-TGFBR3, SIX1/SIX6, GAS7 and ATOH7 to be associated with POAG and its related quantitative traits (endophenotypes). The chapter provides a brief overview on the different GWAS and SNP association studies and their correlation with various clinical parameters important for POAG in the population worldwide, including the Middle East.

Keywords: epidemiology; genetics; GWAS; POAG; quantitative traits; SNP genotyping

1. Introduction

Glaucoma is a chronic and progressive group of optic neuropathies affecting more than 60 million people globally [1]. It is associated with death of retinal ganglion cells resulting in characteristic cupping or degeneration of the optic nerve head and loss of peripheral vision [2]. Primary open angle glaucoma (POAG) is one of the most common types of glaucoma which is clinically characterized by an open and normal anterior iridocorneal chamber angle [2]. POAG can either occur with increased intraocular pressure (IOP) or normal IOP, the latter being referred to as normal-tension glaucoma (NTG).

Although there are many postulated mechanisms of retinal ganglion cell damage, the exact etiology of POAG still remains obscure. The well-recognized risk factors associated with POAG include elevated IOP, age, family history, gender, ethnicity, central corneal thickness, and myopia. A recent large prospective study indicated that POAG with early paracentral visual field loss displays distinct as well common risk factor profiles as compared to those with peripheral vision loss [3]. Raised IOP is the most important and the only modifiable risk factor in the development and progression of POAG. Several large population-based studies in the past have confirmed that the reduction of IOP reduces the progression of glaucoma in patients with or without elevated IOP [4–8].
Similarly, findings of the meta-analysis from the Eye Diseases Prevalence Research Group have shown that the occurrence of glaucoma increases with increasing age among all ethnicities (Europeans, Blacks, and Hispanics) [7,9]. Age was also reported to be associated with POAG in patients with ocular hypertension in two large population-based studies [5,8]. Family history is another important risk factor in the development of glaucoma [7,10–12]. A positive family history of POAG significantly increases the odds (varying from five to 10 times) for the development of POAG [13]. In the Melbourne [14] and Rotterdam studies [11], males showed a trend towards increased risk of POAG which was absent in the Barbados Eye Study [7] and the Beaver Dam Eye Study [10]. Similarly, the Eye Disease Prevalence Research Group [9] reported no gender-related association of glaucoma among the European, African American, and Hispanic subjects. However, a recent systematic review of 3497 POAG cases out of 146,882 participants with gender-specific data showed that the age-adjusted prevalence is higher in men compared to women, and that this finding remains consistent across all ethnic groups provides very strong evidence for the association of POAG with gender [15]. Several studies have shown POAG to be more prevalent with rapid and severe disease progression in people of African-Caribbean as compared to European descent, Hispanics, and Asians [9,16]. Central corneal thickness (CCT) has also been reported to be associated with POAG, particularly in the ocular hypertension patients [17,18]. Although the precise mechanism(s) are still unclear, this may be in part due to the effect of corneal thickness on IOP measurement, and increased susceptibility to optic nerve damage [19,20]. In addition, studies have shown that individuals with thicker corneas are less responsive to topical ocular hypotensive medications [21]. Myopia is also considered to be an important risk factor for POAG as it can increase susceptibility of myopic nerves to glaucomatous damage [22]. Moderate-to-high levels of myopia conferred two- to three-fold increased risk in the Australian [23], US Caucasian [24], and the Chinese populations [25]. Other predisposing factors for POAG include adult-onset diabetes and hypertension. Although there are conflicting reports regarding the risk of POAG in individuals with diabetes [26,27], a recent systematic review and meta-analysis of 13 studies, which included six population-based cohorts and seven case-control studies, showed increased risk of POAG (relative risk of 1.4 and 1.49, respectively) in individuals with diabetes [28]. Multiple epidemiological studies have also reported a role of hypertension as a risk factor for POAG [23,29]. Treatment of hypertensive patients with beta-blockers results in nocturnal hypotension and is a potential risk factor for glaucomatous optic neuropathy [30]. The mechanism(s) by which hypertension induces optic nerve damage are still unclear.

POAG is a genetically complex trait with a substantial fraction exhibiting a significant heritability. Genetic linkage studies of large affected families have so far identified at least 20 chromosomal loci (GLC1A-P) that are linked to POAG. The causative genes that are capable of causing POAG with minimal influence from other gene(s) or the environment and that have been consistently implicated so far include myocilin (MYOC), optineurin (OPTN), WD repeat domain 36 (WDR36), ankyrin repeat and SOCS-box containing 10 (ASB10), Cytochrome P450 family 1, subtype B, polypeptide 1 (CYP1B1), and neurotrophin 4 (NTF4) as reviewed elsewhere [31,32]. Twin studies and family-based studies have discovered a number of genes. However, these disease-causing genes account for <10% of POAG cases in the general population. It is therefore likely that the hereditary aspect of many of the remaining cases of POAG is due to the combined effects of several genes (polygenic) and that gene-environment interactions are important. Quantitative endophenotype traits related to POAG pathogenesis such as IOP, vertical cup-to-disc ratio (VCDR), and CCT [10,33,34] are highly heritable, likely to be influenced at least in part by genes, and are highly polymorphic. Recent advances in genomic technologies and genome-wide association studies (GWAS) have greatly accelerated the discovery and understanding of genes and genomic regions associated with POAG and influencing the quantitative endophenotype traits related to POAG pathogenesis, which will be the main focus of this chapter.
2. Epidemiology of POAG

Recent epidemiological studies suggest that, in 2013, almost 64.3 million people (aged between 40 and 80 years) were affected by glaucoma globally, and this number is expected to increase to 76.0 million by 2020 and to 111.8 million by 2040 due to the population aging [35]. POAG accounts for a major three-quarters (74%) of all glaucoma cases [1]. Another recent meta-analysis estimated the global number of POAG cases in 2015 at 57.5 million, rising to 65.5 million by 2020 [15]. Almost half (47%) of these will be of Asian descent, while a quarter (24%) will be European [1]. The risk and subtypes of glaucoma are known to vary among races and countries [36]. A meta-analysis conducted by the Eye Disease Prevalence Research Group showed that, in the United States, African Americans have a higher POAG prevalence than Caucasians. The prevalence of POAG in individuals ≥40 years old was observed to be 1.86%, including 1.57 million Caucasian and 398,000 African American subjects. In 2020, this number is estimated to rise up to 3.36 million due to the population aging [9]. In all the age groups, there was an increased prevalence of glaucoma in individuals of African descent compared with European-derived individuals [37]. Similarly, a recent meta-analysis of 81 studies including 37 countries, 216,214 participants, and 5266 POAG cases reported that the Black populations had the highest POAG prevalence of 5.2% (95% credible interval (CrI) 3.7%, 7.2%) at 60 years, rising to 12.2% (95% CrI 8.9% to 16.6%) at 80 years. The increase in POAG prevalence per decade of age was found to be highest among the Hispanics (2.31, 95% CrI 2.12, 2.52) and Caucasian populations (1.99, 95% CrI 1.86, 2.12), and lowest in East and South Asians (1.48, 95% CrI 1.39, 1.57; 1.56, 95% CrI 1.31, 1.88, respectively). In addition, men were more likely to have POAG than women (1.30, 95% CrI 1.22, 1.41). It is clearly evident that individuals of African descent are associated with increased risk (estimated incidence is two to five times higher) of developing glaucoma compared with individuals of European descent. The reasons for this increased risk of glaucoma among individuals of African descent are still not clear. The Barbados Eye Study reported a prevalence of 7% in Africans, suggesting an influence of ancestral factors [7]. Several other factors that may also be influential could be physiological or anatomical differences in the optic disc or corneas, environmental factors, social differences or genetics [26].

3. Genotype-Phenotype Association in POAG

Association studies using the candidate-gene approach and GWASs have been particularly useful tools in identifying genetic factors, each of which may have a relatively small effect but contributes to a large number of cases. Unlike the candidate-gene approach, GWAS is an unbiased (without bias to known protein functionality gene) genome-wide approach that compares the genotypic profile of single nucleotide polymorphisms (SNPs) throughout the genome in cases (affected) and controls (unaffected), thus identifying genomic region(s) associated with a disease or trait of interest. The large population sample required in GWASs to achieve a genome-wide statistical significance (p-value of less than $5 \times 10^{-8}$) has been greatly facilitated by the formation of the International Consortia. However, since GWAS can rarely identify functional or causal variant(s), further in-depth genotyping and functional testing in addition to replication studies in independent cohorts of different population groups are considered a standard requirement to conclusively validate genes or genomic regions identified from GWAS. Using this powerful approach (GWAS), recent genetic studies have identified genes or genetic variants with modest effect to be associated with POAG and related quantitative traits (Table 1). These studies have provided better insights into the genetic basis of POAG and improved our understanding of the underlying pathophysiology of the disease.
### Table 1. Genes and polymorphisms identified in POAG using genome-wide and candidate-gene approaches in the Middle East and other populations.

| Studies                  | Gene/Chromosome | SNP ID          | Population * | Study Type | Study Size (POAG/Controls) * | OR/Beta, p Value                  | Any Clinical Association *        |
|--------------------------|-----------------|-----------------|--------------|------------|-----------------------------|-----------------------------------|-----------------------------------|
| **GWAS Studies**         |                 |                 |              |            |                             |                                   |                                    |
| Nakano et al., 2009 [38] | PLXDC2 (10p12.31) | rs7081435       | D: Japan     | GWAS       | D: 1519 R: 857               | OR = 1.49, p = 1 × 10⁻⁵           | −                                 |
|                          |                 | rs7961953       | R: Japan     |            |                             | OR = 1.37, p = 7 × 10⁻⁵           | −                                 |
|                          |                 | rs547984        |              |            |                             | OR = 1.34, p = 6 × 10⁻⁵           | −                                 |
|                          |                 | rs540782        |              |            |                             | OR = 1.34, p = 6 × 10⁻⁵           | −                                 |
|                          |                 | rs693421        |              |            |                             | OR = 1.35, p = 4 × 10⁻⁵           | −                                 |
|                          |                 | rs2499601       |              |            |                             | OR = 1.33, p = 9 × 10⁻⁵           | −                                 |
|                          | TMTC2 (12q21.31) | rs7961953       | D: Japan     | GWAS       | D: 1519 R: 857               | OR = 1.49, p = 1 × 10⁻⁵           | −                                 |
|                          |                 | rs3213787       | Japanese     | GWAS       | D: 305 R: 355                | OR = 2.80, p = 2.5 × 10⁻⁹         | Associated with NPG               |
|                          | ZP4 (1q43)      | rs547984        |              |            |                             | OR = 1.69, p = 4.1 × 10⁻⁶         | Associated with NPG               |
| Meguro et al., 2010 [39] | SRBD1 (2p21)    | rs3213787       | Japanese     | GWAS       | D: 305 R: 355                | OR = 2.80, p = 2.5 × 10⁻⁹         | Associated with NPG               |
|                          | ELOVL5 (6p12.1) | rs735860        |              |            |                             | OR = 1.69, p = 4.1 × 10⁻⁶         | Associated with NPG               |
| Thorleifsson et al., 2010 [40] | CAV1/CAV2 (7q31.1) | rs4236601       | D: Iceland   | GWAS       | D: 36,140 R1: 4239 R2: 879  | OR = 1.36, p = 5 × 10⁻¹⁰          | Nominal association was observed for increased IOP (p = 0.034) |
|                          |                 | rs1052990       | R1: SW, UK, AU |            |                             | OR = 1.36, p = 5 × 10⁻¹⁰          | −                                 |
|                          |                 |                 | R2: China    |            |                             | OR = 1.32, p = 1 × 10⁻⁹           | −                                 |
| Burdon et al., 2011 [41] | CDKN2B-AS (9p21.3) | rs4977756       | AU, NZ       | GWAS       | D: 590/3956 R: 4148         | OR = 1.50, p = 4.7 × 10⁻⁹         | −                                 |
|                          |                 | rs4665461       |              |            |                             | OR = 1.68, p = 6.1 × 10⁻¹⁰        | −                                 |
| Wiggs et al., 2012 [42]  | CDKN2B-AS (9p21) | rs2157719       | US Caucasian | GWAS       | D: 3146/3487                | OR = 0.69, p = 1.86 × 10⁻¹⁸       | Also associated with NPG, OR = 0.58, p = 1.17 × 10⁻¹² |
|                          | SIX1/SIX6 (14q23) | rs10483727      |              |            |                             | OR = 1.32, p = 3.87 × 10⁻¹¹       | Associated with NPG               |
|                          | Sdc2           | rs284489        |              |            |                             | OR = 0.62, p = 8.88 × 10⁻¹⁰       | −                                 |
| Osman et al., 2012 [43]  | CDKN2B-AS (9p21) | rs1083192       | Japanese     | GWAS       | D: 7993 R: 9014             | OR = 0.75, p = 5.2 × 10⁻¹¹         | −                                 |
|                          | SIX1/SIX6 (14q23) | rs1083272       |              |            |                             | OR = 0.79, p = 9.49 × 10⁻⁸        | −                                 |
|                          | NCKAP5 (2p21)   | rs7588567       |              |            |                             | OR = 0.85, p = 3.89 × 10⁻⁶        | −                                 |
| Nakano et al., 2012 [44] | CDKN2B-AS (9p21.3) | rs7865618       | Japanese     | GWAS       | D: 833/686 R: 411/289     | OR = 1.78, p = 9.0 × 10⁻¹¹        | Strongly associated with POAG and POAG/NPG but not with HPG |
|                          |                 | rs523096        |              |            |                             | OR = 1.76, p = 1.6 × 10⁻¹⁰        | −                                 |
| Takamoto et al., 2012 [45] | CDKN2B (9p21)   | rs523096        | Japanese     | GWAS       | D: 286/357 R: 183/514     | OR = 2.13, p = 4.96 × 10⁻¹¹       | Associated with NTG               |
| Chen et al., 2014 [46]   | ABCA1 (5q31.1)  | rs2487032       | Asian Southern Chinese | GWAS       | D: 1007/1009 R: 1899/4965 | OR = 0.69, p = 1.66 × 10⁻³⁷; ORR = 0.73, pR = 2.79 × 10⁻⁹; OR = 1.42, p = 3.18 × 10⁻⁴⁶; ORR = 1.30, pR = 5.77 × 10⁻⁴⁰ | −                                 |
|                          | PMM2 (16p13.2)  | rs3785176       |              |            |                             | OR = 0.69, p = 1.66 × 10⁻³⁷; ORR = 0.73, pR = 2.79 × 10⁻⁹; OR = 1.42, p = 3.18 × 10⁻⁴⁶; ORR = 1.30, pR = 5.77 × 10⁻⁴⁰ | −                                 |
### Table 1. Cont.

| Studies                  | Gene/Chromosome | SNP ID     | Population *                   | Study Type | Study Size (POAG/Controls) * | OR/Beta, p Value | Any Clinical Association * |
|--------------------------|-----------------|------------|--------------------------------|------------|-----------------------------|------------------|---------------------------|
| **GWAS Studies**         |                 |            |                                |            |                             |                  |                           |
| Gharakhani et al., 2014  | ABCA1 (9q31.1)  | rs2472493  | D: Australian                  | GWAS       | D: 1155/1992                | OR = 1.31, $p = 2.1 \times 10^{-10}$ | –                         |
|                          | AFAP1 (4p16.1)  | rs4619890  | R1: Australian                 |            | R1: 932/6862                | OR = 1.20, $p = 7.0 \times 10^{-10}$ | –                         |
|                          | GMDS (6q25.3)   | rs1196985  | R2: US                         |            | R2: 2616/2634               | OR = 1.31, $p = 7.7 \times 10^{-10}$ | –                         |
| Li et al., 2015          | CDKN2A-AS1 (9p21) | rs2157719  | D: Australian                  | GWAS       | D: 3504/9746                | OR = 0.71, $p = 7.0 \times 10^{-10}$ | –                         |
|                          | CDC7-TGFBR3 (1p22) | rs1192415  | R: Asian and European          |            | R: 9173/26,780              | OR = 1.13, $p = 1.60 \times 10^{-8}$ | Associated with optical disk, vertical CD ratio |
|                          | FNDC3B (3q25.31) | rs4894796  | D: Asian and European          | GWAS       | D: 11,972                   | OR = 0.89, $p = 7.93 \times 10^{-5}$ in Asians only | –                         |
| van Koolwijk et al., 2012| GAS7 (17p13.1)  | rs11656696 | D: NL                          | GWAS       | D: 11,972                   | $p = 1.4 \times 10^{-8}$ | Associated with IOP reduction |
|                          | TMCO1 (1q24.1)  | rs7555523  | R: UK, AU, Canada, NZ          |            | R: 7482                     | $p = 1.8 \times 10^{-8}$ | Associated with IOP increase |
| Hysi et al., 2014        | FNDC3B (3p25.31)| rs6445055  | Asian, European                | GWAS       | D: 35,296                   | $p = 4.19 \times 10^{-8}$ | All 4 loci associated with IOP |
|                          | ABCA1 (9q31.1)  | rs2472493  | D: Norwegian and German        | GWAS       | D: 1660                     | $p = 1.2 \times 10^{-5}$ | Associated with IOP         |
|                          | CDKN2A-AS1 (9p21) | rs1196985  | D: 8105                        | GWAS       | D: 1125/4117                | $p = 1.87 \times 10^{-8}$ | Associated with increasing IOP |
|                          | GGA3 (17q25.1)  | rs1362756  | D: 1680                        | GWAS       | D: 1125/4117                | $p = 2.81 \times 10^{-11}$ | Optic disc area (−)/VCDR (+) |
|                          | PKDRE1 (22q13.31)| rs1362756  | D: 1680                        | GWAS       | D: 1125/4117                | $p = 2.1 \times 10^{-10}$ | Optic disc area (+)          |
| Springelkamp et al., 2015| ATOH7 (11q23.3) | rs58073046 | D: NL                          | GWAS       | D: 8105/4117                | $p = 4.23 \times 10^{-2}$ | Optic disc area (−)/VCDR (+) |
|                          | CDH2/TGFBR3 (1p22) | rs1362756  | R: NL, UK                      | GWAS       | R: 129                      | $p = 6.48 \times 10^{-4}$ | Optic disc area (+)          |
| Ramdas et al., 2010 and 2011| ATOH7 (10q22.3-22.1) | rs1590004  | D: NL                          | GWAS       | D: 7730                     | $p = 0.44, p = 2.05 \times 10^{-10}$ | Optic disc area (−)/VCDR (+) |
|                          | CDC7/TGFBR3 (1p22) | rs1192415  | R: NL, UK                      | GWAS       | R: 4455                     | $p = 1.2 \times 10^{-3}$ | Optic disc area (+)          |
|                          | CDKN2B (9p21)   | rs1063192  | D: 1125                        | GWAS       | D: 1125/4117                | $p = 6.7 \times 10^{-3}$ | Optic disc area (+)          |
|                          | SIX1 (14q22.3-q23) | rs10483727 | D: 1125                        | GWAS       | D: 1125/4117                | $p = 7.4 \times 10^{-3}$ | Optic disc area (+)          |
|                          | SALL1 (16q12.1) | rs1362756  | D: 1125                        | GWAS       | D: 1125/4117                | $p = 2.81 \times 10^{-10}$ | Optic disc area (+)          |
| Macgregor et al., 2010   | ATOH7 (10q22.3-22.1) | rs1362756  | D: AU                          | GWAS       | D: 1368                     | $p = 3.4 \times 10^{-10}$ | Explained 2.1% cup area variation in AU cohort |
|                          | RFTN1 (3p24)    | rs690037   | R: UK                          | GWAS       | R: 848                      | $p = 1.6 \times 10^{-6}$ | Explained 2.1% cup area variation in AU cohort |
Table 1. Cont.

| Studies                  | Gene/Chromosome        | SNP ID                   | Population * | Study Type | Study Size (POAG/Controls) * | OR/Beta, p Value       | Any Clinical Association * |
|--------------------------|------------------------|--------------------------|--------------|------------|-----------------------------|------------------------|---------------------------|
| GWAS Studies             |                        |                          |              |            |                             |                        |                           |
| Khor et al., 2011 [56]   | CARD10 (22q13.1)       | rs9607469/D: Asian        | R: NL        | GWAS       | D: 4445                     | \( p = 2.73 \times 10^{-12} \) | Associated with optic disc area |
|                          | ATOH7 (10q21.3-22.1)   | rs7916697/R: NL           |              |            | R: 9326                     | \( p = 2.00 \times 10^{-15} \) |                           |
|                          | CDC7/TGFBR3 (1p22)     | rs1192415/D: Asian        | R: NL        | GWAS       |                             | \( p = 7.57 \times 10^{-17} \) | Associated in Asians      |
| Iglesias et al., 2014 [57] | SIX6 (14q23)          | rs33912345/(His141Asn)  | D: NL, UK    | GWAS       | D: 292/1208                 | \( p = 7.74 \times 10^{-7} \) | Associated with VCDR and POAG |
|                          |                       | rs146737847/(Glu29Lys)   | R: NL, UK    |            | R: 11,473                   | \( p = 5.0 \times 10^{-3} \) | Associated with VCDR      |
| Vitart et al., 2010 [58] | COL5A1 9q34.2          | rs1536482/Croatia, Scotland |              | GWAS       | D: 7711                     | \( \beta = 0.22, p = 7.1 \times 10^{-8} \) | Associated with CCT       |
|                          | ZNF469 16q24.2         | rs12447690                |              |            | R: 2681                     | \( \beta = 0.23, p = 4.4 \times 10^{-9} \) |                           |
|                          | AKAP13 15q24-25        | rs6496932                 |              |            |                             | \( \beta = 0.15, p = 1.4 \times 10^{-8} \) |                           |
|                          | AGR8 13q12.11          | rs1004200                 |              |            |                             | \( \beta = 0.14, p = 3.5 \times 10^{-9} \) |                           |
| Vithana et al., 2011 [59]| ZNF469 (16q24)         | rs12447690/D1: SG-Malay   |              | GWAS       | D1: 3280                    | \( \beta = -5.068, p = 1.92 \times 10^{-14} \) | Associated with CCT       |
|                          |                       | rs9958149/D2: SG-Chinese  |              |            | D2: 3400                    | \( \beta = -6.248, p = 1.63 \times 10^{-16} \) |                           |
|                          |                       | rs1536478                 |              |            |                             | \( \beta = -4.63, p = 3.05 \times 10^{-9} \) |                           |
|                          |                       | rs7044529                 |              |            |                             | \( \beta = 2.7, p = 1.2 \times 10^{-4} \) |                           |
|                          |                       | rs96067                   |              |            |                             | \( \beta = -4.799, p = 5.40 \times 10^{-11} \) |                           |
| Ulmer et al., 2012 [60]  | ZNF469 (16q24)         | rs12447690/D: US-Cau      |              | GWAS       | D: 1117                     | \( \beta = -5.08, p = 0.001 \) | Associated with CCT       |
|                          |                       | rs7481514/NMT (11q25)     |              |            | SNP: US-Cau                 | \( \beta = -6.89, p = 1.03 \times 10^{-5} \) | Associated with reduced CCT and POAG risk in low-tension subset |
| Candidate Gene Studies   |                        |                          |              |            | SNP: 6469                   | OR = 1.28, p = 9.9 \times 10^{-4} |                           |
| Chen et al., 2012 [61]   | 2p16.3                 | rs1533428/China           | SNP          |            | 462/577                     | \( OR = 2.16, p = 0.00025 \) | Associated with late-onset POAG |
| Kim et al., 2014 [62]    | 10p12.31               | rs7098387/Korea           | SNP          |            | 211/904                     | \( OR = 2.0, p = 0.00038 \) | Associated with POAG       |
| Fan et al., 2005 [63]    | APOE 19q13.2           | rs429358/Japan            | SNP          |            | 400/281                     | \( OR = 0.4, p = 0.007 \) | APOE4 confers a protective effect against NTG |
| Lam et al., 2006 [64]    | APOE 19q13.2           | rs429358/China            | SNP          |            | 400/300                     | \( OR = 0.36, p = 0.008 \) | APOE4 confers a protective effect against NTG |
| Lake et al., 2004 [65]   | APOE 19q13.2           | rs429358/UK               | SNP          |            | 155/349                     | \( p = ns \) | None |

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Table 1. Cont.

| Studies            | Gene/Chromosome         | SNP ID       | Population *        | Study Type | Study Size (POAG/Controls) * | OR/Beta, p Value | Any Clinical Association *                                                                 |
|--------------------|-------------------------|--------------|---------------------|------------|-----------------------------|----------------|------------------------------------------------------------------------------------------|
| Cao et al., 2012   | ATOH7 10q21.3-22.1      | rs7011697    | African-Caribbean   | SNP        | 272/165                     | OR = 0.67, p = 0.0096 | Interacts with rs1083192 near CDKN2B to reduce POAG risk                                |
|                    |                         | rs1900004    |                    |            |                             | OR = 1.02, p = 0.9076 | None                                                      |
|                    |                         | rs3858145    |                    |            |                             | OR = 0.98, p = 0.9138 | Associated with NTG                                          |
|                    |                         | rs61854782   |                    |            |                             | p = 0.028          | Showed interaction with RFTN1 rs90437                                      |
| Mabuchi et al., 2012 |                        | rs1900004    | Japan              | SNP        | 425/191                     | OR = 2.69, p < 0.05 | Associated with VCDR in controls but not POAG                                  |
| Chen et al., 2012  | rs3858145               |              | China              | SNP        | 142/289                     | β = −0.088, p = 0.004 | Associated with increased optic nerve area                          |
| Fan et al., 2011   | rs3858145               |              | US-Caucasian       | SNP        | 539/336                     | OR = 1.89, p = 0.025 | Associated with increased optic nerve area                          |
| Dimasi et al., 2012| rs690037                |              | AU, NZ             | SNP        | 873/886                     | OR = 2.12, p = 0.18 | Associated with increased optic nerve area                          |
| Wiggs et al., 2011 | rs4236601               |              | US-Caucasian       | SNP        | 1000/1183                   | OR = 1.31, p = 0.0007 | Significantly associated in women more than men                              |
| Cao et al., 2012   | rs4236601               |              |                    |            |                             | OR = 1.25, p = 0.0084 | Significantly associated in women; and nominally associated with NPG          |
|                    | rs1052990               |              |                    |            |                             | p = 0.039          | (p = 0.039)                                                                      |
| Loomis et al., 2014| rs4236601               |              | US-Caucasian       | SNP        | R1: 976/2132; R2: 1140/2290 | pmeta = 1.07 × 10^−4 | Associated with early paracentral VF defect                                 |
| Kuehn et al., 2011 | rs17588172              |              |                    |            |                             | pmen = 1.59 × 10^−5 | Associated with early paracentral VF defect                                 |
| Cao et al., 2012   | rs9047469               |              | African-Caribbean  | SNP        | 272/165                     | OR = 0.97, p = 0.4802 | No association                                                             |
| Cao et al., 2012   | rs1192415               |              | African-Caribbean  | SNP        | 272/165                     | OR = 1.13, p = 0.5096 | No association                                                             |
| Dimasi et al., 2012| rs1192415               |              | AU, NZ             | SNP        | 873/886                     | OR = 1.14, p = 0.4802 | No association                                                             |
|                    | rs1063192               |              |                    |            |                             | OR = 1.22, p = 0.03 | Showed nominal significance with optic disc area                              |
| Cao et al., 2012   | rs1063192               |              | African-Caribbean  | SNP        | 272/165                     | OR = 0.39, p = 0.0008 | Minor allele was protective against POAG                                     |
| Fan et al., 2011   | rs4977756               |              |                    |            |                             | OR = 0.89, p = 0.4507 | No association                                                             |
| Mabuchi et al., 2012| rs1063192               |              | US-Caucasian       | SNP        | 539/336                     | OR = 0.73, p = 0.0006 | Associated with decreased VCDR and POAG risk                                 |
| Mabuchi et al., 2012| rs1063192               |              | Japan              | SNP        | 425/191                     | β = 0.11, p = 0.0043 | Associated with VCDR; and NTG (p = 0.023)                                     |
| Dimasi et al., 2012| rs1063192               |              | AU, NZ             | SNP        | 873/886                     | OR = 0.74, p = 2.2 × 10^-5 | More strongly associated with advanced open-angle glaucoma                  |
| Burdon et al., 2012 | rs10120688 rs7049105    |              | AU, NZ             | SNP        | 1432/595                    | VCDR − β = 0.016, p = 0.03; IOP − β = −2.135, p = 0.001 | Associated with larger VCDR and lower IOP                                    |
Table 1. Cont.

| Studies                  | Gene/Chromosome | SNP ID       | Population * | Study Type | Study Size (POAG/Controls) * | OR/Beta, p Value | Any Clinical Association * |
|--------------------------|-----------------|--------------|--------------|------------|-----------------------------|------------------|---------------------------|
| Candidate Gene Studies   |                 |              |              |            |                             |                  |                           |
| Mabuchi et al., 2012     | CHEK2 22q12.1   | rs1547014    | Japan        | SNP        | 425/191                     | $\beta = 0.11, \ p = 0.0079$ | Associated with VCDR and HTG ($p = 0.013$) |
| Dimasi et al., 2012      |                 | rs1547014    | AU, NZ       | SNP        | 873/886                     | OR = 0.98, $p = 0.77$ | No association            |
| Dimasi et al., 2012      | COL5A1/RXRA 9q34.2-q34.3 | rs1536482    | AU, NZ       | SNP        | 873/886                     | OR = 0.94, $p = 0.46$ | No association            |
| Dimasi et al., 2012      |                 | rs7044529    |              |            |                             | OR = 1.00, $p = 0.98$ |                           |
| Dessevvi et al., 2010    | COL8A2 1p34.2   | rs274754     | US-Caucasian | SNP        | 100                         | $p = 0.018$       | Associated with corneal thickness |
| Dimasi et al., 2010      | FBN1 15q21.1    | rs17352842   | AU-Caucasian | SNP        | 956                         | $p = 0.02$        | Associated with CCT       |
|                          |                 |              |              |            |                             |                  |                           |
|                          |                |              |              |            |                             |                  |                           |
|                          |                |              |              |            |                             |                  |                           |
|                          | joint > null   |              | Brazil       | SNP        | 87/85                       | OR = 2.4, $p = 0.016$ | TIM0 genotype associated with higher IOP and severe defect of right eye optic nerve and visual field |
|                          | GSTT1/GSTM1 1p13.3 |            | Estonia      | SNP        | 250/202                     | OR = 1.83, $p = 0.002$ | GSTM1 were at significant risk for glaucoma and even higher in smokers (OR = 3.86, $p = 0.012$) |
|                          |                |              |              |            |                             |                  |                           |
|                          | positive > null |              | Sweden       | SNP        | 200/200                     | $p = ns$          | No association            |
|                          |                |              | China        | SNP        | 405/201                     | $p = ns$          | No association            |
|                          |                |              |              |            |                             |                  |                           |
|                          |                 |              | US-Caucasian | SNP        | 443/533                     | –                | Not associated with POAG  |
|                          |                 |              | India        | SNP        | 141/285                     | $p = 0.2$         | No association            |
|                          |                 |              | China        | SNP        | 174/91                      | –                | Rare cause of POAG in Chinese |
|                          | PLXDC2 1p12.31  | rs7081455    | African-Caribbean | SNP | 109/48 | $p = ns$ | No association |
|                          |                 |              | China        | SNP        | 405/201                     | $p = ns$          | No association            |
|                          |                 |              |              |            |                             |                  |                           |
|                          | PAX6 11p13      | rs3026398    | AU-Caucasian | SNP        | 956                         | $p = 0.02$        | Associated with CCT; more strongly with rs662702 haplotype ($p = 0.009$) |
|                          | PLXDC2 1p12.31  | rs7081455    | China        | SNP        | 462/577                     | OR = 1.25, $p = 0.31$ | No association            |
|                          |                 |              | African-Caribbean | SNP | 272/165 | OR = 1.04, $p = 0.8052$ | No association |
|                          | RFTN1 3p24.3    | rs3658145    | China        | SNP        | 142/289                     | $\beta = 25.66, \ p = 0.029$ | Associated with CCT       |

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| Studies            | Gene/Chromosome | SNP ID           | Population * | Study Type     | Study Size (POAG/Controls) * | OR/Beta, p Value | Any Clinical Association * |
|--------------------|-----------------|------------------|---------------|----------------|----------------------------|------------------|----------------------------|
| Fan et al., 2011 [69] | SIX1/SIX6 14p22-23 | rs10483277       | US-Caucasian  | SNP            | 539/336                    | OR = 1.33, p = 0.0043 | Associated with increased VCDR and POAG risk |
| Dimasi et al., 2012 [70] | rs10483277       | AU, NZ           | SNP            |                | 873/886                    | OR = 1.38, p = 6.2 × 10^{-6} | Strongly associated with open-angle glaucoma |
| Cao et al., 2012 [66] | rs10483277       | African-Caribbean | SNP           |                | 272/165                    | OR = 0.77, p = 0.4151 | No association |
| Mabuchi et al., 2012 [67] | rs10483277       | Japan            | SNP           |                | 425/191                    | p = 0.017          | Associated with age at diagnosis in NTG |
| Cao et al., 2012 [66] | rs10483277       | US-Caucasian     | SNP           |                | 262/256                    | OR = 1.32, p = 3.87 × 10^{-11} | Significantly associated with POAG |
| Carnes et al., 2014 [88] | rs10483277       | US—Caucasians    | SNP           |                | 33912345                  | OR = 4.2 × 10^{-10} | Associated with POAG and thickness of retinal nerve fiber layer |
| Mabuchi et al., 2011 [89] | SRBD1 2p21      | rs3213787        | Japan         | SNP            | 370/191                    | p = 0.0003 in NTG and p = 0.0013 in HTG | Associated with HTG and NTG including late-onset |
| Chen et al., 2012 [61] | TLR4 9q33.1      | rs2149356        | Japan         | SNP            | 449/107                    | p = 0.000058     | Associated with NTG |
| Shibuya et al., 2008 [91] | rs7037117        | Japan            | SNP           |                | 215/318                    | p = 0.0095        | No association |
| Cao et al., 2012 [66] | SRBD1 2p21      | rs3213787        | African-Caribbean | SNP          | 272/165                    | OR = 0.73, p = 0.0571 | No association |
| Sharma et al., 2012 [92] | TMCO1 1q24     | rs4656461        | AU, NZ        | SNP            | 1420                        | β = -2.56, p = 0.004 | Correlation with age at diagnosis |
| Ozel et al., 2014 [93] | TMTC2 12q21.31  | rs7961953        | China         | SNP            | 462/577                    | OR = 1.15, p = 0.35 | Strongly associated with IOP |
| Chen et al., 2012 [61] | TMTC2 12q21.31  | rs7961953        | China         | SNP            | 272/165                    | OR = 0.89, p = 0.5559 | No association |
| Cao et al., 2012 [66] | TNFα 6p21.3     | rs1800629        | China         | SNP            | 405/201                    | p = 0.012         | Associated with HTG |
| Wang et al., 2012 [94] | TNFα 6p21.3     | rs4845836        | China         | SNP            | 234/230                    | OR = 0.63, p = 0.017 | Protective for POAG |
| Mossböck et al., 2006 [95] | rs1800629       | rs361525         | AU            | SNP            | 114/228                    | OR = 0.43, p = 0.005 | Not associated among Caucasian |
| Rao et al., 2010 [82] | IAV2 9q34.1     | rs2156323        | India         | SNP            | 141/285                    | p = 0.533         | No association |
| Dimasi et al., 2012 [70] | ZNF469 16q24    | rs1244790         | AU, NZ        | SNP            | 873/886                    | OR = 1.01, p = 0.91 | No association |
| Chen et al., 2012 [61] | ZNF469 16q24    | rs9938149        | AU, NZ        | SNP            | 873/886                    | OR = 0.9, p = 0.46 | No association |
| Cao et al., 2012 [66] | ZP4 1p43        | rs547984         | African-Caribbean | SNP          | 272/165                    | OR = 0.98, p = 0.31 | No association |
| Kim et al., 2014 [62] | ZP4 1p43        | rs693421         | Korea         | SNP            | 211/904                    | OR = 1.4, p = 0.0082 | Associated with POAG |
### Table 1. Cont.

| Studies                | Gene/Chromosome | SNP ID | Population * | Study Type | Study Size (POAG/Controls) * | OR/Beta, p Value | Any Clinical Association * |
|------------------------|-----------------|--------|--------------|------------|-----------------------------|-----------------|---------------------------|
| Li et al., 2015 [48]  | CDKN2B-AS1 9p21 | rs2157719 | Saudi Arabia | SNP        | 605                         | OR = 1.24, p = 0.146 | –                         |
|                        | CDC7-TGFBR3 1p22| rs1192415 |              |            |                             | OR = 1.24, p = 0.146 | –                         |
|                        | FNDC3B 3q25.31  | rs4894796 |              |            |                             | OR = 1.03, p = 0.779 | –                         |
| Neamatzadeh et al., 2015 [96] | TP53 17p13.1 | rs1042522 | Iranian      | SNP        | 65/65                       | OR = 2.1, p < 0.05 | Pro72 allele is associated with POAG risk |
| Emam et al., 2014 [97] | NOS3 7q36      | rs2070744 | Egypt        | SNP        | 160/110                     | OR = 1.86, p < 0.0001 | rs2070744 is associated with high tension glaucoma; and with plasma nitrite/nitrate levels (p < 0.001) |
|                        |                 | rs1799983 |              | SNP        |                             | OR = 1.28, p = 0.21 | –                         |
|                        |                 | 27 bp-VNTR-a/b |              |            |                             | OR = 0.81, p = 0.33 | –                         |
| Abu-Amrero et al., 2013 [98] | CAT 11p13 | rs1001179 | Saudi Arabia | SNP        | 225/403                     | OR = 0.81, p = 0.218 | Associated with age of onset, and trend towards IOP, and duration of glaucoma |
| Abu-Amrero et al., 2014 [99] | SOD2 6q25.3 | rs4880 | Saudi Arabia | SNP        | 226/403                     | OR = 1.0, p = 0.988 | Trend towards age of onset and IOP |
| Abu-Amrero et al., 2012 [100] | CAV1/C2 7q31 | rs436601 | Saudi Arabia | SNP        | 220/405                     | OR = 1.06, p = 0.699 | –                         |
| Abu-Amrero et al., 2012 [101] | LOXL1 15q24.1 | rs1048661 | Saudi Arabia | SNP        | 96/101                      | p = 0.866           | –                         |
|                        |                 | rs3829542 |              | SNP        |                             | p = 0.477           | –                         |
|                        |                 | rs2165241 |              | SNP        |                             | p = 0.176           | –                         |
| Abu-Amrero et al., 2006 [102] | MYOC 1q24.3 | 2229 G/T (G324V) | Saudi Arabia | SNP        | 27/96                       | p = 0.74            | –                         |
|                        | OPTN 10p13     | 412 G/A (T34T) |              | SNP        |                             | p = 0.61            | –                         |
|                        |                 | 469 G/C (Q53H) |              | SNP        |                             | p = 0.28            | –                         |
| Zanon-Moreno et al., 2013 [103] | SLC24A2 20q13 | rs1279683 | Mediterranean | SNP        | 250/250                     | OR = 2.47, p < 0.001 | Associated with POAG risk; and plasma vitamin C levels (p < 0.001) Associated with plasma vitamin E levels (p < 0.001) |
|                        | TTPA 8q12.3    | rs6994076 |              | SNP        |                             | OR = 1.38, p = 0.122 | Associated with POAG risk; and nominal (p = 0.047) gene-gene interaction with SNP rs1279683 |
|                        | SEC14L2/TAP 22q12.2 | rs7372723 |              | SNP        |                             | OR = 2.24, p < 0.001 | –                         |
|                        | GPX4 19p13.3   | rs757228 |              | SNP        |                             | OR = 0.80, p = 0.337 | –                         |
Table 1. Cont.

| Studies                     | Gene/Chromosome | SNP ID       | Population * | Study Type | Study Size (POAG/Controls) * | OR/Beta, p Value       | Any Clinical Association * |
|-----------------------------|-----------------|--------------|--------------|------------|-----------------------------|-------------------------|----------------------------|
| **Candidate Gene Studies**  |                 |              |              |            |                             |                         |                            |
| Zanon-Moreno et al., 2011   | RBP1 3q23       | rs176900     | Mediterranean | SNP       | 150/150                     | OR = 0.97, p = 0.826     | –                          |
|                             |                 | rs190910     |              |            |                             | OR = 0.83, p = 0.315     | –                          |
|                             | SLC23A1 5q31.2  | rs10063949   |              |            |                             | OR = 1.19, p = 0.552     | –                          |
|                             | SLC23A2 20p13   | rs1279683    |              |            |                             | OR = 1.67, p = 0.010     | – Associated with POAG risk and plasma vitamin C levels (p < 0.001) |
| Abu-Amero et al., 2008 [105]| GSTT1/GSTM1 1p13.3 | T0M0        | Saudi Arabia | SNP       | 49/120                      | OR = 5.67, p = 0.06      | GSTT1 and GSTM1 positive genotypes are at risk for POAG |
|                             |                 | T1M0         |              |            |                             | OR = 10.2, p = 0.00001   | –                          |
|                             |                 | T0M1         |              |            |                             | OR = 11.3, p = 0.00001   | –                          |
| Unal et al., 2007 [106]     | GSTT1/GSTM1 1p13.3 | T0M1        | Turkey       | SNP       | 144/121                     | OR = 3.46, p < 0.005     | –                          |
| Al-Dabbagh et al. [107]     | APOE 19q13.2    | rs429358     | Saudi Arabia | SNP       | 60/130                      | OR = 2.75, p = 0.034     | APOE4 allele is a risk factor for POAG |
| Saglar et al., 2009 [108]   | APOE 19q13.2    | rs429358     | Turkey       | SNP       | 75/119                      | p = 0.38                 | –                          |
|                             |                 | rs7412       |              |            |                             | p = 0.12                 | –                          |
|                             | TP53 17p        | rs1042522    |              |            |                             | –                       | –                          |
| Nilforoushan et al. [109]   | MTHFR 1p36.3    | rs1801133    | Iran         | –          | 73/90                       | p = 0.337                | –                          |

* AU—Australia; CCT—central corneal thickness; D—discovery cohort; GE—Germany; HPG—high-pressure glaucoma; HTG—high-tension glaucoma; IOP—intraocular pressure; POAG—primary open angle glaucoma; NPG—normal-pressure glaucoma; NTG—normal-tension glaucoma; NL—Netherlands; NZ—New Zealand; R—replication cohort; SG—Singapore; SW—Sweden; UK—United Kingdom; US—United States; VCDR—vertical cup-to-disc ratio. ** Part of an International Glaucoma Genetics Consortium Replication Study.
4. GWAS and POAG

Nakano et al. described the first GWAS in the Japanese POAG population with patients predominantly having NTG [38]. This was a two-stage GWAS involving a discovery cohort and a replication cohort. The study reported significant loci on chromosomes 1, 10 and 12 that included genes such as ZC4, PLXDC2 and TMCT2 (DKFZp762A217), respectively. However, none of the SNPs achieved a genome-wide significance ($p < 5 \times 10^{-8}$) even in the combined analysis and, therefore, they await further evaluation in additional cohorts. Meguro et al. reported the first genome-wide significant ($p = 2.5 \times 10^{-5}$, odds ratio (OR) = 2.80) association for SNP rs3213787 in SRBD1 in the Japanese NTG population [39]. Two other studies have replicated this finding in a Japanese NTG and high-tension glaucoma (HTG) cohort [89] and a US Caucasian POAG cohort [110], but not in the African-Caribbean cohort [66].

GWASs have been able to identify certain common variants that are of significance to the understanding of POAG pathogenesis. These include SNPs near CAV1 and CAV2 in an Icelandic cohort [40], in TMCO1 and CDKN2B-AS1 in an Australian cohort [41], in CDKN2B-AS1, SIX1/SIX6, and the 8q22 locus in Europeans [42], in GAS7 and TMCO1 in US Caucasians [49], and in CDKN2B-AS1, CDC7/TGFBR3 and FNDC3B in Asian, African and European cohorts [48].

The caveolin genes have been postulated to influence transforming growth factor-beta (TGF-β) or nitric oxide signaling pathways involved in POAG pathogenesis. The locus on chromosome 7q31 has been studied in US Caucasians, Africans, and the Saudi Arabian population with inconsistent results [40,66,71–73,100]. A recent meta-analysis of five studies, including 5774 POAG cases and 40,598 healthy controls, suggested that SNP rs4236601 is associated with POAG risk in Caucasian and Asian populations but not in African and Saudi populations [111]. Australian GWAS identified two loci, TMCO1 (1q24) and CDKN2B-AS1 (9p21), to be associated with advanced glaucoma. The association of the TMCO1 locus with POAG has been replicated in another GWAS for a Caucasian cohort [49], and associated with increase in IOP as well [49,93]; the carriers of risk alleles for SNP rs4656461 have been reported to be associated with a younger age at diagnosis [92]. The ciliary body, trabecular meshwork and retina show abundant TMCO1 expression. However, its precise role in POAG pathogenesis is unclear. So far, there are no published reports of association studies at the TMCO1 locus in the Middle East population.

Since the identification of the association between the CDKN2B/CDKN2B-AS1 locus and POAG in the Australian cohort, several GWASs have replicated this association in the US Caucasian [42], Japanese [43–45], Asian, African, and European populations [48], providing strong evidence for the association of this locus with POAG. In addition, many studies have reported a positive association of SNPs in CDKN2B in several other populations using a candidate-gene approach [66,67,69,70,74]. These SNPs are located in an anti-sense non-protein coding gene, CDKN2BAS, within the CDKN2A/B gene cluster. CDKN2B is a tumor suppressor gene and, with its suggested role in the TGF-β pathway, may play a critical role in glaucoma pathogenesis [112,113]. Interestingly, carriers of the CDKN2B-AS1 risk alleles are associated with larger VCDR [53,54] and low IOP as compared to the wild-type carriers [74]. On the basis of these findings, it has been suggested that the CDKN2B/CDKN2B-AS1 locus of 9p21 may possibly predispose a person to glaucomatous optic neuropathy in a mechanism that may not be dependent on IOP and highlights the importance of the chromosome 9p21 susceptibility locus as a risk factor in the development of POAG [114].

Recently, Li et al. performed a GWAS on 3504 POAG cases and 9746 controls. The positive significant findings of this phase were then replicated in 9173 POAG cases and 26,780 controls across 18 different collections of Asian, African, and European populations including a replication cohort from our center in Saudi Arabia [48]. The study confirmed and provided strong evidence of an association at the CDKN2B-AS1 locus (rs2157719, OR = 0.71, $p = 2.81 \times 10^{-33}$), and also identified SNP rs1192415 in the CDC7-TGFBR3 gene (1p22) showing significant association with POAG (OR = 1.13, $p = 1.60 \times 10^{-8}$) in the Asian, African and European populations, as well as SNP rs4894796 in FNDC3B (3q25.31) showing a significant association in Asians only (OR = 0.89, $p = 7.93 \times 10^{-8}$).
Interestingly, these results were found to be non-significant in the Saudi replication cohort, indicating that the genetic cause for POAG in the Saudi population may be different than those from Asian, African and European descent.

GWAS studies by Wiggs et al. and Osman et al. in the Caucasian POAG and Japanese POAG cases, respectively, have demonstrated a strong association of SNP rs10483727 located in the intergenic region between the SIX1 and SIX6 locus (14q23) [42,43]. SIX6 has been shown to express in the developing and adult human retina [115]. Moreover, the association of SNP rs10483727 in the SIX1/SIX6 region has also been replicated in other Caucasian POAG cohorts [67,69,70,88] but not in the African-Caribbean subjects [66]. After the association of the CDKN2B-AS1 region on chromosome 9p21, the second most consistent association with POAG has been observed in the SIX1/SIX6 locus and so it would be interesting to know if this locus is associated with POAG in the Saudi or other Middle Eastern populations. However, currently there are no published reports of association of SIX1/SIX6 locus with POAG in the middle-east population.

Recently, 11p11.2 (containing multiple genes), ABCA1, ABO, AFAP1, ARHGEF12, FAR2, GGA3, GMDS, PKDREJ, and PMM2 were added to the newly discovered genes associated with POAG [46,47,50–52]. These variants were significantly associated with glaucoma and the related functional visual field loss that could make them future study targets for glaucoma patients in the Middle East.

5. GWAS and Quantitative Endophenotype Traits

The genetic evaluation of quantitative endophenotype traits is often very useful in complex multifactorial diseases to understand the contribution of specific traits to the overall disease phenotype. A similar strategy has been successfully used in POAG to understand the contribution of proposed endophenotypes including IOP, VCDR, optic disc area and CCT to the overall disease process. GWASs have been performed to examine the genetic components of these endophenotypes in POAG and the normal population. van Koolwijk and colleagues performed a GWAS for IOP in POAG patients of European descent and identified SNPs rs11656696 and rs7555523, located in GAS7 and TMCO1, respectively, suggesting a role for these two genes in IOP regulation [49]. Other loci found to be associated with IOP so far include FNDC3B, ABCA1, ABO, 11p11.2, ARHGEF12 [50,52]. Another three loci, FAR2, GGA3, and PKDREJ, did not reach a genome-wide significance level ($p < 10^{-5}$) [51]. Three independent GWASs have evaluated the association of optic disc parameters (VCDR and optic disc area) in the normal general population. The loci associated included ATOH7, CDC7/TGFB3 and SALL1, CARD10 for the optic disc area, and CDKN2B, SIX1, SCY1/LTBP3, CHEK2, and DCLK1, in addition to ATOH7, for the VCDR [53–56]. An exome sequencing also reported the SIX6 locus to influence VCDR ($p = 7.74 \times 10^{-7}$) [57]. A subsequent meta-analysis of the Rotterdam study with the Twin UK study [54] demonstrated a strong association of ATOH7, CDKN2B, and SIX1 in POAG with borderline association for CDC7/TGFB3 and SALL4 (both $p = 0.04$). CARD10 was not found to be associated with African-Caribbean POAG cases [66], whereas CHEK2 was reported to be associated with VCDR and HTG among the Japanese [67] but not in Europeans [70]. Moreover, multiple studies have provided strong evidence of association of ATOH7 [66–69] CDKN2B-AS1 [66,67,69,70,74] and SIX1/SIX6 [69,70] with POAG. CCT is an important risk factor for POAG in individuals with increased IOP, and over 26 loci have been reported [116]. GWASs have identified several loci associated with CCT in the normal general population (Asian and European descent) and POAG cases (US Caucasians). These loci include ZNF469, COL5A1, AKAP13, AVGR8, and COL8A2 [58–60]. The ZNF469 and COL5A1 loci have been found to be associated with CCT in both the Caucasian and Asian cohorts [58,59].

The possible role of these newly discovered loci associated with POAG and its endophenotypes in understanding the pathophysiology of POAG has been elegantly reviewed by Iglesias et al. elsewhere [117]. The review integrates current knowledge in POAG from human and experimental data and dissects the contribution of the newly discovered genetic loci with the known molecular and biological processes, including extracellular matrix remodeling; TGF-β and tumor necrosis factor...
α (TNF-α) signaling; and the vascular tone pathway, that have been implicated in the pathogenesis of POAG.

6. Candidate Genes and POAG

Recent reviews by Takamota and Araie [32] and Janssen et al. [31] presented a list of genes identified from numerous GWAS and association studies thus far. Taken together, the list of almost 50 genes may represent highly likely candidate genes that may be involved in POAG pathogenesis. Many studies have been performed to replicate the GWAS findings in the Asian, African-Caribbean and Caucasian/European populations using the candidate-gene approach [61,66,67,69–76,84,89,92,93]. Also, many studies were performed to test the association of specific known genes/SNPs with POAG using the same approach in different populations including Middle Eastern [61–66,76–87,90,91,94–109]. These SNP replication and genetic association studies in the Middle Eastern and other populations are also listed in Table 1. Among these, consistent findings have been reported for ATOH7 [66–69], CDKN2B (-AS1) [66,67,69,70,74], GSTT1/GSTM1 [77,78,105,106], SIX1/SIX6 [69,70] and TMCO1 [92,93] loci, indicating a potential role of these genes/loci in the pathogenesis of POAG. However, except for the glutathione-S transferase (GST) polymorphism, none of these loci have been either found to be associated with POAG (e.g., CAV1/CAV2, CDC7/TGFBR3, FND3) or the association has not been reported yet (e.g., ATOH7, CDKN2B(-AS1), SIX1/SIX6, TMCO1) in the Middle Eastern population. However, the positive findings of GSTT1 and GSTM1 genotypes in the Middle Eastern population may be very interesting, highlighting the role of anti-oxidants and/or oxidative stress-related pathways/mechanisms in the pathogenesis of POAG in this population. This view is strongly supported by recent meta-analysis studies that examined the association of GST polymorphisms and the risk of POAG [118–120]. We have previously studied SNPs in two of the anti-oxidant genes, CAT (rs1001179) and SOD2 (rs4880) [98,99], in the Saudi POAG patients. However, the studies did not provide any direct association with POAG but indicated a trend towards an association with IOP and age of onset of POAG. In addition, some studies have demonstrated moderate evidence for association of SNPs in TP53, NOS3, SEC14L2/TAP, and APOE [96,97,103,107]. However, these studies have been limited by sample size and would need further investigations in a large population-based cohort. The examination of causative genes such as MYOC, OPTN and LOXL1 in Saudi POAG cases has also provided negative results [102,105]. Table 2 list all genes associated with POAG and their possible role in POAG pathogenesis.

7. Final Remarks

There is significant progress in understanding the genetic basis of POAG, largely due to the application of GWAS methodology in different populations. In recent years, GWASs have identified several loci associated with POAG including CAV1/CAV2, TMCO1, CDKN2B-AS1, CDC7-TGFBR3, SIX1/SIX6, GAS7 and ATOH7.

The association between the CDKN2B(-AS1) locus on chromosome 9p21 and POAG has been extensively established across different populations and represents a major genetic risk factor for POAG. Studies involving the SIX1/SIX6 and the ATOH7 loci affecting the optic disc parameters and POAG itself have also been reproducible. Other loci seem to be more ethnicity-specific. CAV1/CAV2 and CDC7-TGFBR3 loci do not seem to contribute to POAG in the Middle East and the role of other newly discovered loci is yet to be established. Moreover, the GSTT1/GSTM1 genotypes were found to be strongly associated with POAG in the Middle Eastern population and more studies may be needed to examine the role of oxidative stress and anti-oxidant pathways in this population.

Based on the current and new genes identified in glaucoma, it may be possible to develop an algorithm of SNP risk scores to assess the future risk of POAG in patients, which could be clinically useful. However, despite the tremendous progress, the genetic basis of POAG is still not completely understood and further investigations are needed to identify novel genes and pathways contributing to glaucoma that may help define disease-specific targets and facilitate the development of diagnostic and therapeutic strategies.
Table 2. Possible pathogenesis role of various genes associated with POAG.

| Gene   | Gene Name                                | Function                                                                 | Role in Ophthalmic Diseases                                                                 |
|--------|------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| PLXDC2 | Plexin Domain Containing 2               | May play a role in tumor angiogenesis                                     | Possible role through inhibition of angiogenesis and possible involvement in protecting against inflammation |
| TMTC2  | Transmembrane and Tetratricopeptide Repeat Containing 2 | Protein binding calcium ion homeostasis                                  | Unknown                                                                                   |
| ZP4    | Zona Pellucida Glycoprotein 4            | Signal transducer activity                                                | Unknown                                                                                   |
| SRBD1  | S1 RNA Binding Domain 1                  | Nucleic acid binding, RNA binding, hydrolase activity, acting on ester bonds | Appears to contribute to glaucomatous optic neuropathy as a non–IOP-related genetic factor; exact mechanism is not known |
| ELOVL5 | ELOVL Fatty Acid Elongase 5              | Catalytic activity                                                        | Appears to contribute to glaucomatous optic neuropathy as a non–IOP-related genetic factor; exact mechanism is not known |
| CAV1/CAV2 | Caveolin 1/Caveolin 2                 | Receptor binding, structural molecule activity                           | Dysfunction of cellular signaling and transport leading to the damage in tissues            |
| CDKN2B-AS | Cyclin-Dependent Kinase Inhibitor 2B   | Protein coding gene, inhibits CDK4                                        | Associated with systemic diseases inside and outside the eyes causing disruption in cell cycle |
| TMCO1  | Transmembrane And Coiled-Coil Domains 1  | Encoding transmembrane protein                                            | Association with cellular malfunction and oxidative stress                                 |
| SIX1   | SIX Homeobox 1                           | Regulation of cell proliferation, apoptosis and embryonic development.    | Associated with developmental malformation of anterior angle, TM and CB                     |
| NCKAP5 | NCK-Associated Protein 5                | Protein coding gene                                                       | Unknown                                                                                   |
| ABCA1  | ATP-Binding Cassette, Sub-Family A (ABC1), Member 1 | Cholesterol carrying out of the cell                                     | Expressed highly in TM network, thought to be involved in raising IOP                     |
| AFAP1  | Actin Filament Associated Protein 1      | signaling pathways                                                       | Possible involvement in aqueous outflow and IOP                                            |
| GMDS   | GDP-Mannose 4,6-Dehydratase              | Catalytic activity                                                        | GMDS encodes a protein that is required for the first step in de novo synthesis of fucose. Fucose is required for diverse biological functions such as growth factor receptor signalling. Several studies have suggested the effects of growth factors on development of glaucoma |
| CDC7   | Cell Division Cycle 7                   | Phosphorylation                                                           | Impairment of cellular function in CB, TM and RGC                                          |
| FNDC3B | Fibronectin Type III Domain Containing 3B| Poly(A) RNA binding                                                      | Associated with IOP through as yet unknown mechanism                                       |
| Gene     | Gene Name                                    | Function                                           | Role in Ophthalmic Diseases                        |
|----------|----------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| GAS7     | Growth Arrest-Specific 7                     | Protein coding gene sequence-specific DNA binding  | Involved in developmental and functional impairment of RGC |
|          |                                              | transcription factor activity                      |                                                    |
| ABO      | ABO Blood Group (Transferase A, Alpha 1-3-N-Acetylglucosaminyltransferase; Transferase B, Alpha 1-3-Galactosyltransferase) | Basis of the ABO blood group system                | Thought to play a role in IOP elevation; Exact mechanism is not known |
| FAR2     | Fatty Acyl CoA Reductase 2                   | Catalytic activity                                 | Unknown                                           |
| GGA3     | Golgi-Associated, Gamma Adaptin Ear Containing, ARF Binding Protein 3 | Protein sorting and trafficking between the trans-Golgi network (TGN) and endosomes | Unknown                                           |
| PKDREJ   | Polycystin (PKD) Family Receptor For Egg Jelly | May have a central role in fertilization           | Elevated IOP through undetermined mechanism        |
| ARHGEF12 | Rho Guanine Nucleotide Exchange Factor (GEF) 12 | May play a role in the regulation of RhoA GTPase   | Elevated IOP through undetermined mechanism        |
| ATOH7    | Atonal Homolog 7                             | Involved in the differentiation of retinal ganglion cells | Involved in developmental problems of retinal vasculature |
| SALL1    | Spalt-Like Transcription Factor 1            | Organogenesis                                      | SALL1 is involved in development of calcium homeostasis in the endoplasmic reticulum |
| RFTN1    | Raftlin, Lipid Raft Linker 1                 | Formation and/or maintenance of lipid rafts.      | Related to vertical cup-to-disc ratio              |
| CARD10   | Caspase Recruitment Domain Family, Member 10 | Protein binding, receptor signaling                | Developmental problems of neuronal tissues         |
| COL5A1   | Collagen, Type V, Alpha 1                    | Fibril formation                                   | Associated with malformation of connective tissues leading to problems in cornea and TM |
| ZNF469   | Zinc Finger Protein 469                      | Transcriptional regulation                         | Thought to be involved in central corneal thickness |
| AKAP13   | A Kinase (PRKA) Anchor Protein 13            | Protein binding, cAMP-dependent protein kinase activity | Involvement in corneal thickness and disruptions in signaling pathways in CB, TM and RGCs |

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Table 2. Cont.

| Gene    | Gene Name                                      | Function                                      | Role in Ophthalmic Diseases                  |
|---------|------------------------------------------------|-----------------------------------------------|----------------------------------------------|
| COL8A2  | Collagen, Type VIII, Alpha 2                   | Protein binding, extracellular matrix structural constituent | Associated with malformation of connective tissues leading to problems in cornea and TM |
| NTM     | Neurotrimin                                    | Protein binding                               | Unknown                                      |
| APOE    | Apolipoprotein E                               | Protein binding, receptor binding             | Role in oxidative stress and disrupted cellular homeostasis in CB, TM, LC and RGC |
| CHEK2   | Checkpoint Kinase 2                            | Protein kinase activity                       | High expression is associated with problems in optic nerve and cup disk ratio |
| FBN1    | Fibrillin 1                                    | Extracellular matrix structural constituent   | Mutations in FBN1 could cause backward bowing by compromising the mechanical properties of the iris |
| GSTT1   | Glutathione S-Transferase Theta 1              | Glutathione transferase activity              | Oxidative stress in all the POAG-involved tissues |
| NTF4    | Neurotrophin 4                                 | Protein binding, receptor binding             | Retinal ganglion cells survival and apoptosis |
| OPA1    | Optic Atrophy 1                                | Protein binding                               | Involved in Oxidative stress in cornea, CB and TM |
| PAX6    | Paired Box 6                                   | Sequence-specific DNA binding RNA polymerase II transcription factor activity | Developmental impairment of neuro ophthalmic system |
| PLXDC2  | Plexin Domain Containing 2                     | Receptor binding                              | Developmental problems leading to fewer retinal ganglion cells |
| SIX6    | SIX Homeobox 6                                 | DNA binding, protein binding                  | Associated with developmental malformation of anterior angle, TM and CB |
| TLR4    | Toll-Like Receptor 4                           | Receptor binding                              | Involved in Oxidative stress and decreased cellular viability |
| TMTC2   | Transmembrane And Tetratricopeptide Repeat Containing 2 | Identical protein binding | TMTC2 is implicated in calcium homeostasis in the endoplasmic reticulum |
| TNFα    | Tumor Necrosis Factor                          | Protease binding, cytokine activity           | May be activated in reaction to POAG-related indices (increased IOP, oxidative stress and increase in disregulation of cellular homeostasis) |
| VAV2    | Vav 2 Guanine Nucleotide Exchange Factor       | Epidermal growth factor receptor binding      | Unknown                                      |
| LOXL1   | Lysyl Oxidase-Like 1                           | Copper ion binding                            | Through the loss of elastin formation and resulting friction between the iris and the anterior lens capsule |
| ZNF469  | Zinc Finger Protein 469                       | DNA binding                                   | Associated with developmental malformation of connective tissues leading to problems in cornea and TM |
Table 2. Cont.

| Gene   | Gene Name                              | Function                          | Role in Ophthalmic Diseases                                      |
|--------|---------------------------------------|-----------------------------------|-----------------------------------------------------------------|
| Zp4    | Zona Pellucida Glycoprotein 4         | Signal transducer activity         | Unknown                                                         |
| TP53   | Tumor Protein P53                      | Core promoter sequence-specific DNA binding | Unknown                                                         |
| NOS3   | Nitric Oxide Synthase 3 (Endothelial Cell) | Receptor binding                   | Dysregulation of the vascular tone particularly through interaction with endothelial nitric oxide synthase and production of nitric oxide (NO) in the vascular endothelia. This may lead to decreased AH outflow and increased IOP. |
| CAT    | Catalase                              | Catalytic activity                 | Detoxification of reactive oxygen species—linked to POAG through oxidative stress. |
| SOD2   | Superoxide Dismutase 2, Mitochondrial | Oxygen binding, DNA binding        | Possible role through oxidative stress mechanism.               |
| OPTN   | Optineurin                            | Protein binding                    | Through oxidative stress/the mitochondrial caspase-dependent cell death. |
| TTPA   | Tocopherol (Alpha) Transfer Protein    | Transporter activity               | Linked to vitamin C loss and that in turn is linked to POAG development through yet undiscovered mechanism. |
| RBPI   | Retinol Binding Protein 1, Cellular   | Transporter activity, retinoid binding | Through retinol and oxidative stress mechanism.                |
| MTHFR  | Methylene tetrahydrofolate Reductase (NAD(P)H) | Methylene tetrahydrofolate reductase (NAD(P)H) activity | Linked through homocysteine level, link to POAG is not established. |
| GPX4   | Glutathione Peroxidase 4              | Glutathione peroxidase activity    | Effect on decreased level of vitamins E and C. Lower level of vitamin C is linked to glaucoma through unknown mechanism. |
| SEC14L2| SEC14-Like 2 (S. Cerevisiae)           | Phospholipid binding               | Effect on decreased level of vitamin C. Lower level of vitamin C is linked to glaucoma through unknown mechanism. |
| SLC23A1| Solute Carrier Family 23 (Ascorbic Acid Transporter), Member 1 | Nucleobase transmembrane transporter activity | Effect on decreased level of vitamin C. Lower level of vitamin C is linked to glaucoma through unknown mechanism. |
| PMM2   | Phosphomannomutase 2                  | Catalytic activity                 | Expressed highly in TM network, thought to be involved in raising IOP. |
| SLC23A2| Solute Carrier Family 23 (Ascorbic Acid Transporter), Member 2 | 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. Exact link between low vitamin C level and POAG is not determined. |
Since the advent of GWAS studies, more and more genes and SNPs have been discovered in association of POAG. However, the usefulness (in term of clinical application and developing therapeutic modalities) of those discoveries is still limited. It will take multiple genotype-phenotype studies in various centers and multiethnic groups before establishing the applicability of those SNPs and/or genes to POAG or POAG clinical indices. As for the development of new therapeutic agents, the process will be lengthy and may take several years before effective therapeutic modalities for POAG are available. The whole process from discovering new genetic markers (SNPs) or genes to developing new therapeutic agents may take several steps and many years. Those steps are: (i) Discover those genes and/or SNPs associated with POAG, which is underway thanks to new emerging technologies in molecular genetics such as exome sequencing and GWAS technologies. This may take up to 10 years to complete; (ii) Establish the association of various SNPs and genes with POAG in various ethnicities, larger cohorts, and in multiple centers. This is important as initial discovery studies are conducted on specific ethnicities and in smaller cohorts; (iii) Conduct functional studies in order to understand how those genes and/or SNPs contribute to POAG pathogenesis; (iv) Develop therapeutic agents based on our understanding of the function of the genes associated with POAG. This step is the longest and expected to take at least 10–15 years. This should not hold us back or make us think less of genetic studies as those may prove to be the only way to improve our current understanding of the etiology of glaucoma and facilitate the development of diagnostic and therapeutic strategies.

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