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Review

Candidate genes involved in the susceptibility of primary open angle glaucoma

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ABSTRACT

Purpose: Glaucoma is a common disease often identified by high intraocular pressure, characteristic optic neuropathy and vision loss. It is currently a leading cause of blindness worldwide with no known cure. Primary open angle glaucoma (POAG) is the most common type of glaucoma worldwide. It is a multifactorial disease where both genetic as well as environmental factors are involved in the pathogenesis.
Results: Till date, at least 29 genetic loci have been found to be linked to POAG. However, the role of only three underlying genes Myocilin (*MYOC*), Optineurin (*OPTN*) and WD repeat Domain 36, (*WDR36*) is well established. Also, the role of Cytochrome P450, family 1, subfamily B, polypeptide 1 (*CYP1B1*), Glutathione S-transferase mu 1 (*GSTM1*) and Neurotrophin (*NTF4*) has been fairly identified. Association studies have found that 66 loci with 76 genes associated to POAG till date, but even more studies are required to confirm their role in the disease pathology. Gene mutations in various populations have been identified by genetic studies to establish that about 5% of POAG is currently attributed to single-gene or Mendelian forms of glaucoma and others caused by the combined effects of many genetic and environmental risk factors, each of which do not act alone to cause glaucoma.
Conclusion: Although the clinical progression of the disease is well defined, the molecular events responsible for glaucoma are poorly understood and thus the etiology of POAG remains a mystery. Despite strong genetic influence in POAG pathogenesis, only a small part of the disease can be explained in terms of genetic aberration. This review is an overview and update on the latest research and progress of genetic studies associated with POAG.

Abbreviations: ACG, angle closure glaucoma; AD, autosomal dominant; ADRB1, beta-adrenergic receptors 1; ADRB2, beta-adrenergic receptors 2; AGTR2, angiotensin II receptor, type 2; ANP, atrial natriuretic polypeptide; APOE, apolipoprotein E; AR, autosomal recessive; ASB10, ankyrin repeat and SOCS box containing 10; ATOH7, atonal homolog 7; BMI, body mass index; BMP4, bone morphogenetic protein 4; BMP7, bone morphogenetic protein 7; BMPR2, bone morphogenetic protein receptor type II (serine/threonine kinase); CAV1/CAV2, caveolin 1/caveolin 2; CCT, central corneal thickness; CDC7/TGFBR3, cell division cycle 7/transforming growth factor, beta receptor III; CDH-1, cadherin 1; CDKN1A, cyclin dependent kinase inhibitor 1A; CDKN2B-AS1, CDKN2B antisense RNA 1; CNVs, copy number variations; COCH, coagulation factor c homolog cochlin (*Limulus polyphemus*); COX, cytochrome C oxidase; CYP1B1, cytochrome P450, family 1, subfamily B, polypeptide 1; CYP2D6, cytochrome P450, family 2, subfamily D, polypeptide 6; CYP46A1, cytochrome P450 family 46 subfamily A polypeptide 1; ECM, extracellular matrix; EDNRA, endothelin receptor, type A; ELN, elastin; ELOVL5, elongation of very long chain fatty acids-like 5; GALC, galactosylceramidase; GAS7, growth arrest-specific 7; GLC, glaucoma; GPDS1, glaucoma related pigment dispersion syndrome; GST, glutathione S-transferase; GSTM1, glutathione S-transferase, mu-1; GSTT1, glutathione S transferase, theta-1; GWAS, genome wide association studies; HK2, hexokinase 2; HSPA1A, heat shock 70 kDa protein 1A; HTG, high tension glaucoma; IGF2, insulin-like growth factor II; IL1A, interleukin 1 alpha; IL1B, interleukin 1 beta; Indel, insertion and deletion; IOP, intraocular pressure; JOAG, juvenile open angle glaucoma; LALES, Los Angeles Latino eye study; LHON, Leber hereditary optic neuropathy; LMX1B, lim homeobox transcription factor 1; MFN1, mitofusin 1; MFN2, mitofusin 2; MIM, Mendelian inheritance in man; MMP1, matrix metalloproteinase 1; mtDNA, mitochondrial DNA; MTHFR, 5,10-methylenetetra-hydrofolate reductase; MYOC, myocilin; NAK, NF-kappa-B-activating kinase; NCK2, NCK adaptor protein 2; NCKAP5, NCK-associated protein 5; ND, NADH dehydrogenase; NOS3, nitric oxide synthase 3; NPPA, natriuretic peptide precursor A; NTF4, neurotrophin; NTG, normal tension glaucoma; OAG, open angle glaucoma; OCLM, oculomedin; OLFM2, olfactomedin 2; OPA1, optic atrophy 1; OPTC, opticin; OPTN, optineurin; OS, oxidative stress; PAI-1, plasminogen activator inhibitor-1; PARL, presenilin associated, rhomboid like; PCG, primary congenital glaucoma; PEG, pseudoexfoliation glaucoma; PLXDC2, plexin domain containing 2; PMH, postmenopausal hormone; POAG, primary open angle glaucoma; PON1, paraoxonase 1; ROS, reactive oxygen species; SEC14L2/TAP, SEC 14 like 2/tocopherol-associated protein gene; SIX1/SIX6, sine oculis homeobox, *Drosophila*, homolog of, 1/6; SLC23A2, sodium(+)-dependent L-ascorbic acid transporter 2; SNPs, single nucleotide polymorphisms; SRBD1, S1 RNA binding domain 1; STI1, stress inducible 1; TAP1, transporter, ATP-binding cassette, major histocompatibility complex; TBK1, TANK-binding kinase 1; TIGR, trabecular meshwork-induced glucocorticoid response protein; TLR4, toll-like receptor 4; TM, trabecular meshwork; TMCO1, transmembrane and coiled-coil domains 1; TMTC2, transmembrane and tetratricopeptide repeat containing 2; TNFα, tumour necrosis factor; TP53, tumour protein P53; UTP21, U three protein 21; Vav2, guanine nucleotide exchange factor; VCDR, vertical cup–disc ratio; WDR36, WD repeat domain 36; XPD, xeroderma pigmentosum complementation group D; XRCC1, X-ray cross-complementing group 1; ZP4, zona pellucida glycoprotein 4.

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Contents

1. Introduction

POAG is the most common form of glaucoma among all subtypes (Quigley, 1993) often with autosomal dominant mode of inheritance (Fingert, 2011) in which the intraocular pressure (IOP) is consistently elevated above 22 mmHg (Quigley, 1993). However, POAG can occur at any IOP. The POAG patients having IOP of <22 mmHg are classified as having normal tension glaucoma (NTG) (Werner, 1996) which accounts for approximately one third of all POAG cases (Bonomi et al., 1998).

POAG is a mutifactorial complex disorder where genetic, systemic and environmental factors interact with each other to precipitate the disease (Raymond, 1997; Sarfarazi, 1997). A study by Gong et al. (2007) estimated that inherited and familial POAG cases accounted for approximately 72% of all POAG cases but rarely with Mendelian pattern of inheritance.

1.1. Worldwide incidence

Earlier studies estimated around 60.5 million people with primary glaucoma by 2010, increasing to 79.6 million by 2020 with bilateral blindness in 5.9 million open angle glaucoma (OAG) and 5.3 million angle closure glaucoma (ACG) cases by the corresponding years, (Quigley and Broman, 2006) which in 1995 estimate, was found to cause approximately 14% of blindness worldwide (Thylefors et al., 1995). Recent study on glaucoma global prevalence shows 111.8 million glaucoma cases by 2040 (Tham et al., 2014).

Among the Caucasian races, 75–95% of primary glaucoma was found to be POAG (Leske, 1983). The Los Angeles Latino Eye Study (LALES) found that Latinos in the United States have 4.7% prevalence of OAG (Varma et al., 2004). In the Baltimore Eye Survey, the prevalence of OAG was significantly higher in blacks (4.7%) than in whites (1.3%) (Sommer et al., 1991). A population-based study on the epidemiology of glaucoma in Yazd (Iran), revealed 1.6% with high tension (HT-POAG) and 1.6% with NT-POAG (Suri et al., 2015). On the other hand, the prevalence of OAG in Asians varies widely, perhaps in part because the term Asian encompasses broad racial and ethnic categories. Moreover, in Asian population, ACG is the main cause of morbidity from glaucoma that blinds 10 times more people than OAG does (Foster, 2002). A population based glaucoma prevalence studies in Asians found higher incidence of primary angle closure glaucoma (PACG) than in white patients (Cho and Kee, 2014).

Yogchuan glaucoma study exhibited POAG prevalence of 0.86% among residents aged ≥50 years in southwestern China (Li et al., 2014). A recent study by Cheng et al. (2013) showed POAG prevalence in mainland China to be 0.7% (urban population more affected). Recently, in the health-center-based Korean population, the 5-year incidence of POAG was found to be 0.72% (Kim et al., 2014). Rudnicka et al. (2006) documented OAG rates in Asia to range from 1 to 4%, whereas Ramakrishnan et al. (2003) found the prevalence of OAG in India to be 1.7%. It is estimated that in India, POAG affects around 6.48 million persons (George et al., 2010). The prevalence studies thus show that POAG is more common in the western hemisphere than in the eastern hemisphere, where PACG is more prevalent.

2. Risk factors

The etiology of POAG is still uncertain however, certain factors are known or suspected of having an etiological role. The risk factors of glaucoma involve systemic factors and ocular factors that include IOP and non-IOP factors. The most important risk factor of POAG is IOP. Non-IOP risk factors come from age, central corneal thickness (CCT), duration of optic disc hemorrhage, the degree of severity of glaucoma and glaucoma in both eyes (Zhang et al., 2009). Also, there are studies that suggests role of oxidative stress (OS) in glaucoma (Kumar and Agarwal, 2007). Besides this, the Baltimore Eye Survey identified systemic hypertension, perfusion pressure and possibly the structure and organization of the optic nerve head as potential etiologically significant risk factors in the development of glaucomatous optic nerve damage (Sommer, 1996). Major risk factors associated with POAG was tabulated in a study by Kwon et al. (2009) and was discussed in detail earlier by Omoti and Edema (2007).

Many studies identified few lifestyle factors that are known to modify IOP which may include high wind instruments (Schuman et al., 2000), caffeine (Higginbotham et al., 1989; Avisar et al., 2002), yoga posture (Baskaran et al., 2006), tight neck ties (Teng et al., 2003; Talty and O'Brien, 2005), weight lifting (Vieira et al., 2006) and dietary fat intake (Kang et al., 2004). Moreover, high level of education and high hematocrit level was also found as significant risk factors for incident POAG (Kim et al., 2014). Other risk factors include use of anti-inflammatory corticosteroids (Clark, 1995). Cigarette smoking (Kang et al., 2003), alcohol intake (Kang et al., 2007) and body mass index (BMI) (Gasser et al., 1999) are not yet identified as important risk factors in POAG. Though, a recent study on African American population found association between BMI and blindness with POAG (Charlson et al., 2015). Several studies reported that exercise (Marcus et al., 1970; Qureshi et al., 1996; Martin et al., 1999) and postmenopausal hormone (PMH) use are associated with lower IOP and enhanced