Genetic Susceptibility to Normal Tension Glaucoma (NTG)

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Author’s contribution

This work was carried out by the author BSS. Author BSS read and approved the final manuscript.

ABSTRACT

Aims: The Purpose of this short article is to summarize the recent developments in the genetics of normal tension glaucoma (NTG).

Background: Glaucoma is one of the leading causes of irreversible blindness. Primary open-angle glaucoma (POAG) is the most common type of glaucoma in most populations and is frequently associated with elevated intraocular pressure (IOP). However, patients with POAG can also have IOP within the normal range and they are classified as having normal tension glaucoma (NTG) – most likely an independent entity. In NTG, the optic nerve head is just susceptible to normal IOP. Therefore, factors other than elevated IOP are likely to play a role in the pathogenesis of glaucoma. Although factors such as myopia, older age, vasospasm, ischemia and vascular insufficiency are indicated to be associated with the development of NTG, substantial percentage of NTG patients (21%) have a family history of glaucoma suggesting that these patients may have a genetic predisposition for developing NTG.

Methodology: Using the keywords or phrases such as glaucoma, genetics, normal tension glaucoma, open-angle glaucoma and retinal ganglion cell, the literature search was carried out.

Results: NTG is a genetically complex disorder and many genes have been reported to be associated with the development of glaucoma. However, none of them account for a substantial portion of patient population. A complex glaucoma pathogenesis may include interplay among several factors such as genetic, epigenetic and environmental factors. Therefore, an understanding of IOP independent mechanisms of development

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of NTG is important.

**Conclusion:** NTG is relatively a less explored avenue of research. There has been paucity of research into the genetic basis of NTG.

**Keywords:** Blindness; degeneration; ganglion; gene; glaucoma; retina.

1. **INTRODUCTION**

Glaucoma is a multifactorial degenerative optic neuropathy and causes permanent damage of the retina and optic nerve [1] resulting in blindness. It is estimated that glaucoma affects nearly 70 million people worldwide [2]. The condition is characterized by the slow progressive loss of retinal ganglion cells (RGCs), optic nerve axons and visual field damage. It is the second leading cause of blindness and most often associated with elevated intraocular pressure (IOP). Epidemiological studies suggest that primary open-angle glaucoma (POAG) is the most common type of all glaucoma types and many patients have high IOP [3]. A host of genetic and environmental factors are considered to be contributing to glaucoma phenotypes [4-5]. For instance, in certain population, older age, history of thyroid disease, higher IOP and myopia have been reported to be significant risk factors for POAG [6-9]. These environmental risk factors exert their effects on IOP (either by decreasing or increasing) and/or the rate of RGC apoptosis.

Normal tension glaucoma (NTG) is a sub set of POAG – most likely an independent entity. Approximately one third of all Caucasian POAG patients have statistically normal (10-21 mmHg) IOP [10-11]. However, such patients show typical pathological cupping of the optic nerve similar to POAG. Therefore, factors other than elevated IOP are likely to play a role in the pathogenesis of glaucoma. In support of this is the finding that in some glaucoma patients significant IOP reduction does not prevent progression of disease and they continue to lose vision [12-13]. NTG is most prevalent in Japanese (3.6%) and Korean (2.04%) populations than in the Caucasian population (0.6%) [14-15]. In Japanese population, 92% of patients with POAG had NTG with an IOP of 21 mm Hg or less [16]. In Korean population, POAG with low IOP is the most common form accounting for 94.4% of the total number of cases [17]. Many individuals have IOP elevation without optic nerve damage and some individuals develop optic nerve degeneration without elevated IOP [18]. Therefore, it has been proposed that elevation in IOP is neither necessary nor sufficient for the onset of the progression of the disorder or optic nerve damage [18-20]. An understanding of IOP independent mechanisms of RGCs loss is therefore important in NTG. Factors such as myopia, older age, vasospasm, ischemia and vascular insufficiency are indicated to be associated with the development of NTG. However, a substantial percentage of NTG patients (21%) have a family history of glaucoma suggesting that these patients may have a genetic predisposition for developing NTG [21]. The aim of this short article is to summarize the recent developments in the genetics of NTG and no attempt has been made to discuss the entire field of glaucoma.

1.1 **Genetic Factors in NTG**

Glaucoma is genetically heterogeneous and many genes have been reported to be associated with the development of glaucoma [22]. The monogenic forms are rare in NTG and therefore, for the majority of cases a multigenic inheritance was proposed. For instance, a genetic locus (GLC1P) for familial NTG has been localized on chromosome 12q14 and
780 kbp duplication within this locus has been identified. Immunohistochemical, microarray expression and northern blot analyses suggest that duplication of TANK–binding kinase –1 (TBK1) gene is likely responsible for glaucoma in the patients analyzed [23-24]. This gene is expressed in the nerve fiber layer, ganglion cells and microvasculature of the human retina. It is suggested that its duplication may involve dysregulation of gene expression [25] or chromosomal rearrangement that may disrupt other genes. Recently, genome wide association studies (GWAS) have also identified a strong association of one single SNP (rs 523096) located on chromosome 9p21 in Japanese NTG patients [26]. Studies also demonstrate that genes in the GLC1F locus may be associated with the pathogenesis of NTG in Japanese patients [27]. In addition, microsatellite analysis of the GLC1B locus on chromosome 2 suggests that D2S176 marker had the strongest significant association implicating a candidate gene on chromosome 2 for further studies [28].

Association studies have also identified risk alleles in the SiRNA binding domain 1 (SRBD1) and fatty acid elongase 5 (ELOVL5) genes for NTG [29] but their significance remains to be established. In addition, association of single SNP in optineurin (OPTN), mitofusin-1 (MFN-1), mitofusin –2 (MFN-2), presenilin associated rhomboid –like (PARL) and optic atrophy (OPA1) genes has been reported for NTG [30-33]. Among these genes, OPA1 gene is interesting because many clinical characteristics of NTG are similar to OPA1. Therefore, it is possible that pathogenic mutations in OPA1 gene may be responsible for NTG. The OPA1 gene encodes a protein involved in mitochondrial metabolic functions. Hence it was proposed that NTG could be considered as a hereditary optic neuropathy of mitochondrial dysfunction [34]. However, the above mutational studies on OPA1 gene are based on relatively small sample sizes and more comprehensive studies did not reveal an association with OPA1 gene polymorphisms [31,35-38]. This could be due to ethnic differences in the association between OPA1 gene polymorphisms and NTG. There are also inconsistent reports regarding OPTN gene association with NTG [39-40]. It is likely that mutations in the OPTN gene are associated with rare cases of NTG patients and families. However, the mechanism involved of OPTN gene in glaucoma pathogenesis remains elusive.

Similarly, apolipoprotein E (ApoE) polymorphisms were reported to be associated with Chinese and Tasmanian populations [41-42] but not in another population [43]. In German population, studies suggest that myocilin (MYOC), OPTN and WDR-36 (tryptophan and aspartic acid repeat domain 36) gene variants are rare causes of NTG [44-48]. Mutations in these genes are already known to be associated with POAG that are characterized by elevated IOP. This may suggest that mechanisms of development of NTG may be very complex. Matrix metalloproteinases (MMP-9 and MMP-14) are involved in tissue modeling in glaucomatous optic neuropathy [49]. These metalloproteinases (genes) are found to be upregulated in NTG [50]. Similarly, an altered gene expression in lymphocytes has been found in NTG patients [51]. The significance of these findings in relation to NTG remains to be elucidated. Many other genes have also been studied for their involvement in NTG but they are not found to be associated with NTG (Table 1) suggesting that they may not have any role in the pathogenesis of optic neuropathy in NTG.
Table 1. A partial list of genes that are reported to be either associated or not associated with NTG

| Gene  | Association | No association |
|-------|-------------|----------------|
|       | Seq. change | Reference      | Gene  | Reference |
| OPA1  | IVS 8+4 C to T | [86]           | ApoE  | [43]       |
|       | IVS 8+32 T to C | [31,38,87]     | LHON  | [92]       |
| OPTN  | Met98Lys    | [88]           | p53   | [93]       |
|       | His26Asp    | [89]           | Toll-like R2 | [56]   |
| Glu50Lys | 677 C to T | [90]           | IL-1 alpha | [94] |
| MTHFR |              | [91]           | IL-1 beta | [95]   |
|       |              |                | LOXL-1 | [96,97]   |

OPA1 = optic atrophy; OPTN = optineurin; ApoE = apolipoprotein E; LHON = Leber’s hereditary optic neuropathy; p53 = tumor suppressor protein; IL-1 = interleukin-1; MTHFR = methylenetetrahydrofolate reductase; LOXL-1 = lysyl oxidase like 1; IVS = intervening sequence.

Endothelin-1 is a vasoconstrictor and hence it may reduce the blood flow to the optic nerve head [52]. This may result in ischemia and that may cause RGCs death. It is also possible that it may change the axonal transport of the optic nerve that may have direct effect on optic nerve function [53]. In accordance with this is the finding of association of endothelin receptor type A gene polymorphism with NTG [54-55]. Although the function of this 3'-untranslated region (UTR) polymorphism is unknown, it may alter the level of gene expression. Similarly, toll-like receptor 4 (TLR4) mediate immune response to exogenous and endogenous ligands [56]. They may also interact with heat shock proteins which are implicated in glaucoma. Multiple SNPs in the TLR4 gene are reported to be associated with the risk of NTG in some populations but not in a Korean population [57-58]. In particular, one SNP (rs 7037117) in the 3'-UTR of the TLR4 gene is associated with NTG and this may also participate in the regulation of mRNA stability, translation and localization. Although the immunoregulation of heat-shock proteins is an important component of glaucoma [59] the factors contributing to the development of NTG have not been understood. In addition, natriuretic peptide gene polymorphisms and HLA-DRB1 gene are not associated with NTG suggesting that these genes do not play a role in the pathogenesis of NTG [60-61].

1.2 Animal Models

Transgenic mice expressing mutant human MYOC [62-63], OPTN [64] and WDR 36 [65] genes have been developed. These mice exhibited glaucoma. These heterologous mutant genes also affected retinal ganglion cell growth leading to a progressive retinal degeneration. For instance, E50K mutant OPTN gene selectively induced the death of RGCs and this was inhibited by antioxidants [66-67] suggesting that cell death was mediated by oxidative stress. Animal models representing NTG have also been developed but some of them are suitable as models of ischemia or optic nerve injury [68-69]. However, one model is particularly interesting for further discussion. For instance, it is well known that glutamate is the major excitatory neurotransmitter in the mammalian retina. Therefore, it is suggested that excessive stimulation of glutamatergic system could be the risk factor for the death of RGCs in glaucoma [70-71]. The solute carrier family 1 member 3 (SLC1A3) gene encodes a gliotype glutamate aspartate transporter (GLAST). This transporter is regulated to remove glutamate from the extracellular fluid in the retina. Because of this, extracellular glutamate concentrations will be kept below the neurotoxic level. Therefore, it has been proposed that GLAST dysfunction and the resultant elevation of glutamate levels may contribute to the death of RGCs in glaucoma patients. In accordance with this is the finding that mice deficient
with GLAST and excitatory carrier –1 (EAAC-1) exhibit spontaneous RGC death and optic nerve degeneration without elevated IOP [72-73]. However, there were no statistically significant differences in the allele frequency of SLC1A3 gene between NTG and normal patients [74]. Similarly, apoptosis signal-regulating kinase –1 (Ask-1) deficient mice are less susceptible to ischemic injury [75]. Studies on GLAST+/−: Ask-1−/− and GLAST−/−: Ask-1−/− mice suggest that Ask-1 activation is involved in NTG like pathology in both neural and glial cells. They also exhibit reduced RGC death, decreased axonal loss and mild visual disturbance [76]. These animal models are a powerful system for investigating mechanisms of neurodegeneration in NTG and developing therapies directed at IOP independent mechanisms of RGCs death [72]. In this respect, Ask-1 may be a potential therapeutic target for NTG.

1.3 Concluding Remark

Glaucoma is one of the leading causes of irreversible blindness. It is characterized by progressive degeneration of retinal ganglion cell and optic nerve. Although glaucoma is associated with elevated IOP, studies have shown that a subset of patients with POAG has normal IOP. This condition is called NTG and patients with NTG show typical pathological cupping of the optic nerve. Hence factors other than elevated IOP are likely to play a role in the pathogenesis of glaucomatous optic neuropathy in individuals with NTG. In support of this proposal is the finding that in some glaucoma patient’s significant IOP reduction does not prevent progression of disease [12,13]. Glaucoma including NTG is a genetically complex disorder and genes play a significant role in the pathogenesis. A complex glaucoma pathogenesis may include interplay among several factors such as genetic, epigenetic and environmental factors.

At present IOP is the only modifiable risk factor for the prevention or progression of glaucoma and low IOP is associated with reduced progression of visual field defect [77-78]. However, this cannot be applied to NTG. Recent development on stem-cell therapy may be interesting. The initial results of clinical trials in patients using stem-cell therapy showed some visual benefits with no sign of tumorigenicity [79-84]. Therefore, stem-cell therapy may be a promising approach to treat patients with retinal disease in the future. However, further research will be needed and an understanding of the role of epigenetics is also important to the success of the stem cell-based therapies [85]. In the future, studies will uncover the epigenetic mechanism contributing to glaucoma. A strong emphasis must be placed on epigenetics in the analysis of complex phenotypic variation. It may be necessary to develop a human methylation map to understand the difference in transcript expression. Epigenetic mechanisms in ophthalmology are truly exciting areas of research.

COMPETING INTERESTS

Author has declared that no competing interests exist.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.
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