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# **Emerging Concept of Genetic and Epigenetic Contribution to the Manifestation of Glaucoma**

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<http://dx.doi.org/10.5772/52279>

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## **1. Introduction**

In recent years many mutations in genes that are responsible for several Mendelian eye diseases have been identified and characterized. Genome-wide association studies also advanced our knowledge of complex diseases [1-4]. However, for many diseases, variation in phenotype with a single genotype, disease susceptibility among individuals, discordance in monozygotic twins, progressive nature of the disorder and age-related onset cannot be explained by accumulating mutations alone [5-6]. Therefore, there must be another layer of information. This missing link could be epigenetic factors. The term epigenetics refers to the mitotically heritable changes in the pattern of gene expression without any changes in the DNA sequence and the term epigenomics denotes the study of epigenetics on a genome wide basis. Epigenetics is an emerging field in ophthalmology and is involved in the regulation of gene expression during normal eye development. It has also a role in the etiology and progression of several common human diseases [7]. Epigenetic regulation through environmental factors such as diet, smoking and pollution may result in changes in gene expression that may lead to an increase in disease susceptibility, variation in phenotype and progressive nature of many common diseases such as age-related macular degeneration and glaucoma. These epigenetic changes may be age-related and cell or tissue specific. They may also persist throughout the lifetime of an individual. An understanding of the role of epigenetics is important to the success of the stem cell-based therapies [8]. Although epigenetic studies on glaucoma are limited at present [9], in this short article, an attempt has been made to summarize this emerging concept of genetic and epigenetic contribution to the manifestation of glaucoma.

## 2. Genetic contribution to glaucoma: Classification and pathophysiology

Glaucoma is a group of complex, genetically and clinically heterogeneous condition and affects all age groups throughout the world [10]. Approximately 70 million people worldwide are affected and it is one of the leading causes of bilateral blindness in humans [11]. The glaucomas are classified into primary and secondary glaucomas and within these two groups the disorder is divided into primary open-angle (POAG; the trabecular mesh work seems to be open and unobstructed by the iris), primary closed angle (PCAG; partial or complete anterior chamber angle closure) and primary congenital glaucoma (PCG; which mainly affects children). The disorder is characterized by the progressive degeneration of the retinal ganglion cells (RGCs) and is frequently associated with elevated intraocular pressure (IOP) [12]. A host of genetic and environmental factors contribute to the glaucoma phenotypes. For instance in certain population, older age, history of thyroid diseases, higher IOP and high myopia have been reported to be significant risk factors for POAG [13-16]. Similarly, drinking coffee, antioxidant intake and post menopausal hormone use may influence the development of POAG. These environmental risk factors exert their effects on IOP (by decreasing or increasing) and/or the rate of retinal ganglion cell apoptosis. In advanced glaucoma, the cone photoreceptors were also affected suggesting that photoreceptors may also be sequentially damaged in the disorder [17].

Epidemiological studies suggest that POAG is the most common type of glaucoma in most populations and is consistently associated with elevated IOP [18-19]. 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 [20]. In NTG, the optic nerve head is just susceptible to normal IOP. This may be due to the difference in the ultra structure of the optic nerve head or due to micro-level of biochemical agents. It is only a limited subset of patients with elevated IOP will develop POAG. This is consistent with the finding that, a significant number of glaucoma patients although respond well to therapies to lower the eye pressure, continue to lose vision [21-22]. Many individuals have IOP elevation without optic nerve damage (they are considered as having ocular hypertension) and some individuals develop optic nerve degeneration without elevated IOP [10]. 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 [10, 23-24]. Recent research suggests that transforming growth factor - beta (TGF - beta) and tumor necrosis factor - alpha (TNF - alpha) signaling pathways may contribute to the optic nerve disease in glaucoma [10].

## 3. Primary open-angle glaucoma (POAG)

The genetic basis of glaucoma is not fully understood. However, familial aggregation, occurrence of bilateral PCG in monozygotic twins and environmental factors such as advanced age, race, vascular risk factors, diabetes and hypertension suggest a multifactorial contribution to the etiology of the disease [12, 25-26]. Although details about the inheritance of the

disease remain unclear, candidate gene, genome-wide association and traditional linkage studies have identified at least 14 chromosomal loci that are influencing POAG [27-29]. However, glaucoma-causing genes have been identified in only three of these loci including myocilin (MYOC; also called GLC1A), optineurin (OPTN) and WDR 36 (tryptophan and aspartic acid repeat domain 36). Subsequent studies have demonstrated that mutations in MYOC and OPTN genes are associated with POAG accounting for less than 5% of all POAG cases [29-30]. The WDR 36 gene may be a minor disease-causing gene in adult onset POAG [31] at least in German population. This suggests that more than 90% of the genetic contribution of POAG cases is unknown. Additionally, association studies have identified at least another 27 genes (Table 1) that are reported to be involved in glaucoma. However, these results are either not replicated in other populations or contradictory and hence their role in glaucoma is not still understood. Recently, genome wide association studies have also identified Si RNA binding domain 1 (SRBD1) and fatty acid elongase 5 (ELOVL5) genes as new susceptibility genes for NTG [32] as well as POAG but their significance remains to be established.

#### 4. Biology of mutant genes

Although the exact role of MYOC and OPTN genes in the pathogenesis of glaucoma is unknown, it was suggested that myocilin might be involved in the trabecular meshwork (TM) homeostasis. Interestingly, MYOC mutations Y437H and I477N were shown to sensitize cells to oxidative stress induced apoptosis. Similarly, invitro transfection experiments suggested that mutations in MYOC might also cause mitochondrial defects that may lead to TM cell death. Additionally, biological and cell biological studies demonstrated that mutant MYOC was misfolded and accumulated in the endoplasmic reticulum (ER). This leads to ER stress and activates the unfolded protein response that may cause cellular toxicity and death. However, MYOC gene overexpression is not a cause or effect of elevated IOP. Similarly, OPTN may have a role in reducing the susceptibility of RGCs to hydrogen peroxide-induced cell death. Mutations in OPTN gene may also cause oxytosis and apoptosis. For instance, OPTN gene regulates endocytic trafficking of transferrin receptor that is important for maintaining homeostasis. The E50K mutation of OPTN was shown to impair with trafficking and this may have implications for the pathogenesis. The TM is the target tissue in the anterior chamber. The development and progression of glaucoma was reported to cause the oxidative damage to the tissue. These changes can be minimized by the use of anti-oxidants and IOP lowering substances. Therefore, it is possible to reduce the progression of POAG by preventing the oxidative stress exposure to the TM tissue. The WDR gene on the other hand, encodes a member of the WD (tryptophan and aspartic acid) repeat protein family and the members of this family are involved in a variety of cellular processes such as apoptosis and signal transduction. Mutations in the gene may interfere in its normal functions. Despite strong genetic influence in POAG pathogenesis, only a small part of the disease can be explained in terms of genetic mutations.

Gene	Chromosomal location	Gene	Chromosomal location
ANP	1p36.2	TNF	6p21.3
MTHFR	1p36.3	NOS-3	7q36
GSTM1	1p13.3	PON1	7q21.3
IL-1beta	2q14	TLR4	9q32-q33
NCK2	2q12	IGF2	11p15.5
OPA1	3q28-q29	CDH1	16q21.1
PARL	3q27	TP53	17p13.1
EDNRA	4q31.2	APOE	19q13.2
CDKN1A	6p21.2	NTF4	19q13.3
HSPA1A	6p21.3	AGTR2	Xq22-q23

ANP = Atrial natriuretic peptide; MTHFR = methylenetetrahydrofolate reductase; IL-1beta = interleukin 1-beta; NCK = adapter protein 2; OPA1 = optic atrophy-1; PARL = presenilin associated rhomboid-like; EDNRA = endothelin receptor type A; CDKN1A = cyclin dependent kinase inhibitor 1A; HSPA1A = heat-shock 70 kD protein 1A; TNF = Tumor necrosis factor; NOS-3 = nitric oxide synthetase -3; PON1 = paraoxonase -1; TLR4 = toll-like receptor 4; IGF2 = insulin-like growth factor 2; CDH-1 = E-cadherin; TP53 = tumor protein p53; APOE = apolipoprotein E; NTF-4 = neurotrophin 4; AGTR2 = angiotensin II receptor type 2; GSTM1 = glutathione S-transferase mu 1; Asterisk (\*) = detailed references can be found in ref. # 18.

**Table 1.** A partial list of genes that are reported to be associated with POAG and NTG \*

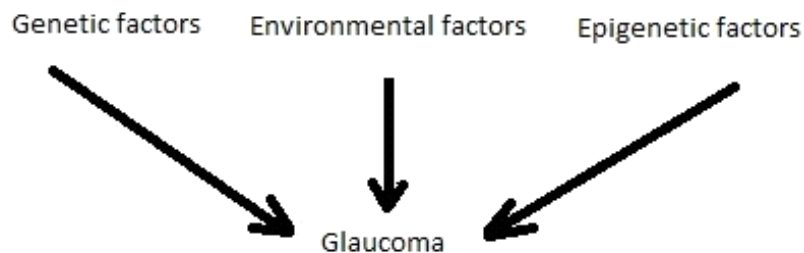
**5. Primary angle-closure glaucoma (PACG)**

PACG also involves progressive and irreversible degeneration of the optic nerve with gradual visual field loss. It is estimated that in Saudi Arabia 40% of glaucoma patients belong to PACG. Although hereditary component for PACG exists, causative genes have not been identified except occasional differences in the frequency of polymorphisms in some genes. For instance, variations in Best disease (BEST1), hepatocyte growth factor (HGF), matrix metalloproteinase - 9 (MMP-9) and methylenetetrahydrofolate reductase (MTHFR) genes have been reported [28]. However, some of these results were not extended to other populations.

**6. Primary congenital glaucoma (PCG)**

In children, PCG is an important cause of visual loss and diagnosed during the neonatal period. It is a heterogeneous group of disorder and is characterized by an elevated IOP due to an abnormal development of the aqueous outflow system. The majority of PCG cases are sporadic but there are some familial cases. The familial condition is inherited as an autosomal recessive trait with variable expression and penetrance. Recently three PCG loci (2p21, 1p36 and 14q24.3-q31.3) corresponding to GLC3A, GLC3B and GLC 3C genes respectively, have been

mapped. More than 60 different mutations in CYP1B1 (or GLC3A) – a member of the cytochrome P450 superfamily enzyme-encoding gene - have been reported in several PCG families [33-38]. Mutations in CYP1B1 were associated with wide range of phenotypes and the alterations of this gene could impair the morphogenesis of the outflow angle because it has been suggested that CYP1B1 gene participates in iridocorneal angle development [39]. In short, the current concept of glaucoma pathogenesis (Fig. 1) suggests that it is a group of heterogeneous optic neuropathies caused by genetic, epigenetic and environmental factor [40].



**Figure 1.** A complex glaucoma pathogenesis may include interplay among several factors such as genetic, epigenetic and environmental factors.

## 7. Inherited glaucoma in animals

Inherited glaucoma also occurs in several breeds of dogs including beagles. Primary glaucoma in beagles is inherited as an autosomal recessive trait and appears when the animals are 9 to 18 months old. The pathogenesis, clinical signs and pharmacological responses of glaucoma in beagles have been investigated and reported previously [41-43]. Glaucoma in beagles however, does not involve mutations in MYOC and CYP1B1 genes [44-45]. Similarly, mutations in MYOC gene are unlikely to play a role in the pathogenesis of PCAG in Shiba Inu dogs [46]. Recently, a candidate gene for the beagle model has been isolated [47] and the mutant protein is suggested to be altering the processing of the extracellular matrix that may affect the aqueous humor outflow thereby contributing to the elevated IOP. However, the mechanism underlying RGCs death is not well understood. Interestingly, it was reported that impaired neurotrophin signaling or compromised trophic support as well as p53 mediated apoptosis may not be the underlying mechanism of RGCs death in a beagle model of glaucoma [48]. Recently, there has been some success in stem cell therapy in animal models [49]. Transplantation of induced pluripotent stem (iPS) cells restored retinal structure and function in degenerative animals. Therefore, these animal models are very useful in further understanding of the pathogenesis as well as drug development in glaucoma.



## 8. Pigmentary dispersion syndrome, pigmentary glaucoma and Axenfeld-Rieger syndrome

A number of ocular conditions such as pigment dispersion syndrome (PDS), Axenfeld-Rieger syndrome (ARS) can lead to secondary open-angle glaucoma. PDS affects the young people and is characterized by the presence of TM pigmentation, iris-transillumination defects, Krukenberg spindle and backward bowing of the iris [50]. It is transmitted in a direct linear manner from parent to sibling [51]. Genetic analysis revealed a homozygous mutation (C677T) in methylenetetrahydrofolate reductase gene (MTHFR) in a patient [52] and the higher level of plasma homocysteine was suggested to be associated with pigmentary glaucoma. Additionally, a gene responsible for the PDS has been mapped to chromosome 7q35-q36 [53]. Regarding pigmentary glaucoma, the risk of developing it from PDS is about 10% at 5 years. Young myopic men are most likely to develop the disorder [54]. Interestingly, PDS and pigmentary glaucoma are not associated with mutations in lysyl oxidase like-1 (LOXL1) and tyrosinase related protein-1 (TYRP1) genes [55-56]. Another anterior segment disease with the risk of developing congenital glaucoma is called ARS. It is a rare autosomal dominant disorder with genetic heterogeneity and exhibits a range of congenital malformations of the anterior segment of the eye. In addition, patients with ARS may present systemic malformations such as mild tooth abnormalities, craniofacial dysmorphism, sensory hearing loss and congenital heart defect. It is caused by mutations in paired-like homeodomain 2 (PITX2) and forkhead box C1 (FOXC1) genes [57-61]. In the United States, it has been estimated that mutations in PITX2 and FOXC1 genes are associated with 25% - 30% cases of ARS [62]. In severely affected patients, digenic inheritance of mutations in PITX2 and FOXC1 has also been reported [63].

## 9. Epigenetics: Three major types of epigenetic modifications

A vast spectrum of epigenetic changes has been described. The most common epigenetic variations involve DNA methylation, various modifications of histones, microRNA (miRNA) and small non-coding RNA expression. All these factors can modulate the expression of genes that in turn may affect phenotypes and response to drugs. DNA methylation may be tissue specific [64] and disrupts the transcriptional activity of genes by affecting the accessibility of transcription factors. A large number of CpG residues are concentrated in a region of DNA sequence (CpG island). Methylation of cytosine may reduce or prevent the binding of sequence specific transcription factors. This results in changes in gene expression. The CpG region methylation also regulates the expression of a large number of miRNA. On the other hand, genomic hypomethylation may lead to genome instability. This kind of epigenetic abnormality can be influenced by environmental factors such as tobacco smoking, dioxin and nutrition [65] and can lead to complex disorders. Studies including monozygotic twins also suggest that non-Mendelian and complex diseases (including neurological and psychiatric disorders) are likely to be caused by the combination of genetic and epigenetic factors [66]. DNA methylation and its maintenance may depend upon chromatin-associated

factors and histone modifications but it is not clear how DNA demethylation process is achieved [67-68].

The other epigenetic marks are posttranslational modifications such as acetylation, methylation and phosphorylation of N-terminal tails of histone proteins. They may also regulate gene activity [66] because they affect the chromatin structure. For instance, acetylation of histone H3 and H4 leads to the formation of euchromatin and deacetylation leads to heterochromatin (tightly packed) formation (see below). These can also be influenced by environmental factors such as diet. Similarly, miRNAs regulate (down regulation) the translation of mRNAs by binding to their complementary sequence in the 3'untranslated region [69] and small RNAs are involved in gene silencing at the transcriptional level [70].

## 10. The potential role of epigenetics in glaucoma

The eye is a model organ for epigenetic studies because external ocular tissues are exposed to the outside environment and may be sensitive to epigenetic effects. Although the epigenetics is well known in diseases such as cancer [71], and hereditary and environmental determinants have been long suspected for eye disorders [72], epigenetic studies on eye disorders are slowly progressing [9; 73-74]. For instance, retinal and lens differentiation involves specific changes in DNA methylation, expression of non-coding RNA and nucleolar organization [73]. In addition, cell-specific DNA methylation may play an important role in modulating eye specific genes [64]. Similarly, histone modifications were involved in the pathologic course of retinal ganglion cells [75] and site-specific DNA hypomethylation permits the expression of interphotoreceptor retinoid binding protein (IRBP) gene [76]. Overexpression of mutant OPTN (E50K) is also found to induce RGC apoptosis [77-78]. Recently, it was also shown that histone deacetylase 4 (HDAC4) was involved in the survival of retinal neurons by preventing apoptosis of rod photoreceptor and bipolar cells [79-80]. Additionally, histone acetyltransferase p300 was found to promote intrinsic axonal regeneration [81]. Similarly, in an animal model (rat/mice), it has been observed that there was a regional gene expression changes including pro-survival, pro-death and acute stress genes [82-84]. Moreover, miRNAs can act as either oncogenes or tumor suppressor genes and can influence the growth of uveal melanoma [85]. Similarly, smoking and nutritional factors were involved in the etiology of age-related macular degeneration (AMD) in addition to genetic susceptibility [65].

Another example to illustrate the epigenetic effect is the pseudoexfoliation syndrome (XFS), which is one of the most common subtypes of POAG. It is the major risk factor for secondary POAG. The condition is characterized by a pathological accumulation of the whitish material in the anterior segment of the eye, predisposing to glaucomatous optic neuropathy [86]. The disorder is frequent among Icelanders, increases with age and rarely identified in people below the age of 50. Mutations in the LOXL1 gene were found to be associated with XFS in the Caucasian Australian population. [87]. However, this does not account for the large difference in disease prevalence between different populations. This raises the possibility of unidentified genetic, racial and environmental modulators [88]. In support of this is

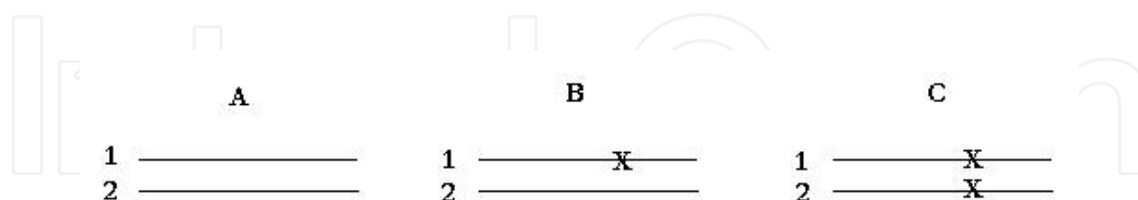


the finding that XFS may be associated with geographic and climatic factors such as sun exposure and ambient temperature [89]. The mechanisms involved are not known at present. Retinal cell death, the most common pathophysiology of all forms of glaucoma involves many factors such as oxidative stress, mitochondrial dysfunction, excitotoxic damage, axonal transport failure, deprivation of neurotrophic factors and activation of intrinsic and extrinsic apoptotic signals [90-91]. Some of these could be modulated by epigenetic changes. In support of this is the finding that heavy smoking, exposure to pesticides and nutrient intake was significantly associated with POAG [92-94]. This suggests that the interaction between gene and environmental factors may play a role in the pathogenesis of glaucoma. Intrauterine exposure (obesity and diabetes), variable DNA methylation and environmental factors may also have profound influence on adult epigenetic status. Thus in general, epigenetic may provide an additional layer of important information on inherited as well as age-related eye disorders including glaucoma.

## 11. Pharmacogenetics and pharmacoepigenetics in glaucoma

Adverse drug reactions (ADRs) and individual variations in drug response were well known in medicine. There are many systemic and other drugs that produce adverse effects in eye care [95-96]. For instance, many steroid drugs induce glaucoma in some patients [97]. Therefore, efficacy and safety are important aspects of initiation of any medication. Presently, there are no biochemical markers (proteins or genes) to predict which group of patients develops ADR and which group does not. Physicians in all medical branches have to make a guessing game to find out, which medication will work best for a given patient. This trial-and error method is often inefficient. Now because of the advancement in genetics, physicians will have better opportunities to treat individual patients based on their genotype (Fig. 2). In order to understand the relationship between genes and inter-individual variations in drug response, two related fields namely pharmacogenetics and pharmacogenomics have been developed. They have taken massive studies on genetic personalization of drug response [98]. Some of the pharmacogenetic studies that are related to eye disorders including glaucoma have been discussed previously [99-100]. For instance, heterozygosity in N363S mutation in glucocorticoid receptor gene has been found to be associated with steroid induced ocular hypertension in Hungarian population although it may not be the major risk factor in the pathogenesis of elevated IOP. Similarly, a beta-adrenergic antagonist timolol has been used for the treatment of glaucoma. However, a topically administered eye drop may cause adverse cardiovascular and respiratory effects. Recent investigation of a single nucleotide polymorphism (SNP) in beta-adrenergic receptor suggests that this polymorphism may be associated with positive clinical response to topical beta-blockers. In addition, R296C polymorphism in CYP 2D6 (cytochrome P450) gene may confer susceptibility to timolol induced bradycardia. Patients with CC genotype were unlikely to suffer from timolol induced bradycardia and those with TT genotype were found to suffer. Many studies address the pharmacology of several glaucoma medications but it is still not possible to explain the variable IOP response to glaucoma drugs between patients [101] using their

genotype alone. This missing link could be due to several factors including environmental factors such as chemicals, alcohol, tobacco, diet and other drugs. In addition, age and gender may contribute to the physiological and biochemical status of the targeted cells (with respect to gene expression). Therefore, it is not simply genetics or environment but it is the interplay between them that is important in pharmacology and medicine.



**Figure 2.** A schematic illustration of the relationship between genotype and drug response of an individual. Two horizontal lines 1 and 2 (panels A to C) denote a pair of homologous genes encoding a drug-metabolizing enzyme. In panel A, genes are normal and hence the individual is a fast responder and metabolizes the drug more efficiently. Therefore high doses are needed to treat. In panel B, the individual is heterozygous for the mutation and metabolizes the drug slowly. Therefore, lower doses are needed to avoid side effect or toxicity. In panel C, the individual is homozygous for the mutation and metabolizes the drug very poorly. Therefore, it may have fatal effect. The X mark denotes mutation.

## 12. Concluding remarks

Epigenetic is an emerging field in ophthalmology. One benefit of understanding epigenetic changes is at the level of treatment. Epigenetic modifications are reversible. For instance, disease associated DNA methylation can be reversed by inhibitors such as adenosine or deoxycytidine. However, these reagents might become cytotoxic and may lead to a wide spread DNA hypomethylation that may be resulting in and causing destabilization of genome. We need to develop less toxic inhibitors of DNA methyltransferases. Similarly, inhibitors of histone deacetylase (HDAC) may have some therapeutic applications. For instance, HDAC inhibitors have been found to have protective effects in animal model of ischemia and optic nerve damage in the retina [71, 102-103]. 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 [104-105]. 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 [106-111]. 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 [8]. 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.

## Glossary

Apoptosis: genetically programmed cell death

Chromatin : a complex of nucleic acids and proteins

Euchromatin: a less condensed, mostly transcriptionally active chromatin

Heterochromatin: a highly condensed chromatin

Histones: small DNA binding proteins

miRNA: short regulatory non-coding RNAs

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