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The Genetics of Primary Open Angle Glaucoma Interventions: Therapeutic Directions and Future Predictions

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Authors' contributions

This work was carried out in collaboration among all authors. Author BCU designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors BCU, MOA, CC, TE, LU, BA and SNI managed the literature searches of the study. All authors read and approved the final manuscript.

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ABSTRACT

The "multifactorial chronic optic neuropathy" known as primary open angle glaucoma (POAG) is typified by a "progressive loss of retinal ganglion cells (RGC), structural damage to the retinal nerve fiber layer (RNFL) and optic nerve head (ONH), as well as abnormalities in the visual field." High

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intraocular pressure (IOP), age, genetics, family history, race, etc. are the main risk factors. One of the pathological implications of POAG is “pressure-induced” ONH damage, which results in modifications to the expression of retinal genes. The ensuing fluid backup raises IOP, which damages optic nerve and results in POAG. Numerous susceptibility genes and environmental factors contribute to the “genetic heterogeneity” of POAG, according to genetic studies. “A set of twelve chromosomal loci, referred to as GLC1A through GLC1L, have been mapped for POAG. Three genes—myocilin (MYOC), optic neuropathy-inducing protein (Optineurin, OPTN)), and WD repeat domain 36 (WDR36)—have been identified as the GLC1A, GLC1E, and GLC1G”. A better understanding of the molecular genetic pathways and the pathological mechanisms involving the disease-causing genes, may help clarify the pathophysiology that leads to the disease and a targeted treatment. The role of genetics in POAG highlights the importance of genes in recent research advances, their future directions, applications, and therapy. The advent of modern genetic discoveries and future directions in vector engineering makes the cure for POAG possible. The paradigm shift in glaucoma treatment has moved from direct RGC and ONH therapy to targeting associated brain centers.

Keywords: Primary open angle glaucoma: glaucoma gene; mutation; gene locus; gene therapy; genetic mapping; mendelian inheritance; gene transfer vector transduction; vector engineering.

1. INTRODUCTION

POAG is a complex type of glaucoma with multiple causes. “It is a chronic optic neuropathy distinguished by the progressive loss of retinal ganglion cells, leading to structural damage to the ONH and RNFL, and resulting in visual field defects” [1]. Although the exact origin is uncertain, POAG is mostly thought to be caused by "inefficiency" of the trabecular meshwork (TM), which slows down the aqueous outflow facility and causes an “imbalance in the aqueous humor's (AH) production and drainage, raising the IOP” [2].

Gene mutation is the genetic basis of POAG, and these POAG mutation-causing genes are grouped into two distinct classes with very unique characteristics. First-class mutations have minimal effects from other genes or the environment and can cause POAG on their own. These single-gene variants of glaucoma often have an “autosomal dominant” inheritance pattern and are inherited according to the Mendelian trait. These mutations are uncommon in normal eyes and always result in POAG. The genes that cause POAG mutations are the MYOC and OPTN genes. Risk alleles are a class of mutations that may help induce POAG in conjunction with other glaucoma risk alleles and environmental variables, but they may not cause the disease on their own [3].

“There are roughly 12 chromosomal loci in POAG, which are mapped and given the names GLC1A through GLC1L. The GLC1A gene on 1q23-q25, the GLC1E gene on 10p15-p14, and the GLC1G gene on 5q22.1 have been identified as MYOC, OPTN, and WDR36, respectively. Among these, OPTN is especially connected to cases of NPG”. Of the families with hereditary POAG, 16.7% have OPTN mutations. Eighty percent of those families carried the most common E50K mutation. Of those impacted by E50K, 18% exhibited elevated IOP readings, while the rest had normal values [4]. There are a wide range of genetic techniques and approaches to treatment of POAG and future cures, including genetic screening, gene manipulations, and the use of various models towards future therapeutic directions. New therapeutic techniques that directly target axonal integrity and prevent cell death have emerged recently, including promising gene therapy-based strategies. These efforts are part of the ongoing search for an effective means of combating “neurodegeneration”. With routine genetic screening for disease susceptibility, an appropriate diagnosis of glaucoma in patients could be highly beneficial. The development of clinical characteristics that characterize glaucoma phenotypes linked to certain mutations is necessary before DNA-based diagnostic testing may yield any meaningful clinical data. The genetic testing for MYOC and OPTN mutations makes understanding of the underlying pathophysiology clearer. This prompts the creation of fresh DNA-based diagnostic procedures and treatment modalities [5]. Advances in the field of vector engineering during the past few years have yielded safe delivery systems that do not produce an

inflammatory response, are able to act locally, and have negligible distribution to organs other than the targeted eye [6].

2. THE GENETIC PREVALENCE

Globally, glaucoma is the leading cause of irreversible and preventable blindness. It is the second most common cause of blindness globally, impacting around 70 million people—more than 2.5 million of whom live in the United States alone. It is the primary cause of blindness among Black Americans and the third most common cause of visual impairment and blindness among White Americans [7]. Conversely, POAG accounts for 12.3% of blindness globally. The frequency of POAG in individuals over 40 is 1.86%. The prevalence of POAG varies significantly between ethnic groups; among black African populations, it might occur up to five times more frequently than in European populations. Blacks have a 3–4 times higher prevalence of POAG than Caucasians, and they are also up to 6 times more vulnerable to optic nerve injury [8]. Specifically, individuals of African descent are three to five times more likely to develop POAG, and they tend to experience a more severe progression of the disease, with a higher risk of blindness [9].

According to published data, 72% of all POAG cases may be attributed to hereditary and familial causes. While early twins studies found the heritability of POAG to be roughly 13%, population-based research has also shown familial clustering of POAG cases that suggests a genetic basis; first-degree relatives carry a lifetime glaucoma risk of 22%, which is a 9-fold greater risk. POAG heritability has been estimated to be 70% in recent and much larger studies, and 93% in more current researches. “At some point in their lives, relatives of POAG patients are at a 22% risk of acquiring glaucoma, while relatives of normal controls are at a 2-3% risk” [10]. Certain research has examined the relationship between genetics and familiarity. For example, “the Baltimore Survey found that 50% of patients with POAG exhibited positive familiarity”, indicating the significance of the genetic abnormality in the development of pathology [1].

3. GENETIC MECHANISMS AND PATHWAYS IN POAG

3.1 Genetic Mechanisms

1. According to genetic theories, axon cell loss is caused by a genetic propensity. This results in the release of chemicals such as glutamate, an excitotoxic neurotransmitter. Apoptosis in nearby cells is triggered, secondary to other molecules released into the environment, including free radicals, nitric oxide, and calcium [11].

2. It has been shown by transgenic mice that the GLU50LYS mutation in OPTN, causes retinal ganglion cells to die. They have proposed that a disturbance of the connection between OPTN and the GTP-binding protein Rab8 and its consequences for protein trafficking, could be the cause of OPTN-mediated glaucoma [12].

3. The trabecular meshwork cell (TMC) experiences apoptosis as a result of the unfolded protein response (UPR) triggered by the mutant MYOC protein, which causes endoplasmic reticulum (ER) stress. This ultimately results in glaucoma because of the increased resistance to aqueous humor outflow and elevated intraocular pressure (IOP). Three ER transmembrane proteins initiate a series of signaling cascades that are activated by ER stress. These three sensors play a major role in transducing UPR signaling: inositol-requiring enzyme 1 alpha (IRE1α), activating transcription factor 6 alpha (ATF6α), and protein kinase R-like endoplasmic reticulum kinase (PERK). Apoptosis occurs in cells when there is a persistent protein folding deficiency. Thus, cellular damage is the outcome of ongoing or chronic ER stress. However, in non-stressful circumstances, a glucose-regulated protein (GRP78), also referred to as binding-immunoglobulin protein (BIP) or 78 KD, binds to the luminal domain of PERK, IRE1α, and ATF6α to inhibit their activation. BIP dissociates from PERK, IRE1α, and ATF6α and binds to unfolded proteins when misfolded and unfolded proteins build up in the ER lumen. This promotes ATF6α translocation to the Golgi apparatus as well as PERK and “IRE1α homodimerization and autophosphorylation” [13].

4. MYOC seem to have a cell-specific relationship with the mitochondria within the TM and also the astrocytes. TMC that

overexpresses the Pro370Leu mutant MYOC exhibits signs of mitochondrial malfunction, which could make TM cells more susceptible to cellular assaults that could result in decreased function or possibly cell death. Pro370Leu mutant myocilin transfection may make TM cells more susceptible to different cellular stressors, resulting in decreased functionality and explaining the connection between myocilin and mitochondria. Reduced mitochondrial membrane potential, elevated levels of cellular reactive oxygen species (ROS), and diminished ATP production, along with impaired calcium regulation in the cytoplasm and mitochondria of TM cells, are indicative of mitochondrial dysfunction in TM cells overexpressing the Pro370Leu mutant myocilin [14].

5. Myocilin raises calcium levels, maybe via calcium channel dysregulation. The TM cells' calcium-dependent contractibility regulates the aqueous humor's outflow, preserving intraocular pressure. An excessive calcium input results from the L-type calcium channel not closing, which raises the intraocular pressure (IOP) and leads to membrane depolarization, TM contraction, and decreased outflow [14].

6. The ultimate result of all pathogenic pathways generating POAG is RGC death. There are numerous proposed processes for how this happens. These include oxidative stress, mitochondrial dysfunction, neurotrophic factors, autoimmunity, pressure-induced damage of the ONH that results in changes in retinal gene expression, and astrocyte response to IOP fluctuations. The lamina cribrosa bows backward as a result of elevated IOP, kinking the axons as they leave through the lamina pores. Cell death may result from focal ischemia, axonal neurotrophin depletion, or disruption of axoplasmic flow. A process exerts pressure on the RGC, leading to ischemia and hypoxia of the ONH, culminating in cell death due to oxygen and energy shortages and glutamate-induced excitotoxicity. Concurrently, levels of inflammatory mediators increase and the flow of trophic factors alters. These events cause axotomy, blindness, and obstruction of both anterograde and retrograde axonal transport [15].

7. Neurite outgrowth in neural cells was inhibited by overexpressing wild-type MYOC or the P370L and Q368X mutants, which may have potentially contributed to the onset of neurodegenerative glaucoma [16].

3.2 Epigenetics and Signaling Pathways

Epigenetics focuses on the changes in organisms resulting from the modification of gene expression rather than on changes to the genetic code itself. It involves the study of heritable variations that affect gene function without altering the “DNA sequence, leading to a change in phenotype without a change in genotype." In addition to being a naturally occurring and recurring shift, age, environment, lifestyle, and illness status can all have an impact. Increased risk of POAG is a result of genetic predisposition and environmental factors working together with epigenetics. Epigenetic changes can change cellular “signaling pathways," regulate gene expression, and increase or decrease an individual's vulnerability to different diseases. According to certain research, glaucoma may be related to low oxygen levels. Retinal development is governed by epigenetic mechanisms, and disturbances in these processes can lead to eye disorders like hereditary retinal ganglion cell degeneration, optic neuritis, and glaucoma. Lamina cribrosa cells demonstrate the impact of epigenetic factors in causing glaucoma, potentially offering new therapeutic targets. These factors operate through various pathways, including calcium-calpain signaling, Rho kinase, and TGF-β, among others [17].

3.2.1 Histone and DNA modification

Heritable nonencoded genetic alterations that activate or deactivate genes, such as DNA demethylation and histone acetylation, are the subject of epigenetics. It also involves modifications brought about by noncoding RNAs such as microRNA and long noncoding RNA (lncRNA), as well as repressive changes such as “histone deacetylation and DNA methylation.” Gene expression “and/or cellular signaling pathways” can be modulated by epigenetic alterations, which may impact an individual's susceptibility to a variety of disorders, including POAG [18].

3.2.2 Brain derived neurotrophic factor [BDNF]

A protein known as BDNF is produced by “the brain and retina, among other organs that support the growth, differentiation, and survival of neurons.” This protein is crucial for the survival of RGCs. BDNF and other neurotrophic factors are often carried to the RGCs from the brain. In glaucoma, on the other hand, the elevated IOP “decreases neurotrophic levels in the RGCs” by obstructing axonal transit at the optic nerve head [19].

3.2.3 Epigenetic pathways in collaboration with other predisposing factors

1. TGF-β signaling pathway: TIGR has been proposed by several authors as a potential gene for outflow blockage in glaucoma, given that corticosteroids can raise IOP in a significant proportion of glaucoma patients. One of the cytokines, TGF, is implicated in numerous signaling cascades that result in chemotaxis, proliferation, differentiation, or fibrosis. TGF-2 is the most relevant to the eye of the “three isoforms of TGF (TGF-1, TGF-2, and TGF-3),” as it has been linked to POAG pathophysiology [20].

2. Calcium-calpain pathway: Many neurodegenerative disorders, including glaucoma, are characterized by disruptions in calcium homeostasis. The extracellular calcium inflow into RGCs is accelerated by the elevated IOP associated with this condition. Calpain is a cysteine protease that cleaves calcineurin when it is activated by calcium. Calcineurin then causes BAD to be dephosphorylated and releases cytochrome c, which causes RGCs to undergo apoptosis [21].

3. Rho signaling pathway: By changing the contractile cell adhesive and permeability barrier that are typical of TM and Schlemmer's canal tissue, as well as by affecting the synthesis of extracellular matrix and fibrotic activity, the activation of Rho GTPase/Rho kinase signaling in the trabecular outflow pathway raises intraocular pressure. ”The Rho, Rac, and Cdc42 subfamilies” make up the Rho family, which is involved in actin cytoskeletal structure, adhesion, proliferation, and cell migration [22].

4. GENETIC BASIS OF POAG

4.1 Mutation of POAG Genes

Genetic changes known as mutations are enough to make a gene malfunction and result in disease. The genetic foundation of POAG is gene mutation. The mutations caused by POAG fall into two different types, each with their own special traits. First-class mutations have minimal effects from other genes or the environment and can cause POAG on their own.

These single-gene glaucoma variants often have “an autosomal dominant inheritance pattern” and follow the “Mendelian trait” inheritance pattern. Like the MYOC and OPTN genes, “these mutations almost always result in POAG and are rarely seen in normal eye”. Another category of genetic alterations is known as "risk alleles." While they might not independently cause disease, these mutations could hasten the progression of POAG when combined with other risk genes for glaucoma and environmental factors [3]. Genome-wide association studies (GWAS) “compare the genomes of patients with POAG to those with normal eyes to identify genetic risk factors and gene sequences that are statistically more prevalent in individuals with glaucoma” [23].

4.2 Gene Isolation in POAG

The advent of cost-effective, high-throughput DNA genotyping has made it possible to identify multiple genes that are involved in POAG vulnerability. Understanding these disease-causing genes sheds light on the fundamental pathogenesis of inheritable eye diseases. Identifying genes that cause a disease can reveal its important biological pathways and illuminate the mechanisms of the disease’s development. Specific mutations confirm a patient's diagnosis and can help predict their clinical trajectory. Many phenotypes of inherited eye diseases, like glaucoma, have been linked to particular mutations [24]. The genes responsible for POAG, specifically “myocilin (MYOC), optineurin (OPTN), and TANK binding kinase 1 (TBK1),” have shed light on the pathogenesis of glaucoma. These three genes can all have mutations that result in POAG, as a Mendelian characteristic inheritance. Mendelian POAG's disease-causing mutation presents an opportunity for targeted therapy to correct the particular molecular flaw the mutation causes [25].

5. PATTERN OF INHERITANCE IN POAG

“Glaucoma may be inherited as Mendelian dominant or Mendelian recessive traits (usually early-onset forms of the disease) or may exhibit

a heritable susceptibility consistent with complex trait inheritance (typically adult-onset forms of the disease)." In other words, all ages are susceptible to the disease, with early disease onset starting before the age of 40 and exhibiting Mendelian hereditary, while the adult onset sets in after the age of 40 and is inherited as complex features. Adult-onset glaucoma, such as POAG, has considerable heritability and “exhibits Mendelian inheritance patterns." The complexity of genetic contributions to certain diseases arises from the interplay of multiple genetic variables and environmental influences. Identifying the genes responsible for diseases with complex inheritance patterns is particularly challenging. Rare types of POAG that typically “affect children and young adults are inherited through Mendelian patterns," implying that a single gene can be passed down as either recessive or dominant traits. Consequently, while genetic variations associated with adult-onset glaucoma are common and have less significant biological effects, the genes responsible for early-onset glaucoma are uncommon and have more substantial biological impacts [5].

5.1 Simple/Single form of Genetic trait and Mendelian Inheritance in POAG

Although the genetics of glaucoma is complex generally, certain cases are primarily caused by abnormalities or mutations in a single gene. Early-onset open angle glaucoma (OAG) is among the many glaucoma variants that are often “inherited as Mendelian dominant or Mendelian recessive disorders." The simplest conceptual model for how genes can lead to disease is seen in Mendelian disorders. These diseases can result from a single genetic anomaly, and if this defect is transmitted by the parents to their children, the disease may be inherited. “Common forms of inheritance of Mendelian disorders include autosomal dominant, autosomal recessive, and X-linked recessive." “Such genetic alterations, sufficient to cause a gene to malfunction and result in disease, are termed mutations." “A classical Mendelian inheritance pattern is one in which a genotype at one locus is both necessary and sufficient for the phenotype to be expressed” [26].

5.2 Complex form of Genetic Trait and Inheritance in POAG

More complicated genetic bases underlie other cases of POAG, which result from the interaction of numerous genetic and environmental risk factors, none of which alone can cause glaucoma. Although these characteristics are equally widely identified in normal persons, they are more frequently detected in POAG patients. It is more challenging to discover genes that cause disorders with complex inheritance. From a conceptual standpoint, it may be said that no single risk factor is sufficient to cause a disease on its own and that not every case of disease will have each risk factor. In genetic research and clinical practice, taking into account “ethnic origin and familial aggregation,” the suggested classification could serve as a useful guide [27].

5.3 Complex form of POAG Inheritance Supported by Linkage Studies

“Glaucoma is characterized as a ‘complex' disease, with phenotype exhibiting heterogeneity, polygenic inheritance, phenocopies, and incomplete penetrance” [28]. Considering these glaucoma unique features, traditional linkage analyses have been extensively employed to determine the association of various forms of glaucoma with specific loci, using one or more families that have multiple affected members. As we enter the era of known genomic sequences, innovative genetic methodologies and techniques become essential for researching complex human diseases. Numerous genes have been discovered through traditional family linkage analysis methods, especially those with high penetrance that encode fundamental Mendelian disease traits [29].

5.4 Risk Alleles in POAG Mutation

The etiology of POAG is multifactorial, as it demonstrates a variable age of onset and severity. Among the risk factors for POAG are high IOP, aging, genetic disposition, environment, family history of POAG, African heritage, myopia, and maybe the existence of certain systemic disorders like hypertension and diabetes. Other risk factors are: race, central corneal thickness and refractive error. So far, “more than 25 POAG risk factor genes have been found,” and there are yet more to be found. In POAG, IOP is thought to be the most significant risk factor. However, glaucoma is not caused by these risk factors on their own [30].

5.4.1 Multiple genetic influence, familiarity and family history

Several genes have been identified as being connected with POAG. Though these genes only

account for less than 5% of all POAG in the general population, genetic impact plays a significant part in the development of POAG. It is believed that gene-environment interactions are significant and that the hereditary component of POAG is probably “polygenic.” It has long been known that a variety of “disease-causing mutations in the MYOC, OPTN, and WDR36 genes” are the root cause of familial types of POAG [31]. The US surgeon general has affirmed the importance of family history and familial aggregation. It has long been known that a strong hereditary component accounts for a significant number of inherited and familial cases of POAG [27]. “First and second degree relatives of affected patients are at risk because genetic variables account for 16–20% of the incidence of POAG,” according to studies. There is evidence of gene-gene interaction and a complex inheritance pattern that controls the process [17]. One of the strongest risk variables for POAG is family history. It is clinically significant because, according to the population-based Rotterdam Study, “first-degree relatives of POAG patients have a 9-fold higher lifetime risk of getting glaucoma than relatives of controls.” One of the risk factors for developing POAG is having a first-degree relative with the disease. Numerous studies have reported on this, with odds ratios ranging from 3 to 13. If a sibling of the affected relative is involved, the risk is assumed to be even higher. Compared to parents or children, siblings of an afflicted patient had the highest probability of having POAG [32].

6. TOOLS FOR MOLECULAR GENETICS IN POAG

An enhanced classification of POAG could emerge from discovering the specific genetic mutation responsible for the disease rather than relying on the current imprecise clinical categorization. Because glaucoma is heritable, molecular genetic tools may be used in its research and studies. The tools will offer the opportunity of identifying particular genes required to preserve a normal intraocular pressure and stabilize the optic nerve, in addition to identifying gene abnormalities linked to the disease [33].

6.1 Mendelian Autosomal Dominant and Autosomal Recessive trait in POAG Inheritance

“Glaucoma inheritance is complex with multifactorial trait. It is associated with the Mendelian autosomal dominant or autosomal recessive trait." Abnormalities in single genes linked with extreme phenotypes, such as severe optic nerve degeneration or significantly increased intraocular pressure, lead to Mendelian autosomal dominant and recessive types of glaucoma.

However, the majority of POAG patients do not exhibit extreme phenotypes. It is not believed that single gene abnormalities are the cause of the underlying genetic etiologies, but rather from the combined effects of several hereditary variables that, although individually cause mild changes in intraocular pressure and optic nerve damage, also jointly contribute to a more serious condition [34].

6.2 Epigenetics

Epigenetics is ‘‘the study of changes in gene function that are mitotically and/or meiotically heritable and do not entail a change in DNA sequence." It refers to the heritable changes in a cell's gene expression profile that are not due to alterations in the DNA sequence. Epigenetic modifications determine whether genes are active or inactive, due to the regulation of DNA. These alterations are connected to DNA and do not change the order in which the strands of DNA are arranged or the building block. These alterations might endure for several generations in addition to the rest of the cell's existence through cell divisions. “Within the complete set of DNA in a cell (the genome), all of the modifications that regulate the activity (expression) of the genes is known as the epigenome” [35]. Epigenetics causes a change in phenotype without a corresponding change in genotype, and it influences how cells interpret their genetic code. It may be employed to characterize attributes of an entire organism as well as attributes that are transmitted from a parent cell to its daughter cells during cell division. Rather than changing the genetic code itself, it deals with changes in organisms brought about by changes in gene expression. “This modification can modulate gene expression and/or alter cellular signaling pathways, which may affect individual susceptibility to various diseases. Epigenetic inheritance thus refers to the transmission of certain epigenetic marks to offspring." Its modifications, in contrast to genetics, are reversible; they do not alter the DNA sequence, but they can alter how the body interprets a DNA sequence. Although epigenetic modifications occur frequently and naturally, a

number of variables, including age, environment, lifestyle, and illness condition, might affect them. These elements may interact with the genome to affect how genes are expressed, which may show up at different times in an individual's life or even in the offspring. Moreover, epigenetic factors contribute to the onset of conditions such as glaucoma, specifically impacting the lamina cribrosa cells [36].

6.3 Linkage Analysis and Technique

The linkage technique is the most useful instrument being used to decipher the genetics of POAG. This method looks into the genetic causes of POAG by examining patterns of familial inheritance. It is useful for identifying the location of a disease gene without any prior understanding of the underlying pathophysiology of the disease. “The linkage analysis relies on the fact that genes that lie close to one another on a chromosome are less likely to be separated by the process of recombination during meiosis than those that lie far apart. Such genes will therefore tend to be inherited together and are described as “closely linked” [37].

6.4 Genome Wide Association Study (GWAS)

GWAS are another method of identifying genes contributing to complex diseases and POAG. They are powerful tools for investigating the genetic architecture of human diseases and are more effective than linkage analysis in identifying genes with marginal effects that could be involved in the onset of the disease. Thousands of GWAS have been conducted on the human genome to date in an effort to find Sops linked to a broad range of complicated human disorders. "All of the published GWAS results are kept up to date in an NIH database." “GWAS use single-nucleotide polymorphism (SNP) arrays to statistically identify relationships” between common genetic variants found in the human genome and disease. “They serve as biological markers, assisting researchers in identifying genes linked to specific diseases." GWAS offers the benefit of not requiring a specific disease model, in enabling the identification of areas involved in previously unknown pathogenesis. Although GWAS has identified more than ten genes associated with POAG on an individual basis, variants in these genes do not predict POAG in populations. They find genes that increase the likelihood of developing complicated types of POAG, which are brought about by the interaction of several genes, such as CAV1/2, CDKN2B-AS1, ATOH7, SIX1, TMCO1, TLR4, SRBD1, and ELOVL5 [38].

6.5 Sib-Pair Analysis

Sib-pair analysis offers important new information about the genetic makeup of glaucoma disorders. This method can clarify disease mechanisms and aid in the identification of susceptibility loci. It entails examining sibling pairs in order to determine the genetic characteristic trait or disorder. “The primary goal is to determine whether siblings who share a common genomic segment (measured by genetic markers) tend to express the same disease phenotype (or similar quantitative trait values).” There are no presumptions made by sib-pair analysis on the underlying genetic model. Finding genomic loci demands a high level of penetration. Siblings have different genetic markers genotyped. The parts of the genome inherited from a common ancestor are known as identical by descent (IBD) segments, and this is the focus of the investigation [39]. This method can be used by researchers to determine the genetic basis of complex features.

6.6. Family - Based Association Analysis

It has been stated that a key tactic in genetic association analysis is the family-based design. In this, “genotypes are divided into between-family and within-family components. The components are permuted separately, and then association analysis is performed on the within-family component, between-family component, or their sum." This offers the capability to enhance genetic loci with rare variants, population stratification, and heterogeneity management methods. Also genetic contributions from different loci can be directly estimated, variants can be transmitted alongside phenotypes, and the influence of an allele's parental origin can be discovered. However, “family-based association tests (FBAT) can apply any type of pedigree structure, including missing parental data, multiple siblings, and extended pedigrees. The standard FBAT only uses within-family information, and therefore if a basic FBAT analysis is performed, a sizeable portion of genetic data will remain utilized” [40].

7. PENETRANCE AND POAG GENETICS

7.1 POAG Genes

“Genes are chunks of DNA that contribute to particular traits or functions by coding for proteins

that influence physiology. Alleles are different versions of a gene, which vary according to the nucleotide base, present at a particular genome location. An individual's combination of alleles is known as their genotype." Genes determine individual traits, like the organism's genotype, and they are one in number per genus locus, although the diversity in phenotypic expression is largely due to alleles, like the organism's phenotype, and they are two in number per genus locus. The genotype of an organism is made up of the complete set of its genes. There are causative genes identified as having associations with POAG. Six loci have been identified with the causal genes. These are: MYOC, which is mainly mutated in people with juvenile onset, on locus GLC1A mapped to chromosome (1q32), and OPTN mutations primarily occur in people with low-pressure POAG on locus GLC1E to chromosome (10p25). Also reported was "chromosomal mapping of a new POAG locus on 5q22.1, designated as GLC1G, and identification of its causative gene, WDR36, from within this region" [41].

7.2 Gene Penetrance in POAG

"Penetrance in genetics is the proportion of individuals carrying a particular variant (or allele) of a gene (genotype) that also expresses an associated trait (phenotype)." "In medical genetics, the penetrance of a disease-causing mutation is the proportion of individuals with the mutation that exhibit clinical symptoms among all individuals with such mutation" [42]. The penetrance of a gene may depend on factors, such as environmental influences or interactions with other genes. Several genes have been associated with POAG: MYOC**,** OPTN**,** WDR36**,** and others. These genes may have different levels of penetrance, which means the proportion of individuals who carry a gene variant and express its related trait [43].

7.2.1 High penetrance POAG-causing genes

High penetrance signifies that most or all carriers of a gene variant will develop POAG. With complete penetrance, genes for a trait are expressed in all the population who have the genes. In other words, all of the individuals in a population who carry a specific genotype express the corresponding phenotype. When an allele is highly penetrant, it means that the traits or features it produces will almost always be visible in an individual who carries it. This means that people who have the mutation that causes the disease will experience the disease's clinical symptoms [44]. The MYOC gene, which accounts for 3%–4% of instances across various populations, was the first gene linked as a cause of POAG. The second gene linked to POAG was OPTN. They suggested that OPTN mutations may account for 16.7% of hereditary NTG forms and 13.6% additional risk factor "in both familial and sporadic" instances. "Primary open-angle glaucoma displays a strong heritability but is genetically heterogeneous." There are other high-penetrance POAG-causing genes with controversy, which include WDR36 and NTF4. Recently, rare mutations linked to POAG in a new gene called neurotrophin-4 (NTF4) have been found in Chinese and European populations. Experts are highly unsure of the roles played by WDR36, NTF4, and their variations in the pathogenesis of glaucoma due to their controversial roles in POAG [45].

7.2.2 Low penetrance POAG-causing genes

"Glaucoma is characterized as a 'complex' disease, with a phenotype that exhibits heterogeneity, polygenic inheritance, phenocopies, and incomplete penetrance". Low penetrance signifies that only some or few carriers will develop POAG. 'Incomplete/ Reduced/ Low penetrance allele manifests "when some individuals who do not or fail to express the trait, even though they carry the allele". It indicates that this allele will only sometimes produce the symptoms at a detectable level. However, some genes do not show complete penetrance, and less than 100% of the individuals who bear a particular genotype express the corresponding phenotype, in cases of incomplete penetrance. Reduced penetrance is a term used exclusively for autosomal dominant disorders, until recently. A number of chromosomal regions and genetic variants have been identified as being linked to or associated with POAG and related endophenotypes. Linkage analysis identifies linkage of different forms of glaucoma to particular loci and association studies identifies genes contributing to complex diseases in genome-wide association. They are genetic approaches in the investigation of the genetic basis of POAG. Genome-wide association studies (GWAS) are more powerful compared with linkage analysis in discovering genes of small effect that might contribute to the development of the disease [45].

8. INSIGHT INTO CURRENT DIAGNOSIS OF POAG AND THE PARADIGM SHIFT TO MOLECULAR GENETICS

The present diagnosis of POAG falls within the comprehensive assessment of the ONH, RNF, and visual field for assault resulting from elevated IOP. This is achieved with ophthalmic instruments and computer-based diagnostic imaging. However, the emphasis is gradually shifting to molecular genetics through genetic screening, diagnosis, and gene therapy for POAG.

8.1 The Paradigm Shift to Genetic Diagnostic Approach

The genetic approach for glaucoma intervention and therapy is a paradigm shift from the conventional diagnosis to seeking genetic therapy and a permanent cure. Molecular genetics would clearly become beneficial in some specific situations, like screening of family members for autosomal dominant POAG of early onset. This approach is equally indicated for diagnosis, treatment, prognosis, counseling, and research purposes.

8.1.1 Genetic testing /screening and benefits

Glaucoma being a leading cause of blindness requires the development of an accurate diagnostic test for presymptomatic detection of individuals at risk. Ocugene is a non-invasive in-office test where the DNA sample of the patient is collected using cheek brushes. With this, the clinician identifies people at risk, particularly genetically predisposed non-glaucomatous family members whose diagnosis cannot be established with the current glaucoma testing. With Ocugene, 15–20% of POAG patients tests are positive and 99% sensitive. It is useful for both diagnostic and prognostic purposes. If the genetic defect responsible for the disease in the family is identified, it is possible to screen offspring to determine their risk of disease and potentially take preventative action [46]. The ordering of diagnostic tests that will aid genetic discoveries, like identifying specific genetic mutations by clinicians, provides detailed understanding of the natural history of the patient's glaucoma as well as information for genetic counseling. A diagnostic test identifies individuals at risk in the family and offers the opportunity for closer follow-up and immediate institution of glaucoma therapy. This, however, offers hope for the actualization of primary prevention for various glaucoma. For instance, if testing for the MYOC mutation, which is the mutation causing POAG in a family, is identified, then the individual concerned can be tested for that mutation.

Ocugene's diagnostic accuracy lies in its precision in advanced genetic testing to identify glaucoma risk, when compared to traditional method. It is based on presymptomatic detection of people at risk of disease before occurrence, while other traditional ocular tests detects functional and structural defects. Ocugene offers a high level of sensitivity and specificity in picking out genetic predisposition to POAG better than the traditional method. Its reliability is proven by its consistency in results from studies and clinical trials in the population, while traditional ocular tests is not. Information from genetic testing may guide life choices such as occupation in early onset, while traditional methods may not. The diagnostic value of Ocugene is demonstrated by its screening methods like cascade genetic testing, the direct sequencing method, and a multiplication approach, which the traditional methods lack. Ocugene may experience limitations and challenges like genetic focus, accessibility, false positive/negative, limited scope, environmental and other genetic influence, etc [47].

8.1.2 Paradigm in neurodegeneration research

"There is also a paradigm shift in glaucoma treatment from applying therapy directly to RGC and ONH to targeting associated brain centers. Research has shown that glaucomatous nerve damage in the eye may spread to major visual centers of the brain. This is associated with a well-known process in other neurodegenerative diseases. When the damage spreads, nerve cells in the brain related to visual function begin to shrink and die. Treatments could be targeted at these brain centers. Recent research suggests that cells in the retina other than RGCs are equally affected or equally contribute to the rate of decline of the ganglion cells. This means looking at the occurrence of neurodegeneration in a new light, with research underway to identify connections in the brain and how these connections may be strengthened" [48].

9. VECTOR ENGINEERING STRATEGIES IN POAG THERAPEUTICS

The genetic therapy in POAG requires the understanding of the molecular and cellular

mechanisms leading to treatment and vector-associated setbacks, which has resulted in the development of highly sophisticated gene transfer tools with improved safety and therapeutic efficacy. “The four basic prerequisites for any genetic therapy targeted at an ocular disease are: (1) An efficient and nontoxic gene delivery technique. (2) Sufficient characterization of the genetic basis of the disease to select an appropriately matched therapeutic approach. (3) Proper control of the expression of the therapeutic gene. (4) The availability of an animal model of the disease for preclinical testing” [49].

9.1 Gene Transfer Technique and Viral Vectors

A successful gene therapy depends on safe and effective gene delivery as a prerequisite. Gene transfer technology relies on the first step of replication and, at the same time, builds blocks to prevent the production of infectious viruses. “Transduction is the key principle in gene transfer therapy. It is a non-replicative or dead-end infection that allows heterologous (i.e., non-viral) genetic information to be delivered to a precise cell. To do so, the viral genome is radically rearranged to eliminate genes essential for replication and pathogenicity while making space for the heterologous genes.” As illustrated in Fig. 1, for gene therapy to be effective, the therapeutic gene must be delivered to the patients' target cells via a carrier molecule known as a vector. At present, the most prevalent vector is a genetically modified virus that carries normal human DNA. Regardless of their origin, strain, or family, viruses have developed sophisticated ways to arrive and penetrate certain target cells. Once inside, they seize control of the cellular machinery, expressing their genes and producing progeny particles [50].

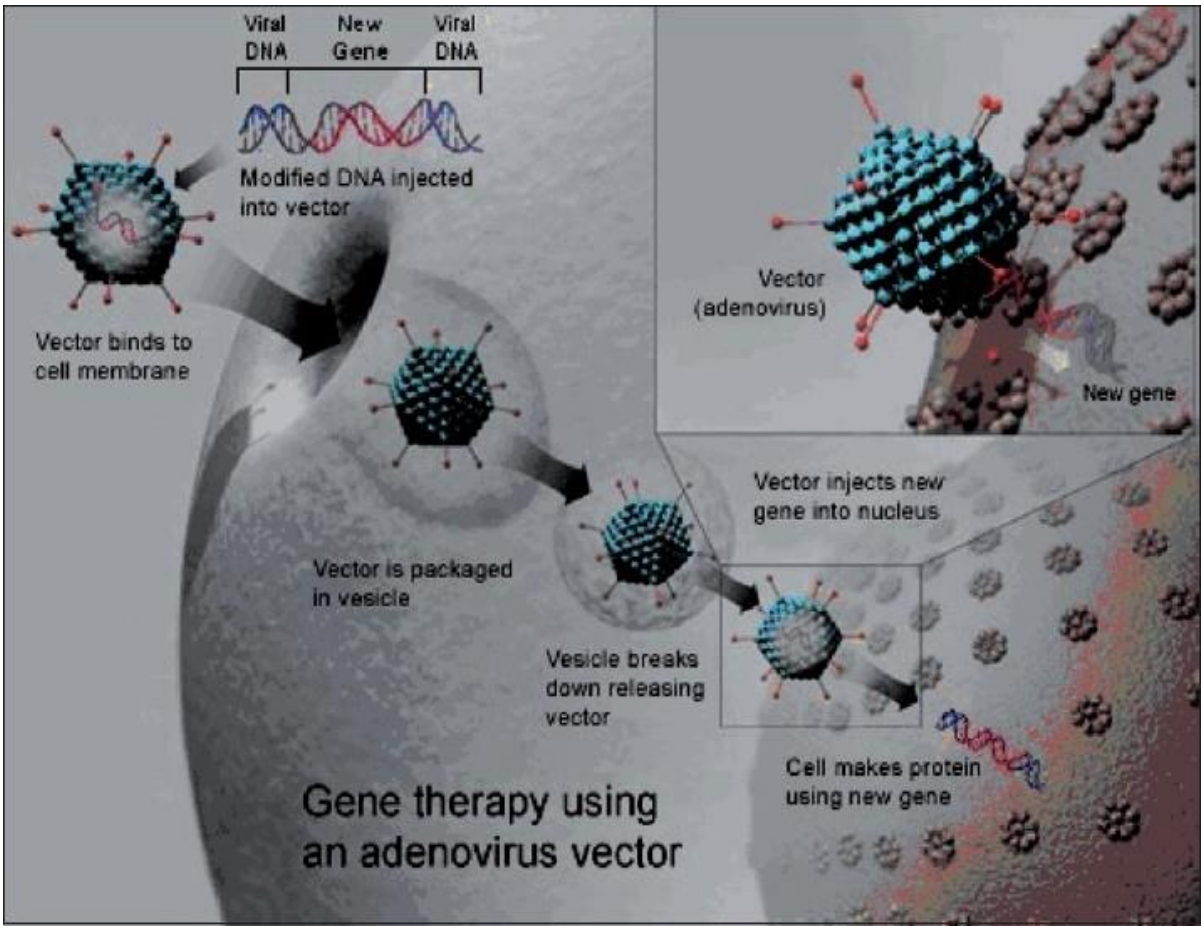

Fig. 1. “Modified virus vector in which a new gene is incorporated and delivered to the diseased cell”
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2992156/figure/F0001/

9.2 Routes of Administration and Delivery of Genes

Gene transfer therapy could be delivered or administered to the target organs through the following routes: intravitreal delivery, intracameral delivery and transcorneal administration.

Evidence suggests that BDNF may serve as a neuroprotective agent in glaucoma. Consequently, RGCs rely on the trophic support of BDNF, which is retrogradely transported from target brain areas to the ganglion cell bodies in the retina [51].

9.3 Gene Delivery Vectors, and Targets

“Current gene delivery vehicles, namely vectors, are categorized into two classes: DNA (non-viral) vectors and viral vectors. Both types of vectors can directly deliver genes into the human body." However, “viral vectors take advantage of the infectious nature and gene-shuttling capability of certain viruses but are deliberately engineered to minimize harm by removing as many viral genes as possible." On the other hand, non-viral vectors, which include plasmids, nanoparticles, and liposomes, are safer but less efficient than viral vectors. “The recent advances in gene delivery techniques proved to be much improved in both safety and efficacy. Viral vectors are more commonly used than non-viral delivery due to their superior gene transfer efficiency. Viral vectors inherit many intrinsic features from their parental viruses. In many cases, these features are double-edged.” [52].

9.3.1 Target genes and tissues

“The appropriate target structures or cell types for glaucoma gene therapy are TM, ciliary epithelium, ciliary muscle, RGCs, and Muller cells.” Their involvement in aqueous production, drainage, and the pathogenesis of glaucomatous damage accounts for this. “There are about six delivery systems (vector viruses) with the ability to deliver genes to the relevant tissues or cells. They include adenoviruses, adenoassociated viruses, herpes simplex viruses (HSVs), lentiviruses, feline immunodeficiency virus, human immunodeficiency virus (HIV), lithesome, and naked DNA.” [53].

9.3.2 Vectors and selected target areas

Numerous viruses that infect mammals are being studied for their potential as gene delivery vectors and have evolved spontaneously to serve as such for gene therapy. “With the surface proteins on viral particles, it can interact with their corresponding receptors on target cells, which triggers the cellular uptake process known as ‘endocytosis’. Once inside a target cell, viruses eventually deliver their genetic information in the form of DNA into the nucleus for viral gene expression” [54].

The Anterior segment: As shown in Table 1, numerous studies have demonstrated that adenovirus vectors deliver transgenes to the TM very effectively following intracameral injection. The intracameral transmission of vectors transports the viruses straight to the TM because of the normal flow of aqueous humor. Table 1 lists additional vectors that can be used to deliver to the structures of the anterior part of the eye, such as liposomes, lentiviruses, and HSV [55].

The Posterior segment: Gene delivery via intravitreal delivery method is now recognized as the preferred route to transfer genes to RGCs. Adenovirus vectors can be efficiently used to deliver genes to Müller cells through intravitreal injection. However, adenovirus-mediated gene transfer to RGCs remains significantly limited [51].

10. ADVANCES IN THERAPY AND FUTURE PREDICTIONS IN GENETIC INTERVENTIONS IN POAG

10.1 Advances in Genetic Interventions in POAG Therapy

10.1.1 Gene therapy

“Gene therapy is a technique for correcting defective genes responsible for disease development." In theory, “a normal copy of the gene can physically take the place of the flawed gene and restore the gene function of the cell. The aim of gene therapy presently is to add a useful gene to the cell or tissue that suffers the consequences of the flawed gene. In some cases, the new gene may code for an entirely different protein whose function compensates for the protein encoded by the flawed gene.” “This involves the treatment, cure, or prevention of human diseases through the application of DNA or RNA”. This can be accomplished in two ways, depending on the disease type: either by delivering a functional therapeutic gene to replace the damaged or absent endogenous

Table 1. Glaucoma relevant tissues and available vector systems [55]

"Tissue Type	Vector	Route
Trabecular Meshwork	Adenovirus	Intracameral
		Intracameral
	Adeno-associated virus	Intracameral
	serotypes 2, 3, 4	Tissue culture
	Herpes simplex virus	Intracameral
	Lentivirus	Intracameral
	Liposomes	Intracameral
Ciliary Epithelium	Adenovirus	Intracameral
		Lens culture
	Adeno-associated virus	
	Herpes simplex virus	Intracameral
	Lentivirus	
	Liposomes	
Ciliary Muscle	Adenovirus	
	Adeno-associated virus	
	Herpes simplex virus	Tissue culture
	Lentivirus	
	Liposomes	
Retinal Ganglion Cells	Adenovirus	Intravitreal
	Adeno-associated virus	Intravitreal
	Herpes simplex virus	Intravitreal
	Lentivirus	Retrograde
	Liposomes"	

Source: Mahdy: "Gene therapy in glaucoma-3, therapeutic approaches".
[Downloaded free from http://www.ojoonline.org on Wednesday, September 28, 2016, IP: 92.110.98.90]

equivalent, or by employing a variety of advanced techniques to lower the levels of a detrimental faulty gene product using non-viral vectors, modified viral vectors, and naked "oligonucleotides", where a new gene is integrated into and delivered to the cell that is diseased. "A general approach to gene therapy is to use an altered ('recombinant') virus to carry the gene of interest to the desired tissue". "Using genetic engineering techniques, the viral DNA is modified so that the viral genes required for virus proliferation are removed and the therapeutic gene is put in their place. Such a virus may invade the diseased tissue, become incorporated into the host DNA, and express the desired gene. Because the modified virus does not have the viral genes required for viral replication, the virus cannot proliferate, and the host cell does not die." Limitations associated with modified viral vectors may include toxicity of patients, immunological and inflammatory reactions, problems with gene targeting and control, etc. Research is currently being carried out on other viral vectors that may improve these setbacks and be helpful for gene therapy, in addition to non-viral methods for introducing therapeutic genes into diseased tissue [56].

10.1.2 Neuro-Protection

"Neuroprotection is the ability for a therapy to prevent neuronal cell death by intervening in and inhibiting the pathogenetic cascade that results in cell dysfunction and eventual death." It is a "non-IOP-related intervention that can prevent or delay glaucomatous neurodegeneration." Neuroprotection relatively preserves the neuronal integrity, structure, and function in case of an insult, with an implied reduction in the rate of neuronal loss over time. The goal of these innovative glaucoma treatment approaches is to enhance the neuroprotection of the optic nerve's axons as well as the cell soma of RGCs. Traditionally, genes encoding defense genes, antiapoptotic proteins, and neurotrophins have been chosen to protect RGCs [57].

10.1.3 Rho-associated protein kinase (ROCK) inhibitors

The Rho/ROCK signaling pathway is crucial to the glaucoma etiology. The inhibition of Rho kinase, which is essential for reducing IOP, has been identified as an effective treatment target. Actomyosin dynamics are regulated across varieties of cell types by Rho kinase, a

downstream effector of Rho GTPase signaling. Its “inhibitors decreased fibronectin and smooth muscle actin. This suggests that TM rigidity and acellular matrix production mediated by the Rho pathway may be involved in decreasing aqueous humor outflow and raising IOP.” Rho kinase inhibitors decrease IOP by relaxing the TM, which improves AH outflow, and they also lessen cell stiffness, which increases outflow [58].

10.1.4 Combinatorial gene therapy

“Pathways to promote RGC survival and axonal regeneration are not usually overlapping. For either promoting neuroprotection or inducing axonal regeneration, different signaling pathways and regulatory molecules are critical. The combination of both strategies in a single-gene therapy approach would likely be highly beneficial for glaucoma. With an efficient neuroprotective approach, more RGCs will survive the injury and, thus, be available to successfully regenerate their axons in response to a proregenerative stimulus. On the other hand, an effective regenerative approach will guarantee the integrity of the axons of RGCs that have already been partially or completely lost, with the potential to recover neuronal function and favor cell survival in the long term, inclusive of retrograde neurotrophic support from the axonal targets.” The genetic maneuver of apoptosis-related genes such as BAX and Bcl-2 may produce divergent effects on each of the separate regeneration and neuroprotective pathways. ”The gene knockout of the proapoptotic protein BAX and the constitutive overexpression of the antiapoptotic protein Bcl-2 are very efficient strategies to prevent the neurodegeneration of RGCs, with survival of almost all cells in the ganglion cell layer of the retina but cannot efficiently regenerate their axons” [59].

10.1.5 Nanomedicine in glaucoma

Nanotechnology introduces a potential paradigm shift in the approach towards reduction of intraocular pressure.” The unparalleled possibilities in the glaucoma treatment method were due to a new vista opened up by increased capacity to maneuver matter at the molecular level. “Recent advancements may offer novel drug delivery vectors to enhance bioavailability and uptake, as well as instruments that could improve intraocular pressure-reducing surgical outcomes. As drug delivery vectors, nanomaterials exhibit unique chemical and physical properties that, in conjunction with drug molecules, may potentially increase the availability of a pharmaceutical compound to a target site. These properties include increased rates of permeability through barriers, protection of nanoparticle-loaded drug molecules from degradation, and prolonged contact time between the drug and target tissue” [60].

10.1.6 Poly-Therapeutic (Combination) Strategy

Poly-therapeutic or combination treatment combines two or more medications or other therapies or interventions to treat a single condition with one or multiple symptoms. Since “it is now widely recognized that lowering IOP in the treatment of glaucoma is not enough, the combination treatments such as IOP-lowering drugs with neurotrophic factors and/or antioxidants and/or anti-apoptotic agents may be necessary.” Polytherapeutic techniques, alongside neuroregenerative and neuroprotective methods, may represent the future direction of medical treatment [61].

10.1.7 Calcium channel blockers (CCBs)

By stopping calcium-mediated apoptosis, enhancing ocular blood flow, and delaying the advancement of visual field abnormalities, CCBs have been linked to glaucoma neuroprotection. It has been demonstrated that applying calcium channel blockers topically to the optic nerve can stop the increase in intracellular calcium, hence averting acute superficial axonal damage. “In particular, brovincamine and nilvadipine are 2 CCB’s that permeate the blood-brain barrier and selectively influence the optic nerve circulation without appreciably affecting systemic circulation.” However, this process is sped up by calcium ionophores [62].

10.1.8 Neuro-Enhancement

The idea behind neuroenhancement is to support wounded RGCs and improve their function prior to their death. They are currently in the early phase of human trials. “One promising potential therapy is an implant that provides sustained delivery of ciliary neurotrophic factor (CNTF), a growth factor known to promote the growth and survival of nerve cells. This concept is being considered for future glaucoma therapy. Further research is on the development of possible drugs delivered slowly in biodegradable form through sub-conjunctival injection near the cornea,

potentially providing pressure reduction for up to 3–6 months" [48].

10.2 Predictions and Perspectives in POAG Therapies and Cure

10.2.1 Gene silencing technique using small interfering (si) RNA

A gene-silencing treatment called RNA interference (RNAi) can eradicate the mutant myocilin proteins in the TM entirely. Its application could be either mutation-dependent or mutation-independent, depending on the engineering method of small interfering (si) RNA used.

This tactic can treat the POAG brought on by the MYOC gene mutation by reversing the disease process of TMC. Numerous protein-misfolding disorders brought about by gain-of-function mutant proteins can also be treated with this method. "The readily available siRNA can be delivered to the intact human TM by intracameral perfusion. The delivered naked siRNA is functional, inhibiting not only the targeted gene but also their downstream effectors. This functional intracameral delivery might be of use to protect the TM from unwanted insults and could have important therapeutic applications" [13].

10.2.2 Routine screening for disease susceptibility

With the current genetic research in POAG, there is a clear indication of high hopes of better therapeutic directions and cures. In the near future, screening of individuals routinely for disease susceptibility may become possible with the functional interaction of TMCO1 genes and GAS7 with known glaucoma disorder genes. This depends on the variation between the decrease in cost and its increase in sensitivity and specificity of genotyping. Nonetheless, the lamina cribrosa, optic nerve, retina, ciliary body, as well as the TM, all have high levels of expression for these genes [63].

10.2.3 Identification of genetic mutations

In POAG, the identification of validated and replicated genetic mutations provides hope for accurately identifying the key pathways leading to the death of RGC. Due to the accumulation of insufficiently folded mutant MYOC in the ER, initiating the unfolded protein response, ultimately triggering cell death, employing newly proposed RNAi as a gene-silencing treatment to eradicate mutant MYOC entirely from human trabecular meshwork (HTM) cells [64], will in turn be identified as novel treatment strategies.

10.2.4 RNA interference (RNAi)

RNAi is a valuable approach that addresses the underlying cause or symptoms of a disease by inhibiting the expression of a specific protein. In RNAi treatment, lower concentrations or doses are required with fewer adverse effects [65]. "RNAi may be as valuable in modeling diseases, studying the effects of silencing-specific genes in vitro and in vivo, as it is in treating them," and as we can see in some other novel strategies.

11. CONCLUSION

Modern genetic approaches and techniques have challenged the current belief that glaucoma is just a treatable (but not yet curable) disease, with intraocular pressure (IOP) being the only modifiable risk factor. That the therapeutic reduction of IOP decreases the chances of developing glaucoma and slows the progression of the disease advancement.

The understanding of the pathophysiology and genetic mechanisms of POAG advances the sophistry of the evolving novel tools like gene transfer technique, gene silencing model, nanotechnology, neuroenhancement, etc; in leveraging the therapeutic efficacy in POAG intervention.

Molecular genetics offers great promise that would throw more light on the genetic contributions to POAG disease and the change in approach to its diagnosis and treatment. Ultimately, gene therapy has considerable promise as the future cure of POAG by replacing the current conventional drops.

The sensitivity and specificity of genotyping, the current neurodegenerative research targeting associated brain centers, the gene mapping unraveling their defects through specific disease classification, the screening of individuals routinely for disease susceptibility, and the important diagnostic precision of POAG disease-specifics to individuals, are the expected shift to a new frontier and insight into the future predictions of POAG permanent cure.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It was not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests existed.

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