Chapter

Molecular Genomics of Glaucoma: An Update

Govindasamy Kumaramanickavel, Siddhita Jadhav, Sugirdhana Parthiban Ramsait and Pinakin Gunvant Davey

Abstract

Glaucoma is in the top five age-related eye disorders with increasing prevalence globally. Past research has led to the understanding of glaucoma as a neurodegenerative disease. Glaucoma phenomics could be syndromic or non-syndromic. Globally primary open angle, primary angle closure and primary pseudoexfoliation glaucomas are widely present. The genetics and genomics of glaucoma are heterogeneous, both clinically and genetically. Glaucoma has heritability associations, particularly with central corneal thickness, retinal nerve fibre layer and peripapillary atrophy. Ocular embryogenesis genes when mutated could cause either local (*in situ*), pan-ocular or systemic syndromic glaucoma phenomics. In glaucoma, except for a few single gene causes, most of the associations have been shown with innumerable gene single-nucleotide polymorphisms and epigenetic factors. The biological mechanisms in glaucoma are mechanical strain, inflammation, oxidative stress, vascular dysregulation, and immune imbalance, which independently or collectively contribute to the neurodegeneration and visual morbidity. Biomarkers in glaucoma have experimental study biases and therefore today we cannot apply them effectively in clinical practice and henceforth that demands further research to understand the fundamental basis of the disease. However, the knowledge gained in research will translate into early detection and biomolecular interventional strategies, having traction toward personalised medicine.

Keywords: age-related eye diseases, biomarkers, biomechanisms, epigenetics, glaucoma, genomewide associations, genetics, gene therapy, neurodegeneration, neuroprotection, personalised medicine

1. Introduction

Genetics is usually the study of a gene and the corresponding physiological trait or disease phenotype, which is inherited through generations; whereas genomics is the study of all the genes, genes expressed in the person's genome which are responsible for a physiological or pathophysiological phenotype (phenomics) in the health or disease. The phenotype of glaucoma is heterogeneous, varying from a spectrum of normal tension, high tension to retinal ganglion cell death and visual morbidity. Similarly, the molecular genomics of glaucoma is complex, which is unlike corneal, lens or retinal genomics, where the seat of the disease is localised to the site of the

respective tissues. However, in contrast glaucoma is pan ocular – extending from the anterior segment to posterior segment of the eye and the optic nerve, and thus, several anatomical regional tissues of the eye and genes, gene expressions are the stakeholders in the molecular mechanism of glaucoma. In addition, the disease outcome is measurable in the tears, aqueous humour, ciliary body, trabecular meshwork, vitreous body, lamina cribrosa (superficial nerve fibre layer, retinal ganglion cells, prelaminar region, laminar region, retrolaminar region), retina, optic nerve, serum and blood, which collectively blurs a single cause and effect of the glaucoma machinery [1, 2]. At the same time, these candidates remain to be the barriers and opportunities in glaucoma screening measures, early clinical detection, effective clinical management, valuable prognostication and futuristic molecular interventions.

The genetics of glaucoma is less of Mendelian and more of complex nature, perhaps more diverse compared to any other age-related eye diseases (ARED), like for example, age-related macular degeneration (AMD). In glaucoma genomics, there are very few genes which behave as a Mendelian single gene disease, while several genes and single nucleotide polymorphisms (SNPs), gene expression modulations, correspond to the pathophysiological traits as a neurodegenerative disease. There are a couple of hundred genes, several hundred SNPs, and many microRNAs which all are associated with ARED glaucoma phenomics. Many of the genomewide association studies are robust, where large collaborative sample sizes, validation studies, across different populations have been designed, executed and published. The molecular mechanisms of glaucoma are a spectrum of clinical outcomes played by several biological actors, beginning from inflammation, oxidative stress, extracellular matrix dysregulation, immune system imbalance, neuroprotection, neurodegeneration, apoptosis, metabolites accumulation, to abnormal lipid factors. However, most of the molecular genomic factor studies are not robust and are unfortunately poorly validated. Besides, glaucoma manifests in the elderly as a result of mix and match with other AREDs visual morbidities like cataract, corrected or uncorrected refractive errors, AMD, and diabetic retinopathy and therefore usually may not be isolated. For example, a person with glaucoma may have cataracts and/or AMD as well, again this could be another bias factor in the molecular genomics laboratory studies. Nevertheless, in this review, we shall have an in-depth overview of the molecular genetics and genomic factors associated with the pathophysiological mechanisms of glaucoma. However, the review also provides a larger insight into the visual impairment, prevalence, and comorbidities, besides the genetics and genomics of glaucoma. However, it is beyond the scope of the review to provide a gist of all the biological, experimental, epidemiological, genetic and genomic studies in glaucoma and hence, kindly refer to the references provided at the end, for further information.

2. Glaucoma in general

2.1 Visual impairment, age-related disorders and the central role of glaucoma

In the elderly, glaucoma cannot be viewed as an isolated pathology and it is frequently associated with other age-related visual and systemic comorbidities like ocular (cataracts, age-related macular degeneration, type 2 diabetes mellitus and its complications, visual impairments, diabetic retinopathy) and non-ocular (airways diseases, coronary artery disease, hypertension, heart failure, dementia, depression, et cetera). Besides, the treatment of glaucoma will have an effect on some of the morbidities mentioned [3]. As the population of the aged increase, common causes of

visual morbidity increase significantly. In 2015, the three top causes of blindness were preventable - cataract, uncorrected refractive error (URE) and glaucoma, whereas for visual impairment it is URE, cataract and AMD. Effective and largescale eyecare service is required to combat these problems [4]. In 2017, Ackland et al., published that 253 million people are visually impaired with 217 million moderately or severely visually impaired (MSVI) and 36 million blind and they estimate that by 2050 these numbers would climb sharply to 588 million MSVI and 115 million blind globally [5]. About 89% of the VI live in low or middle-income countries and 55% of them are women. About 1.1 billion people have uncorrected functional presbyopia. Though the prevalence of VI has reduced from 4.58% to 3.38%, more thrust has to be given to reduce it further [5]. Eckert et al., estimated the cost of blindness as US$ 7.8 billion in the US and the cost of MSVI as US$ 16.5 billion, however, Gordois et al., estimated the cost of VI as a staggering US$ 3 trillion and the direct costs as US$ 2.3 trillion and also mentions that these figures could increase by 20% by the year 2020 [6]. Another non-profit organisation of Prevent Blindness in America estimates that the economic burden of adult vision problems (AMD, cataract, diabetic retinopathy, glaucoma, refractive errors, VI and blindness) in the US in 2007 as US$ 54.1 billion annually, which includes direct medical, direct-other and loss of productivity costs, however, they revised the figure to US$ 139 billion in a 2013 report [7].

In 2015, it was estimated that the moderate to severe VI affected 216.6 million globally, with the URE being the leading cause, and blindness prevalent amongst 36 million with cataract outnumbering the other causes [4]. The proportion of those with preventable or treatable blindness and VI is reducing in trend over the decades, fortunately, as mentioned earlier, due to the control of infectious and nutritional causes. And amongst those with visual morbidity, aged individuals comprise the maximum, having the distribution variable between the developed and developing countries [8, 9]. ARED, such as AMD, cataract, diabetic retinopathy (DR), glaucoma and refractive errors are the key components of global visual morbidity and cataract forms more than half of all those affected in the group. Amongst those, 70–74 years of age 37% have cataract, 10% AMD, 3% glaucoma and 2% DR [10]. Out of the 285 million with VI and blindness, those above 50 years of age constitute 65% of the VI and 82% of blindness. In addition, due to poor socio-economic status and biological element like longevity, 75% of those affected with ARED are women and this factor is consistent irrespective of the fact that whether women live in developed or developing countries [11, 12].

In Germany, ARED commonly found were cataract, dry eye, AMD and glaucoma, furthermore, they found that the aged individuals had different combinations of these conditions [13]. Asia has one of the highest representations of the blind, with India having the highest prevalence of 11.9% and Malaysia with the lowest of 0.3% [14]. Due to the robust epidemiological studies, ARED in Asia includes, along similar lines to that of the West, cataract, refractive errors, glaucoma, DR and AMD. AMD is prevalent in both the developed and developing countries as being the cause of blindness and VI, the prevalence of the disease is higher in the West, but the emerging trends and patterns from China, India, Japan, Mongolia, Singapore to Taiwan are echoing the West, due to the growing aged populations [14]. ARED in Iran had a similar pattern to most Asian countries with 35.8% having either cataract, AMD, glaucoma or DR and moreover one in two of those over 75 years of age have these conditions [15]. In the US, a third of the subjects were either 80 years or over who had cataract, AMD, primary open-angle glaucoma (POAG), DR or VI and two-thirds had late AMD. In addition, POAG, VI and DR were prevalent at a higher age amongst

Hispanics and Blacks, whereas cataract and late AMD prevalence were higher amongst the Whites [16]. The prevalence of ARED in Canada increased alarmingly after the age of 75 years [17]. In high-income Eastern and Central European countries, blindness and mild to severe VI reduced between 1990 and 2015 from 0.26% to 0.15% and from 1.74% to 1.27%, respectively and similar trends were observed in Australasia, North America and Western Europe. One in 28, above 40 years have low vision in the USA [18]. Conflicting reports are available in the US demonstrating that vision screening methods could improve the visual status of a community, in older adults [19]. In Britain, Prasad et al., observed that diabetes was not the primary factor for the prevalence of blindness and MSVI, whereas non-diabetes factors were particularly responsible [20, 21]. In Latin America for the elderly, 50 years of age or above, the prevalence of blindness varied from 1.1% in Argentina to 4.4% in Guatemala, with cataract being the foremost reason, however, DR and glaucoma are rising and infectious diseases are declining [22]. In the population of Indian origin in Singapore, 40 years or above, the prevalence of VI and blindness were 3.4% and 0.4% respectively, far lower than in India, for which cataract, DR, AMD and glaucoma were the leading causes and the first was the primary cause [23, 24]. ARED in Singapore Indians 40 years or above irrespective of education level, literacy or immigration types were deteriorating and active screening measures should be implemented rather than voluntary enrolment is emphasised [25].

With the ageing population, rising in proportion across the world despite the fall in birth rates, the corresponding increase in morbidity and mortality amongst the group is worrying. Universal health coverage and eye health objectives are persevering to reduce global visual morbidity for which robust databases are key to achieving the goals [26–28]. Biological understanding of ARED, not only clinical screening, is equally important for the prevention and management of the diseases. Oxidative stress and inflammation are the key causative mechanisms for ARED. Autophagy mechanisms also play both protective and detrimental outcomes in ARED and therefore nurturing preventive and therapeutic strategies [29]. Malnutrition and anaemia have been associated with poor vision besides other systemic disorders in the elderly, in a study from southern India [30]. In a southern Indian glaucoma study, primarily around three-quarters were due to cataract and the remaining were because of glaucoma, cystoid macular oedema, optic atrophy and corneal scars and these were significantly associated with ageing ($p < 0.0001$) [31].

2.2 Prevalence of glaucoma

Globally, the five leading causes of visual impairment are, URE, cataract, AMD, glaucoma and DR. However, glaucoma is the second leading cause of loss of vision in the world. About 60.5 million people are estimated to be affected globally by glaucoma in 2010, which is equivalent to the population of Italy, and about 8.4 million of them will be suffering from bilateral irreversible blindness and there are closely varying estimates according to other studies [32]. These figures could rise to 111.8 million in 2040 and the global prevalence of glaucoma presently is around 3–4% [33, 34]. POAG is highest amongst African and Hispanic races and is found amongst all races, whereas primary angle closure glaucoma (PACG) is the highest in Asia [35, 36]. Primary congenital glaucoma (PCG) is a less common type, however primary exfoliative glaucoma (PXFG) is a comparatively more frequent disorder resulting in most common glaucoma related blindness, rather than the other types. In a focused metanalysis of five glaucoma prevalence studies in India by Geroge et al., it was

estimated that in 2010 about 11.2 million would be affected with the disease and out of which 6.48 million would have POAG and 2.54 million, PACG and these figures should have increased in the decade that has passed since the publication [37]. The economic burden of glaucoma in the United States calculated by Rein et al., in 2006 was around US$ 2.9 billion, in this context we should take note that the majority of glaucoma cases are undiagnosed [38]. Studying five major prevalence studies in India, the age-standardised prevalence ranges of those 40 or 50 years or above with POAG was—1.29% to 4.24% and for PACG—0.5% to 1.11% and the reason for the wide range of variations are largely due to disparities in clinical and epidemiological study methodologies. Childhood glaucoma is constituted by primary congenital glaucoma and juvenile open angle glaucoma, which affects 1 in 10,000 to 100,000 children worldwide and the former is more prevalent in high consanguineous marriage geographical regions [33]. Pigmentary glaucoma or pigment dispersion syndrome is caused by PMEL gene variants only less than 50% of those with the variants get affected. PMEL is involved in melanin pigment synthesis, storage and transport and these pigments get deposited in the trabecular meshwork and increase the IOP.

3. Genetics & genomics of glaucoma

'Glaykoseis', a blindness in the elderly, as mentioned by Hippocrates—the Father of Modern Medicine, dates back to 400 years before Christ emerged and Amida, a Byzantine physician, named it as 'Amaurosis' [39]. Before 1850, POAG was termed as amaurosis, black cataract or gutta serena. The eyes were observed to be hard and angle-closure glaucoma caused green or grey pupils and hence the name glaucoma (blue, green or grey and viriditate occuli) and in 1850 after the ophthalmoscope invention, the scenario changed, when the term 'Glaucoma' was christened to the disease, which has not changed until today [39]. Ganglionic optic neuropathy is the pathological defect of glaucoma which leads to a painless visual loss. The molecular genetics and medical biology of glaucoma have intrigued scientists for a while, however, whatever knowledge that we have gained today is not yet as clear as compared to the inherited retinal degenerative diseases (IRDD).

3.1 Heritability of glaucoma

In the earlier days, twin studies were the proof to establish if a disease is caused by heritable or environmental factors. The twin studies in 1987 established that the heritability of POAG at 0.135 [40]. In addition, two recent robust studies with genomewide array data though parked the heritability of POAG between a wide range of 24–42% [41, 42]. The risk factors for developing glaucoma are age, ethnic origins (African Americans, Hispanics), gender (women), genetics, hypertension and increased intraocular pressure prescription drugs [43]. The prevalence of POAG was highest amongst the African race descent, then Asians, but the lowest was amongst the Europeans, showing racial and genetic preponderance. However, the genetics of the disease is complex with only 10% having Mendelian inheritance.

Central corneal thickness, intra-ocular pressure (IOP), optic disc area and vertical cup/disc ratio (VCDR) have high heritability associations across populations. Asefa et al., looked at the anterior chamber size, central corneal thickness (CCT), corneal hysteresis, cup-to-disc ratio, cup-shape, cup-size, disc-size, intraocular pressure, peripapillary atrophy (PA) and retinal never fibre layer thickness (RFNLT) in a

metanalysis [44]. And the highest heritability was observed in CCT (h^2 = 0.81), RFNLT (h^2 = 0.73) and PA (h^2 = 0.73) [44].

3.2 Mendelian genetics of glaucoma

There are very few single gene defect causations in non-syndromic glaucoma, so far, four PCG loci have been located—GLC3A, B, C and D. The GLC3A region in 2p21 has the CYP1B1 gene and about 150 or so autosomal recessive mutations have been associated with PCG. The majority of patients with PCG/CYP1B1 mutations are found in Saudi Arabia and Slovakia gypsy population and these mutations have variable expressivity and incomplete penetrance with a wide range of clinical phenotypes [45]. PCG is present across the world and being an autosomal recessive disease, is more frequent in consanguineous populations, has a widely varying incidence of 1 in 1250 to 1 in 22,000 in different parts of the world and is one of the paediatric causes of blindness in India [46–48]. A consanguineous south Indian family with PCG was investigated by using homozygosity analysis. The microsatellite markers D2S177 and D2S1346 were tightly linked to CYP1B1 and the Q110X mutation in exon 2 of the gene was co-segregating in all the affected [49]. A newborn in the family was found to be a heterozygous carrier to the relief of the family during genetic counselling [45]. CYP1B1 plays a critical role in the development of the trabecular meshwork (TM) and acts in the removal of reactive oxygen species, regulating oxidative stress and production of periostin which influences the mechanical strength and structural integrity of the TM [45]. GLC3B and C have not resulted in any gene till date, but GLC3D location at 14q24 has resulted in null mutations in LTBP2 and PCG phenotype correlation. LTBP2 (latent transforming growth factor beta binding protein 2) is a matrix protein that performs cell adhesion and tissue repair processes.

Optineurin (OPTN) gene mutation is one of the causes of POAG in various populations, though it is rate. In OPTN, M98K variation is associated with POAG across populations and in our study, was less frequent cause of the disease as it was found that in 4% of HTG and 6% of NTG patients compared to the controls [50]. OPTN plays critical role in Golgi complex maintenance, membrane trafficking, exocytosis, interacts with myosin VI and Rab8.

A sensational MYOC gene location for glaucoma was identified by Stone et al. in 1997 and is one of the most investigated in glaucoma genetics [51]. The sensational was though short-lived in the history of genetics of glaucoma and it lost its steam as the frequency of the mutations started to fall to very small proportions amongst the global glaucoma populations. When we screened 100 POAG/JOAG patients for the MYOC gene, we found a G144A, Gln48His substitution, which was novel at that time, in 2% of the patients, the change was also found in another four affected members of a JOAG family. MYOC was found to not play a significant role amongst glaucoma patients in India [52]. Juvenile open angle glaucoma (JOAG) was described in a large pedigree in the US seventy years ago and today the Phe369Leu MYOC mutation was identified in the family [53].

3.3 Molecular genetics of syndromic glaucoma

Syndromic glaucoma, which are also Mendelian in nature, may not be uncommon in the paediatric age group, hence glaucoma may be associated with additional ocular

and systemic phenotypes like aniridia, anterior segmental dysgenesis, collagen or vascular disorders, immunogenetic diseases, metabolic disorders and nanophthalmos. The embryogenesis of the eye is complex with both the ectoderm and neuroectoderm involved together in the formation. Mutation in genes, infections acquired during or after pregnancy, ageing and systemic disorders affect the development of the eye [45]. Axenfeld-Rieger syndrome, a disorder is prevalent in 1:200,000 individuals, which affects the anterior segment like defective cornea, iris and the extraocular features include facial, dental and skeletal abnormalities. Peters' anomaly, an autosomal dominant disorder, is another common condition affecting the anterior segment development where cornea, iris and lens resist to separate, leading to central corneal opacity and non-ocular features like cleft lip/palate, short stature, physical and mental retardation. Aniridia is another developmental condition accompanied by photophobia and poor visual acuity. The genetics of syndromic glaucoma is Mendelain.

WAGR syndrome with **W**ilms tumour, **a**niridia, **g**enitourinary anomalies and intellectual disability earlier mentioned as mental **r**etardation. In WAGR syndrome there will be chromosomal deletion at the 11p13 region which harbours many genes including mutated WT1 and/or PAX6 genes and the affected have glaucoma as well. Hence, aniridia patients should undergo an abdominal ultrasound to rule out WAGR syndrome and renal tumour. There is a rare condition of Gillespie syndrome, where patients have aniridia, ptosis and corectopia with mutation in the ITPR1 gene [54].

Collagen vascular diseases like Stickler syndrome and osteogenesis imperfecta patients have glaucoma due to trabecular meshwork impedance. Stickler syndrome patients have myopia, cataract and retinal giant tear, the iris ciliary process is long and covers the trabecular meshwork blocking the aqueous flow. The gene variants in COL2A1 and COL11A1 cause autosomal dominant Stickler syndrome, whereas variations in COL9A1 cause autosomal recessive type. Osteogenesis imperfecta has COL1A1 and COL1A2 gene variants manifesting in an autosomal dominant manner. Osteogenesis imperfecta is a collagen bone disorder with a variable five phenotypes, all mostly have low mineral density leading to bone fragility (hence the name brittle-bone disease), blue sclera, abnormal cornea, glaucoma, poorly formed dentine, the ligaments are hyper lax, cardiovascular disease and hearing loss [55]. Immune-related disorders like Aicardi-Goutieres syndrome (AGS) and Singleton-Merten syndrome (SGMRT), are severe and fatal conditions with a plethora of genes involved in RNA processing like ADAR, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, TREX1 and the gene IFIH1 responsible for innate immunity. In a severe type, patients could have cerebral atrophy, congenital glaucoma, hepatosplenomegaly, intracranial calcification, leukodystrophy, microcephaly, thrombocytopenia and death are not uncommon. Singleto-Merten syndrome is caused by variants in the DDX58 and IFIH1 genes and has glaucoma as a clinical feature.

Nanophthalmos, with small fully formed eyes, could be inherited as both autosomal dominant and recessive types. There are several genes involved in this condition (CRB1, BEST1, FAM111A, MFRP, MYRF, PRSS56 and TIMEM98), which has additional systemic features like congenital diaphragmatic hernia, cardio-pulmonary abnormalities, glaucoma and urogenital anomalies, causing some rare genetic disorders like Kenny-Caffey syndrome [56]. MYRP, CRB1 and BEST1 are genes associated with retinal degenerative genetic disorders. TEK/ANGPT1 genes' variants independently resulted in haploinsufficiency-based primary congenital glaucoma. The genes have a critical role in the structure and function of Schlemm's canal and trabecular meshwork [57].

PITX2 (Paired Like Homeodomain 2) in chromosome 4q25 and FOXC1 Forkhead Box C1 are transcription factors jointly involved in the anterior segment development. Mutations or copy number variations in these genes result in anterior segment anomalies, due to haploinsufficiency, like Axenfeld Reiger syndrome or Peters' anomaly [58]. Axenfeld first described the anomaly in 1920 and later was added more by Reiger in 1934 [56]. A majority of the children with mutations in PITX2 and FOXC1 develop glaucoma [56]. Non-ocular systemic features include variable phenotypes like facial/dental anomalies, pituitary involvement, umbilical anomalies, syndromes like SHORT, short FRAME, cardiac defects, sensorineural deafness and myotonic dystrophy [56]. The development of the eye is highly complicated and well-studied in Drosophila and humans [59]. PAX6 gene in humans or ey gene in drosophila is the chief conductor of the biological symphony of eye development. PAX6 (Transcription factor Paired Box 6) gene in chromosome 11p13 mutation is associated with mostly aniridia but rarely Peters' anomaly and other ocular defects have also been reported [58]. Peters' anomaly could be caused by a variety of genes like PAX6, PITX2, FOXC1, CYP1B1 and B3GALTL as they all collectively during embryogenesis orchestrate the anterior segment development [56].

FOXC1 (forkhead box) gene mutation and haploinsufficiency cause anterior segment anomalies [59]. The MAF basic region leucine zipper (bZIP) transcription factors perform anterior segment and lens development and mutations in the gene in humans cause cataract and ocular developmental defects. CPAMD8 (C3 and PZP-like alpha-2-macroglobulin domain-containing protein 8) mutation causes anterior segment dysgenesis (ectropion uveae, cataract, corectopia, iridodonesis with ectopia lentis) in an autosomal recessive manner [56]. CPAMD8 is involved in the dynamics of aqueous humour.

B3GALTL (Beta-3-Glucosyltransferase) gene in 13q12.3 which glycosylates proteins and when mutated causes Peter Plus syndrome manifesting with ocular and systemic features like abnormal ears, brachydactyly, cleft lip/palate, dextrocardia, dysmorphic face, hydrocephalus and Potter syndrome [56]. SOX2 (SRY-like box2) involved in eye development is mapped to 3q26.3-27 and mutations in the gene cause sclerocornea and anophthalmia [60]. CHRDL1 (Chordin like 1) mutation causes megalocornea and Neuhauser syndrome and the gene is X-linked and located in the Xq23 region [61]. Keratoconus, myopia and glaucoma are associated with glaucoma and hence mutations in the autosomal dominant gene associated with the former is the VSX1 (Visual System Homeobox 1), a transcription factor located in 20p11.21 [62]. Genes like COL4A1, CYP1B1, FGFR2, BMP4, BMP7, FOXE3, MYOC LAMBB2 and LTBP2 are involved in anterior segment anomalies [63].

SIX3 gene mutation causes holoprosencephaly or microphthalmia and iris coloboma [59]. SIX3 interacts with Groucho-related proteins 4 and 5 and functions as an eye development repressor. Besides, PAX6 and SIX3 regulate each other during eye development. Along with FOXE3, MAF, MITF, LHX2, PITX3, PROX1, and SIX3, PAX6 forms the cornea and lens, whereas along with CHX10, EYA1 and PAX2 forms the retina and optic nerve. In addition, genes like BMP4, BMP7, RX and SHH also regulate PAX6 in eye development and mutations in them affects eye development which may result in glaucoma.

In metabolic disorders, the X-linked recessive and autosomal recessive mucopolysaccharidoses [Hurler syndrome (alpha-L-iduronidase), Hunter syndrome (iduronate2-sulfatase), Sanfilippo syndrome (heparin sulphate), Morquino syndrome (N-acetyl galactosamine-6-sulfatase), Maroteauz-Lamy syndrome (N-acetyl galactosamine-4-sulfatase), Natowicz syndrome (hyaluronidase)] gene mutations could result

in defective enzyme causing cataract and glaucoma and the latter by blocking the trabecular meshwork with the glycosaminoglycans [56].

4. Complex genetics and genomics of glaucoma

Syndromic glaucoma is well understood genetically and genomically, with the fundamental knowledge of the cause and effect. However, POAG is a multifactorial disease, where embryological development, genetics, epigenetics, genetic polymorphisms, variable gene expressivity, inflammation and environmental modifiers play a collective complex role and in addition, the penetrance and expressivity may vary between affected individuals [64]. All mentioned earlier, is applicable to most of the lifestyle related complex genetic disorders. This means that the person with a genetic risk may or may not manifest the disease and hence, it is completely unlike the Mendelian genetics. Hence, the disease aetiology, onset, duration, drug response and inheritance are dependent on genetics and environmental modifiers. In addition, some non-genetic modifiers complicate the glaucoma disease status, like smoking, and comorbidities (diabetes, untreated high blood pressure) and near-sightedness [64].

Genetic Epidemiology Research in Adult Health and Ageing (GERA) is part of the UK Biobank (UKB) that has phenotype and genotypes of 500,000 participants aged 40–69 years, which has multi-ethnic glaucoma cases of 7329 and 169,561 controls [65]. Choquet et al., in a GERA study, having 4986 POAG cases and 58, 426 controls comprising of African-Americans, non-Hispanic whites, Hispanic/Latinos, and East-Asian races and ethnicities, identified 24 loci for POAG, out of which 14 were novel and 9 replicated near the genes FMNL2, PDE7B, TMTC2, IKZF2, CADM2, DGKG, ANKH, EXOC2, and LMX1B, across races, but was found higher in African-Americans. Some of the genes had functional influence like FMNL2 and LMX1B – Lmx1b mutations increase the IOP and POAG in mice. A metanalysis of GERA and UKB further identified 24 additional loci expanding the spectrum of the genetics of POAG, however, most of the variants have minimal genetic risk [66]. Burdon et al., have associated the following genes with ocular physiological traits, which are key in maintaining the IOP in POAG - ZNF469, FOXO1, COL5A1, AKAP13, AVGR8, COL8A2, IBTK, LRRK1/CHSY1, C7orf42, ATOH7, TGFBR3, CARD10, CDC7/TGFBR3, SALL1, CDKN2A/B, SIX1/SIX6, FERM8/SCYL1, DCLK1 and CHEK2 [67]. Furthermore, POAG associated candidate genes have been identified, CAV1/CAV2, TMCO1, CDKN2B-AS1, TXNRD2, ATXN2, FOXC1 and GAS7 [68, 69]. Some of the genes are consistent across various studies besides ATOH7, CAV1/CAV2, CDC7-TGFBR3, CDKN2B-AS1, GAS7, SIX1/SIX6 and TMCO1; these are not only associated with POAG but also with the quantitative traits (endophenotypes) [68]. However, some genes having mutations do affect a small proportion of those with POAG, such as cyclin-dependent kinase inhibitor 2B, myocilin (MYOC), neurotrophin 4, optineurin (OPTN), tank binding kinase 1 (TBK1) and WDR 36. Other types of glaucoma like PXFG are associated with LOXL1 and CNTNAP2 and PCG with CYP1B1 and LTBP2 [69, 70]. MYOC, OPTN and TBK1 are used in genetic diagnosis, counselling and clinical management, in addition to this list even CYP1B1 could be added [69]. Verma et al., in a complex gene–gene interaction modelling using NEIGHBOUR, eMERGE datasets and tissue expressing databases identified a new set of genes like GNG7, ROBO1, SUMF1, RYR3, SLC24A3, CCDC3, CARS2, RPS6KA, SETDB1 not only associating with POAG, but also showed that they were expressing in the eye and particularly in the trabecular meshwork [71, 72]. Transforming growth factor-β

(TGFβ) has the basic property of regulating and remodelling the extracellular matrix and hence is one of the candidate genes for glaucoma. TGFB1 –509C > T polymorphism is associated with POAG and therefore we looked at 104 patients with the disease but found no association of the SNP with VCDR, IOP and POAG [73]. VCDR is associated in glaucoma with ABCA1, ASAP1, ATOH7 and ELN gene polymorphisms [68]. GLIS1 (GLIS Family Zinc Finger 1 Kruppel-like transcription factor) variant rs941125 has shown to be associated with glaucoma in humans [74].

Though PXFG and POAG are the leading causes of blindness in glaucoma, PACG is one of the leading causes of blindness particularly in Asia and the blindness due to the latter (PACG) is 10 times more than that of POAG [75]. *PLEKHA7, COL11A1, PCMTD1 and ST18 genes related SNPs located in chromosomes* 11p15, 1p21 and 8q11.23 *were first associated with PACG* [76–78]. In major five Asian countries, a collaborative study was conducted in which 854 cases and 9608 controls (Singapore, Hong Kong, India, Malaysia and Vietnam) with replication studies on 1917 cases and 8943 controls (China, Singapore, India, Saudi Arabia and the UK, including that of the first author [GKM] team) GWAS was conducted to identify genetic factors' associated with the PACG. In the GWAS, three SNPs were significantly associated with PACG in our collaborative cohort - rs11024102 in PLEKHA7 [Pleckstrin Homology Domain Containing A7] (per-allele odds ratio (OR) = 1.22; $P = 5.33 \times 10(-12)$), rs3753841 in COL11A1 [Collagen Type XI Alpha 1 Chain] (per-allele OR = 1.20; $P = 9.22 \times 10(-10)$) and rs1015213 located between PCMTD1 [Protein-L-Isoaspartate (D-Aspartate) O-Methyltransferase Domain Containing 1] and ST18 [ST18 C2H2C-Type Zinc Finger Transcription Factor] on chromosome 8q (per-allele OR = 1.50; $P = 3.29 \times 10(-9)$) [76]. PLEKHA7 (Pleckstrin Homology Domain Containing, Family A Member 7) protein is require for zonule adherens biogenesis and maintenance, *COL1A1 implicated in myopia and MMP9 have been also associated with ACG predisposing traits* [79, 80]. COL11A1 (Collagen Type XI Alpha 1 Chain) protein may play a role in fibrillogenesis regulating the lateral growth of collagen II fibrils. PCMTD1 (Protein-L-Isoaspartate (D-Aspartate) O-Methyltransferase Domain Containing 1) protein is of the methyltransferase superfamily and ST18 (ST18 C2H2C-Type Zinc Finger Transcription Factor) protein inhibits basal transcription activity through target promoters. *There are a myriad of players implicated in PACG as predisposing traits, (extensively reviewed by Ahram et al., Aboobakar and Wiggs) like MTHFR, MFRP, CHX10, HGF, RS; PO1, C3orf26, LAMA2, GJD2, ZNRF3, CD55, MIP, ALPPL2, ZC3H11B, PRSS56, ABCC5, MYOC, CYP1B1, eNOS, PCMTD1, ST18, HSP70, SPARC, CALCRL, EPDR1, CHAT, FERMT2, DPM2, FAM102A and NEB* [77, 81]. A variety of anatomical, physiological, genetic and environmental factors individually or collectively result in PACG and hence, these associations reveal the larger etiopathogenesis network. There are many SNPs associated with PACG predisposing traits, however, the only gene so far identified which causes ACG is NNO1, which leads to nanophthalmos and hyperopia as well [77].

Primary pseudoexfoliation syndrome (PXFS) has fibrogranular extracellular debris in the anterior segment (besides systemic manifestations) which is made up of complex glycoprotein–proteoglycan that causes glaucoma in many but not all, with a preponderance in Scandinavian and Greek populations. In our cohort, we looked at *LOXL1* [Lysyl Oxidase-Like Protein 1] gene exon 1 polymorphisms - allele G of rs1048661 (R141L) and allele G of rs3825942 (G135D), which are significantly associated with XFS in various populations [82]. About 52 XFS including those with glaucoma were screened for the variations and found that allele G of rs3825942 was significantly associated ($p = 0.0001$) and genotype GG ($p = 0.000305$) with XFS in

our population, which was the first Asian study [83]. Pseudo-exfoliation glaucoma is caused by polymorphisms in the lysyl oxidase like 1 (LOXL1) gene in chromosome 15 with significant associations through GWAS in many populations across the world [81]. Pseudo-exfoliation syndrome, due to the deposition of extracellular fibrillar material (basement membrane, clusterin, elastic fibre contents, elastin, fibrillin-1, laminin, fibronectin, latent TGF-B proteins) crosslinking with LOXL1, hence systemically, it may be associated with cardiovascular diseases, cerebrovascular disorders, dementia like Alzheimer's, pelvic organ prolapse and sensory neural deafness [84]. Non-coding variants in exons 1 and 2 of LOXL1 had conflicting reports [78]. CACN1A1 (Calcium Voltage-Gated Channel Subunit Alpha1 A) gene SNP variant was found to be significantly associated with ACG in the Japanese population which was validated in 17 other countries [78]. CACN1A1 helps calcium ion channel function and hence any dysregulation leads to the accumulation of XFS material on the trabecular meshwork. However, neurological disorders, familial hemiplegic migraine, epilepsy, cerebellar atrophy and episodic ataxia are associated with mutations in this gene. Another large 24 countries study significantly associated with POMP (proteasome maturation protein), TMEM136 (transmembrane protein 136), AGPAT1 (1-acylglyceroal-3phosphate O-acyltransfrase), RMBS3 (RNA binding motif single stranded interacting protein 3), SEMA6A (semaphorin 6A) and they were dysregulated [78]. In another Chinese study, The SNPs associated with the genes DENND1A (rs2479106), INSR (rs2059807), THADA (rs12478601), and TOX3 (rs4784165) [85].

5. Genomic mechanisms of glaucoma

The mechanisms of glaucoma is not understood clearly, however, increased IOP is significantly associated with structural (histopathological) and functional (physiological and molecular) distortions leading to neurodegeneration and glaucomatous modifications [86]. The mechanical physical strain and in addition collective stress effects (oxidative, reduced vascular flow, neurotrophic factors deprivation, metabolic, circulatory, immune, mitochondrial dysfunction, excitotoxicity, neuroinflammation, genetic susceptibility, vascular dysregulation) imposed on the lamina cribrosa, retinal ganglion cells and nearby optic nerve cells prevents the free flow of the axonal transport [86, 87]. Zukerman et al., in a review gave the list of genes associated with increased IOP, namely (in the same order)—*ABCA1* (ATP-Binding Cassette, Sub-Family A (ABC1), Member 1), *ABO* (alpha 1–3-N-acetylgalactosaminyltransferase and alpha 1–3-galactosyltransferase), *ADAMTS8* (ADAM Metallopeptidase With Thrombospondin Type 1 Motif 8), *ADAMTS17* (ADAM Metallopeptidase With Thrombospondin Type 1 Motif 17), *ADAMTS18-NUDT7*,(ADAM Metallopeptidase With Thrombospondin Type 1 Motif 18- Nudix Hydrolase 7), *AFAP1(*Actin Filament Associated Protein), *ANGPT1(*Angiopoietin 1), *ANTXR1(*ANTXR Cell Adhesion Molecule 1), *ARHGEF12* (Rho Guanine Nucleotide Exchange Factor 12), *ARID5B* (AT-Rich Interaction Domain 5B), *ATXN2* (Ataxin 2), *CAV1-CAV2(*Caveolin 1- Caveolin 2), *CDKN2B-AS1*(CDKN2B Antisense RNA 1), *CELF1* (CUGBP Elav-Like Family Member 1), *CYP26A1-MYOF* (Cytochrome P450 Family 26 Subfamily A Member 1- Myoferlin), *FAM125B*, (Family With Sequence Similarity 125, Member B) *FNDC3B(*Fibronectin Type III Domain Containing 3B), *FOXC1* (Forkhead Box C1), *FOXP1* (Forkhead Box P1), *GAS7* (Growth Arrest Specific 7), *GLCCI1-ICA1*

(Glucocorticoid Induced 1- Islet Cell Autoantigen 1), *GLIS3* (GLIS Family Zinc Finger 3), *GMDS* (GDP-Mannose 4,6-Dehydratase), *HIVEP3* (HIVEP Zinc Finger 3), *INCA1* (Inhibitor Of CDK, Cyclin A1 Interacting Protein 1), *LMX1B* (LIM Homeobox Transcription Factor 1 Beta), *LOC171391*, *MADD* (MAP Kinase Activating Death Domain), *MIR548F3* (MicroRNA 548f-3), *MYBPC3* (Myosin Binding Protein C3), *NDUFS3* (NADH:Ubiquinone Oxidoreductase Core Subunit S3), *NR1H3* (Nuclear Receptor Subfamily 1 Group H Member 3), *PDDC1* (Parkinson disease 7 domain containing 1), *PKHD1* (PKHD1 Ciliary IPT Domain Containing Fibrocystin/Polyductin), *PTPRJ* (Protein Tyrosine Phosphatase Receptor Type J), *RAPSN* (Receptor Associated Protein of the Synapse), *RPLP2-PNPLA2* (Ribosomal Protein Lateral Stalk Subunit P2- Patatin Like Phospholipase Domain Containing 2), *SIX1/SIX6* (SIX Homeobox 1/SIX Homeobox 6), *SEPT9* (Septin 9), *SEPT11* (Septin11), *TFEC-TES* (Transcription Factor EC- Testin LIM Domain Protein), *TMCO1* (Transmembrane And Coiled-Coil Domains 1) and *TXNRD2* (Thioredoxin Reductase 2) [2]. Majority of the genes' mechanism to cause glaucoma is not understood, however, LMX1B (LIM homeodomain) alters anterior segment development and aqueous humour dynamics; MADD (MAP kinase activating death domain) performs through TNF-a-mediated microglial activation; NR1H3, a nuclear receptor, changes IOP through ABCA1 regulated aqueous humour dynamic alterations and SEPT9, a septin protein, acts through cytoskeletal alterations [2]. In the eye, genes could specifically act at certain parts, like trabecular meshwork (LMX1B, ABCA1), ciliary body (LMX1B), lamina cribrosa (ELN), superficial retinal nerve fibre layer (NR1H3, ABCA1, MADD, ASAP1, ATOH7) and prelaminar region (SEPT9) region [88]. LMX1B mutations have been associated with nail-patella syndrome (nail dysplasia, the patella is absent or is hypoplastic, chronic kidney disease) and a third of these patients develop glaucoma, due to increased IOP [89].

There are several genes significantly associated with CDR, namely, as cited alphabetically by Zukerman et al., – *ABCA1* (ATP-Binding Cassette, Sub-Family A (ABC1), Member 1), *ABG*, *ADAMTS8* (ADAM Metallopeptidase With Thrombospondin Type 1 Motif 8), *ASAP1* (ArfGAP With SH3 Domain, Ankyrin Repeat And PH Domain 1), *ASB7* (Ankyrin Repeat And SOCS Box Containing 7), *ATOH7* (Atonal BHLH Transcription Factor 7), *ATOH7-PBLD* (Atonal BHLH Transcription Factor 7- Phenazine Biosynthesis Like Protein Domain Containing), *BMP2* (Bone Morphogenetic Protein 2), *CARD10* (Caspase Recruitment Domain Family Member 10), *CDC7-TGFBR3* (Cell Division Cycle 7- Transforming Growth Factor Beta Receptor 3), *CDKN2B* (Cyclin Dependent Kinase Inhibitor 2B), *CDKN2B-CDKN2BAS* (Cyclin Dependent Kinase Inhibitor 2B-CDKN2B Antisense RNA 1), *CHEK2* (Checkpoint Kinase 2), *COL8A1* (Collagen Type VIII Alpha 1 Chain), *CRISPLD1* (Cysteine Rich Secretory Protein LCCL Domain Containing 1), *DCLK1* (Doublecortin Like Kinase 1), *DGKB* (Diacylglycerol Kinase Beta), *DUSP1* (Dual Specificity Phosphatase 1), *ELN* (Elastin), *ENO4* (Enolase 4), *EXOC2* (Exocyst Complex Component 2), *F5* (Coagulation Factor V), *FAM101A* (Family With Sequence Similarity 101, Member A), *GAS7* (Growth Arrest Specific 7), *HSF2* (Heat Shock Transcription Factor 2), *PDZD2* (PDZ Domain Containing 2), *PLCE1* (Phospholipase C Epsilon 1), *PSCA* (Prostate Stem Cell Antigen), *RARB* (Retinoic Acid Receptor Beta), *RERE* (Arginine-Glutamic Acid Dipeptide Repeats), *RPAP3* (RNA Polymerase II Associated Protein 3), *RPE65* (Retinoid Isomerohydrolase RPE65), *RREB1* (Ras Responsive Element Binding Protein 1), *SALL1* (Spalt Like Transcription Factor 1), *SCYL1* (SCY1 Like Pseudokinase 1),

SIX1 (SIX Homeobox 1), *SIX6* (SIX Homeobox 6), *SSSCA1* (Sjogren'S Syndrome/ Scleroderma Autoantigen 1), *TMTC2* (Transmembrane O-Mannosyltransferase Targeting Cadherins 2), and *VCAN* (Versican) [90]. Some of them have been linked with both CDR and IOP - *ABCA1*, *ABG*, *AFAP1*, *CAV1*, *GAS7* and *LMX1B* [2, 91]. RPE65 gene mutations result in Leber congenital amaurosis and early childhood onset retinitis pigmentosa [92]. ABCA1 is associated with cholesterol metabolism and liver function and is associated with retinal ganglion cell death and normal physiology [91]. ELN modifies the normal activity of elastin resulting in optic nerve head degeneration; ASAP1 is associated with giant cell medicated retinal ganglion cell loss and ATOH7 is connected with Muller cell differentiation and retinal ganglion cell genesis [90]. The degenerative patterns are seen in different structures of the RGC—soma atrophy, nuclear shrinkage axonic insult, and deteriorating changes in the synapses and dendrites, finally extending to the amacrine and bipolar cells [87]. Adding to the complexity, a transcriptome wide association studies identified SIX6 and CDKN2A/B to be associated with POAG and these are also linked to cardiovascular diseases and cancer [93]. The mitogen activated protein kinase p38 and Jun N terminal kinases are activated through several signalling pathways which initiate the degeneration of the soma of the RGC [94]. Subsequently, activation of the apoptotic pathway is triggered and the BCL2 gene family BAX is prompted in monkeys, rabbits and humans as well [95, 96].

6. Neuroprotection & neurodegeneration genomics in glaucoma

Glaucoma is nowadays considered to be a chronic neurodegenerative disorder which has decreased sensitivity to colour and contrast, blurry vision and reducing the field of vision with nil signs or symptoms [45]. The transcription factors, transporters, glycosylation proteins, and mutations will result in loss of function, low-risk variants gene expression modifications due to RNA splicing and transcription activities. Epigenetic activities like DNA methylation, histone body acetylation, deacetylation, structural chromatin modification and transcription. Micro RNAs miR24, miR29, miR204, miR146a [45]. In mice with optic nerve crush and glaucomatous damage could be rescued with miR-194 and miR-644-2 inhibitors provided neuroprotection and miR-181a and miR-181d-5p mimics showed neuritogenesis in retinal ganglion cells [97].

Optic nerve head is the primary critical site of degeneration in glaucoma. Axonal deprivation of neurotrophins like brain derived neurotrophic factors and mitochondrial dysfunction leads to axon transport failure [98]. There are other stakeholders in axonal degeneration of RGCs, like reduced blood flow, extracellular matrix remodelling, oxidative stress and reactive gliosis [99]. The Rho/ROCK signalling pathway prevents central nervous system regeneration through transducing inhibitory signals and is a good target for intervention in axon regeneration in glaucoma [100]. P13K/Akt pathway facilitates axonal growth and regeneration by converting PIP2 (phosphatidylinositol bisphosphate) to PIP3 (phosphatidylinositol trisphosphate) which in turn activates protein kinase Akt. This action results in phosphorylation and activation of mTOR (rapamycin), which promotes protein synthesis, motility, cell growth and survival [101]. Jak/STAT is involved in axonal regeneration by the binding of cytokines to the extracellular receptors associated with protein kinase JAK, which activates and phosphorylates the STATs. Axon regeneration is

inhibited by the suppressor of cytokine signalling (SOCS) suppressing the Jak/STAT signalling [101]. Interestingly, in an immunoreactive male Lewis rats for S100B protein (the antibody which is found in high titre in glaucoma patients) showed 43 proteins were dysregulated in the retina, out of which alpha-2 macroglobulin increase was significantly associated with heat shock protein 60, showcasing the role of immunological factors in glaucoma [102].

Glaucomatous pressure leads to the progressive death of the retinal ganglion cells (RGCs), degeneration of the optic nerve and loss of peripheral vision, though normal tension glaucoma happens with the same pathological mechanism, questioning the role of intraocular pressure in the process. The trabecular meshwork is the seat of the pathology with a number of influencing factors like ageing, genetics, mechanical and oxidative stress, all collectively inhibiting the neurotrophic molecules nourishing the RGCs.

Neuroprotection of the retinal ganglion cells is critical for cell survival since several signalling pathways play the role, like JAK/STAT, MAPK, TrkA, TrkB and clinical trials with CNTF (ciliary neurotrophic factor and NGF [nerve growth factor] are in vogue [103]. CNTF is a neuropoietic cytokine belonging to IL6, which binds to the receptor of gp130 to activate JAK/STAT and MAPK to neuroprotect the RGCs [103]. NGF is secreted by nerve tissue (neurons, oligodendrocytes, Schwann cells), immune cells (T cells, mast cells, macrophages), skin cells (fibroblasts, keratinocytes, melanocytes) and smooth cells, which regulate apoptosis, neuronal plasticity, neurogenesis and neuroinflammation [103]. BDNF (brain-derived nerve growth factor), VEGF (vascular endothelial growth factor), PEDG (pigment epithelium-derived factor), GDNF (glial cell line derived neurotrophic factor) and Norrin are some of the other RGC neuroprotective proteins [103].

Epithelial cells, glial cells, leukocytes and neurons produce various neuroprotective factors like brain-derived neurotrophic factor, ciliary neurotrophic factor, glial cell line derived neurotrophic factor, nerve growth factor, norrin, pigment epithelium-derived factor, vascular endothelial growth factor and each in an exceptional way prevent RGC damage which is triggered by the ischaemic neuropathy, glaucoma, ocular hypertension and oxygen-induced retinopathy and the survival is achieved by interventional strategy through activating a variety of signalling pathways like JAK/STAT, MAPK, TrkA and TrKB [103].

The cell and tissue stakeholders in glaucoma are trabecular meshwork, retinal ganglion cell layer, retinal nerve fibre layer, cells in the optic nerve head (lamina cribrosa, optic nerve head astrocytes) and peripapillary sclera around the optic nerve head [104]. These components react to biomechanical stress like compression and stretching and the cell structures that respond are the cell membrane, cytoskeleton (actin microfilaments and tubules), extracellular matrix and nucleus. Gene expression, hence, in these cells are altered with copious TGFbeta2 synthesis in glaucoma models [104].

6.1 Biomarker genomics in glaucoma

Protein biomarkers have been identified in various parts of the eye structure associated with glaucoma, as explained in the review by Cueto et al. [1]. However, caution has to be adopted while interpreting the protein biomarker studies, due to the nature of these studies where different clinical and laboratory methodologies with variable sensitivity and specificity techniques and equipments were used, the sample sizes were too small, many studies are not validated, there are conflicting reports of dysregulation and there is poor consensus, no data between, the aqueous humour, tears, serum and vitreous samples. However, overexpression of the biomarkers could

become neurotoxic and down-regulation and lack of or less expression of neuroprotectors will lead to degeneration of the retinal ganglion cells via the TrkA receptor pathway. Biomarkers could provide early screening and detection of glaucoma in the target population, diagnosis and prognostication. The biomarkers upstream or downstream could be novel targets for therapeutic interventions and visual stability or recovery. Accumulation of biomarkers will distort the blood aqueous barrier due to the inflammation and dysregulation of the extracellular matrix tissue

Serial number	Biomarkers type	Biomarkers
1	Inflammatory biomarkers	Increased: TGFB2, CD44, erythropoietin, TNFA, IL8, serum amyloid A, *CXCL13, CXCL16, CCL13, CCL15, CCL22, CCL24, IL-4, IL-16 (PXFG); autotoxin, Growth differentiation protein 15 and endothelin, Proatrial natriuretic peptide (regulates vascular/neural integrity of adult retina), IL-5, IL-12, IL-15, interferon gamma, fibroblast growth factor, vascular endothelial growth* Decreased: *Secreted frizzled related protein-1, klotho (ageing protein),*
2.	Oxidative stress related biomarkers	Increased: *superoxide dismutase, glutathione peroxidase, malondialdehyde, nitric oxide synthase, carbonyl, hydrogen peroxide, advanced glycation end products.* Decreased: Catalase, vitamins C/E
3.	Extracellular matrix related biomarkers	Increased: Fibronectin; clusterin; periostin Decreased: Hyaluronic acid, fibulin-7, Variably expressed: Connective tissue growth factor, gelatinase. Under regulated: Cystatin C, osteopontin,
4.	*Immune-response-, neurodegeneration-, and apoptosis-related markers*	Increased: Heat shock protein-70, vimentin; heat shock protein-27, transthyretin; *prostaglandin H2 D-isomerase, caspase 14 precursor, CysC, albumin precursor, transferrin; apolipoprotein A4, ALB, antithrombin 3 (SERPINC1),* CD14, CD59, complement factor D, APOA4, chromogranin A, MYB, TIMP1, microfibril-associated glycoprotein 4, agrin, and apolipoprotein C-III, Ig j chain C region, inter-a-trypsin inhibitor heavy chain 4, isocitrate dehydrogenase (NAD) subunit α, ALB, CysC, TIMP2, A2M, PGTDS, NPP2, apolipoprotein A1, APOC3, apolipoprotein E, transthyretin, and α2-macroglobulin, vitronectin, complement factors (C3a, C5b-9), Decreased: *α-enolase (ENO1), actin, and glyceraldehyde-3-phosphate dehydrogenase (POAG, PEXG), transthyretin, prostaglandin H2D isomerase, opticin, interphotoreceptor retinoid-binding protein, apolipoprotein D, SOD1,*
5.	Metabolite based biomarkers	Increased: Homocysteine, diadenosine tetraphosphate, MDA, creatinine, carnitines, aminoacids (glutamine, glycine, alanine, leucine, isoleucine, hydroxyproline, acetylornithine), several phosphatidylcholines, lysophosphatidylcholines, sphingomyelin, glycine (significantly different), pelargonic acid and galactose 1, glucose-1 phosphate, sorbitol, spermidine 2, betaine, taurine, glutamate, Decreased: Adenosine triphosphate/ Adenosine diphosphate, taurine, spermine
6.	Lipid metabolism	Increased: palmitoleic acid, gamma-linolenic acid, arachidonic acid, adrenic acid, hydroxylinoleate, hydroxyarachidonate isomers Decreased: eicosapentaenoic fatty acid, DHA, total ω3 long-chain polyunsaturated fatty acid

Table 1.
Dysregulation of gene expression and biomarkers in primary open angle glaucoma, primary closed-angle glaucoma, primary congenital glaucoma, pseudo-exfoliation glaucoma and neovascular glaucoma are summarised. Please refer to Ceutu et al., for further details [1].

physiology. Similarly, the biomarkers will intervene in the autonomic regulation of the sympathetic system affecting the ciliary body and trabecular meshwork physiological architecture. To date, over 450 biomarkers have been identified which have never been validated across large sample size patients and controls, not across different populations in the world and have not entered the arena of clinical practice, keeping the research door wide open.

Biomarkers have been identified in aqueous humour, optic nerve, retina, trabecular meshwork, tears, vitreous body, serum and blood. Besides, there are biomarkers related to apoptosis, inflammation, oxidative stress, extracellular matrix, immune response, neuroprotection, and neurodegeneration. A fairly extensive list of the biomarkers in glaucoma is provided in **Table 1**, please refer to Cueto et al., for detailed information [1].

6.2 Recent advances of genomic interventional strategies & glaucoma

Gene therapy in glaucoma is promising and is tackled by neuroprotection of the focusing on prevention of neuronal cell soma and axon loss. Another method is of optic nerve axonic regeneration [87]. In neuroprotection gene therapy, mostly in animal studies, what is addressed are overexpressing of growth and neurotrophic factors (brain-derived neurotrophic factor, fibroblast growth factor, ciliary neurotrophic factor), antiapoptotic factors (BAG1, Bcl-X, BIRC4/XIAP), transcription factors (ATF3, Brn3b, CREB, NMDA, KLF7), oxidative stress components (catalase, NRF2, SOD2), Rho/ROCK pathway (exoenzyme C3, RhoA, ROCK2), mitochondrial targets (NMNAT1, DBA2J, OPA1) and other targets (ABCA1, MCT2, Hsp70, MEK1, ULK1, miRNAs) [87]. On the axon regeneration gene therapy, what is targeted are either by overexpression or silencing in the optic nerve, optic chiasma, optic tract - PI3K/Akt pathway (PTEN, P13K, cRHEB, S6K1, GSK3, eIF2B, FGF2, IGF1, neuretin), Jak/STAT pathway (CNTF, IL6, IL22, STAT3, SOCS4, Pim1), Rho/ROCK pathway (RhoA, ROCK2, LIMK-1, LOTUS, PirB), transcription factors (KLF9, c-myc, KLF4, p53, SOX11) and other targets (many including, Lin28, HDAC5, melanopsin, TIMP2, PRPH). The gene and molecules list are selective and not exhaustive. These therapies could also be given in a combinatorial manner. Many of these molecules are awaiting the approval of the FDA, USA for clinical trials [87].

7. Experimental bioinformatics analysis

We used a bioinformatic analysis to arrive at the exhaustive list of genes or genetic factors associated with glaucoma. Genes and variants associated with different types of glaucoma were mined by using the DisGeNET Cytoscape App (version 7.0) [105].

Gene	Gene_Full_Name	Protein_Class
CYP1B1	Cytochrome P450 family 1 subfamily B member 1	Enzyme
LTBP2	Latent transforming growth factor beta binding protein 2	Calcium-binding protein
MYOC	Myocilin	Cellular structure

Table 2.
Genes associated with Juvenile open-angle glaucoma.

The DisGeNET database, retrieves gene-disease and variant-disease associations from curated databases. Analysis was performed for "Gene Disease Networks" and "Variant Disease Network", by selecting "curated" as source and "Eye diseases" as disease class and "Glaucoma" as disease. The plethora list of genes and genetic factors are provided according to the type of glaucoma in **Tables 2–9**.

Gene	Variant	Chr	Position	Consequence	Alleles	Class
CYP1B1	rs104893629	2	38071087	missense variant	T/A	snv

Table 3.
Variants associated with Juvenile open-angle glaucoma.

Gene	Gene Full Name	Protein Class
ADAMTSL1	ADAMTS like 1	Enzyme
ADRB2	Adrenoceptor beta 2	G-protein coupled receptor
ANGPT1	Angiopoietin 1	Signaling
ARSD	Arylsulfatase D	Enzyme
COL1A1	Collagen type I alpha 1 chain	
CYP1B1	Cytochrome P450 family 1 subfamily B member 1	Enzyme
CYP2B6	Cytochrome P450 family 2 subfamily B member 6	
FOXC1	Forkhead box C1	Transcription factor
GLC3B	Glaucoma 3, primary infantile, B	
GLC3C	Glaucoma 3, primary congenital, C	
HTC2	Hypertrichosis 2 (generalized, congenital)	
KIF1B	Kinesin family member 1B	Cellular structure
LOC110599580	CYP1B1 promoter	
LOXL1	Lysyl oxidase like 1	
LTBP2	Latent transforming growth factor beta binding protein 2	Calcium-binding protein
MFN2	Mitofusin 2	Enzyme
MYOC	Myocilin	Cellular structure
PGC	Progastricsin	Enzyme
PLXNA2	Plexin A2	
SH3PXD2B	SH3 and PX domains 2B	
SLC4A4	Solute carrier family 4 member 4	Transporter
STATH	Statherin	
TEK	TEK receptor tyrosine kinase	Kinase
TYR	Tyrosinase	Enzyme

Literature suggests that the inheritance of PCG includes an autosomal-recessive and sex-associated element with variable penetrance. Over 150 variants identified in CYP1B1 gene are responsible for the of PCG. Various studies showed the genes (CYP1B1, LTBP2, MYOC, COL1A1, FOXC1, ANGTP1, TEK) associated with the pathogenesis of PCG.

Table 4.
Genes associated with primary congenital glaucoma.

Gene	Variant	Chr	Position	Consequence	Alleles	Class
ADRB2	rs1042714	5	148826910	Stop gained	G/C;T	snv
ADRB2	rs1800888	5	148827322	Missense variant	C/T	snv
COL1A1	rs72645318	17	50197057	Stop gained	G/A	snv
COL1A1	rs72651658	17	50190861	Missense variant	C/T	snv
CYP1B1	rs79204362	2	38071251	Missense variant	C/T	snv
CYP1B1	rs104893622	2	38071234	Missense variant	C/T	snv
CYP1B1	rs1800440	2	38070996	Missense variant	T/C;G	snv
CYP1B1	rs55989760	2	38071195	Missense variant	C/G;T	snv
CYP1B1	rs56010818	2	38071185	Missense variant	C/T	snv
CYP1B1	rs72549379	2	38071264	Missense variant	C/T	snv
CYP1B1;CYP1B1-AS1	rs28936700	2	38075207	Missense variant	C/G;T	snv
CYP1B1;CYP1B1-AS1	rs104893623	2	38075219	Stop gained	C/T	snv
CYP1B1;CYP1B1-AS1	rs1272655298	2	38074527	Missense variant	C/G;T	snv
CYP1B1;CYP1B1-AS1	rs2567206	2	38076389	Non coding transcript exon variant	G/A	snv
CYP1B1;CYP1B1-AS1	rs72481807	2	38074872	Stop gained	C/A;T	snv
CYP1B1;CYP1B1-AS1	rs9282671	2	38075148	Missense variant	A/T	snv
CYP1B1-AS1;CYP1B1	rs57865060	2	38074704	Missense variant	C/T	snv
CYP1B1-AS1;CYP1B1	rs72549387	2	38075218	Stop gained	C/G;T	snv
FN1	rs1277989297	2	215428270	Stop gained	G/A	snv
LTBP2	rs121918355	14	74555629	Stop gained	G/A;T	snv
LTBP2	rs3742793	14	74603790	Intron variant	G/C	snv
LTBP2	rs61738025	14	74552299	Synonymous variant	C/T	snv
MYOC	rs74315339	1	171652468	Missense variant	C/A	snv
MYOC;MYOCOS	rs752829138	1	171638607	Frameshift variant	TC/-	delins
PAX6	rs121907917	11	31794079	Stop gained	G/A	snv

Table 5.
Variants associated with primary congenital glaucoma.

Gene	Gene_Full_Name	Protein_Class
ABCA1	ATP binding cassette subfamily A member 1	Transporter
ABCB1	ATP binding cassette subfamily B member 1	Transporter
ABCC4	ATP binding cassette subfamily C member 4	Transporter
ABO	ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase	Enzyme
ACE	Angiotensin I converting enzyme	Enzyme
ACOT7	Acyl-CoA thioesterase 7	Enzyme
ACTB	Actin beta	Cellular structure

Gene	Gene_Full_Name	Protein_Class
ACTBL2	Actin beta like 2	
ACTG1	Actin gamma 1	Cellular structure
ACTG2	Actin gamma 2, smooth muscle	Cellular structure
ADAMTS10	ADAM metallopeptidase with thrombospondin type 1 motif 10	Enzyme
ADAMTS17	ADAM metallopeptidase with thrombospondin type 1 motif 17	Enzyme
ADAMTSL3	ADAMTS like 3	Enzyme
ADRB2	Adrenoceptor beta 2	G-protein coupled receptor
AFAP1	Actin filament associated protein 1	
AGBL2	ATP/GTP binding protein like 2	Enzyme
AGER	Advanced glycosylation end-product specific receptor	Receptor
AKT1	AKT serine/threonine kinase 1	Kinase
ALB	Albumin	Transporter
ANGPT2	Angiopoietin 2	Signaling
ANGPTL7	Angiopoietin like 7	Signaling
ANXA5	Annexin A5	
APBB2	Amyloid beta precursor protein binding family B member 2	
APEX1	Apurinic/apyrimidinic endodeoxyribonuclease 1	
APOC3	Apolipoprotein C3	
APOE	Apolipoprotein E	
APP	Amyloid beta precursor protein	Enzyme modulator
AQP1	Aquaporin 1 (Colton blood group)	Ion channel
ARHGEF12	Rho guanine nucleotide exchange factor 12	
ARHGEF7	Rho guanine nucleotide exchange factor 7	
ARSD	Arylsulfatase D	Enzyme
ASB10	Ankyrin repeat and SOCS box containing 10	
ASCC1	Activating signal cointegrator 1 complex subunit 1	
ASCC2	Activating signal cointegrator 1 complex subunit 2	
ATOH7	Atonal bHLH transcription factor 7	Enzyme
ATP10A	ATPase phospholipid transporting 10A (putative)	Transporter
ATXN2	ataxin 2	Nucleic acid binding
AXL	AXL receptor tyrosine kinase	Kinase
B4GALT3	Beta-1,4-galactosyltransferase 3	Enzyme
BAK1	BCL2 antagonist/killer 1	Signaling
BDNF	Brain derived neurotrophic factor	Signaling
BIRC6	Baculoviral IAP repeat containing 6	
BMP4	Bone morphogenetic protein 4	Signaling
BRCA1	BRCA1 DNA repair associated	Enzyme

Gene	Gene_Full_Name	Protein_Class
C1QBP	Complement C1q binding protein	
C3	Complement C3	Enzyme modulator
CACNA1C	Calcium voltage-gated channel subunit alpha1 C	Ion channel
CACNA2D1	Calcium voltage-gated channel auxiliary subunit alpha2delta 1	Ion channel
CALCA	Calcitonin related polypeptide alpha	Signaling
CALCRL	Calcitonin receptor like receptor	G-protein coupled receptor
CARD10	Caspase recruitment domain family member 10	
CAT	Catalase	Enzyme
CAV1	caveolin 1	Enzyme modulator
CAV2	caveolin 2	Enzyme modulator
CCHCR1	Coiled-coil alpha-helical rod protein 1	
CCL16	C-C motif chemokine ligand 16	Signaling
CCL2	C-C motif chemokine ligand 2	Signaling
CCL4	C-C motif chemokine ligand 4	Signaling
CCL4L1	C-C motif chemokine ligand 4 like 1	
CCL4L2	C-C motif chemokine ligand 4 like 2	
CCN2	Cellular communication network factor 2	Signaling
CD40	CD40 molecule	
CDC7	Cell division cycle 7	Kinase
CDH1	Cadherin 1	
CDH5	Cadherin 5	
CDK9	Cyclin dependent kinase 9	Kinase
CDKN1A	Cyclin dependent kinase inhibitor 1A	
CDKN2A	Cyclin dependent kinase inhibitor 2A	
CDKN2B	Cyclin dependent kinase inhibitor 2B	
CDKN2B-AS1	CDKN2B antisense RNA 1	
CDX2	Caudal type homeobox 2	Transcription factor
CHDH	Choline dehydrogenase	Enzyme
CIAO3	Cytosolic iron-sulfur assembly component 3	Enzyme
CLCN2	Chloride voltage-gated channel 2	Ion channel
CLU	Clusterin	
CNTF	Ciliary neurotrophic factor	
CNTN4	Contactin 4	Receptor
CNTNAP4	Contactin associated protein family member 4	
COCH	Cochlin	Receptor
COL11A1	Collagen type XI alpha 1 chain	
COL15A1	Collagen type XV alpha 1 chain	

Gene	Gene_Full_Name	Protein_Class
COL18A1	Collagen type XVIII alpha 1 chain	
COL1A1	Collagen type I alpha 1 chain	
COL5A1	Collagen type V alpha 1 chain	
COL5A2	Collagen type V alpha 2 chain	
COL8A1	Collagen type VIII alpha 1 chain	Extracellular structure
COL8A2	Collagen type VIII alpha 2 chain	Extracellular structure
COX1	Cytochrome c oxidase subunit I	Enzyme
COX2	Cytochrome c oxidase subunit II	Enzyme
CRISP2	Cysteine rich secretory protein 2	Immune response
CRYAB	Crystallin alpha B	
CST3	Cystatin C	
CTSD	Cathepsin D	Enzyme
CUX1	Cut like homeobox 1	Transcription factor
CXCL5	C-X-C motif chemokine ligand 5	Signaling
CXCR3	C-X-C motif chemokine receptor 3	G-protein coupled receptor
CYP1A1	Cytochrome p450 family 1 subfamily a member 1	Enzyme
CYP1B1	Cytochrome p450 family 1 subfamily b member 1	Enzyme
CYP27A1	Cytochrome p450 family 27 subfamily a member 1	Enzyme
CYP2C19	Cytochrome p450 family 2 subfamily c member 19	
CYP2D6	Cytochrome p450 family 2 subfamily d member 6	
CYP46A1	Cytochrome p450 family 46 subfamily a member 1	Enzyme
DBN1	Drebrin 1	Cellular structure
DCLK1	Doublecortin like kinase 1	Kinase
DCN	Decorin	
DDIT3	DNA damage inducible transcript 3	
DDX20	DEAD-box helicase 20	
DDX3X	DEAD-box helicase 3 X-linked	
DLG2	Discs large MAGUK scaffold protein 2	Receptor
DNASE1L3	Deoxyribonuclease 1 like 3	
EBF1	EBF transcription factor 1	
EDN1	Endothelin 1	Signaling
EDNRA	Endothelin receptor type A	G-protein coupled receptor
EFEMP1	EGF containing fibulin extracellular matrix protein 1	Extracellular structure
EGFR	Epidermal growth factor receptor	Kinase
EGR1	Early growth response 1	Nucleic acid binding

Gene	Gene_Full_Name	Protein_Class
EIF2D	Eukaryotic translation initiation factor 2D	Receptor
ELN	Elastin	
ELOVL5	ELOVL fatty acid elongase 5	Enzyme
ESR1	Estrogen receptor 1	Nuclear receptor
ESR2	Estrogen receptor 2	Nuclear receptor
FASTKD1	FAST kinase domains 1	
FBLN1	Fibulin 1	
FBLN5	Fibulin 5	Calcium-binding protein
FBLN7	Fibulin 7	
FBN1	Fibrillin 1	Calcium-binding protein
FHL5	Four and a half LIM domains 5	Transcription factor
FLNB	Filamin B	
FLOT1	Flotillin 1	
FN1	Fibronectin 1	Signaling
FNDC3B	Fibronectin type III domain containing 3B	
FOXC1	Forkhead box C1	Transcription factor
FUT7	Fucosyltransferase 7	Enzyme
FZR1	Fizzy and cell division cycle 20 related 1	Enzyme modulator
GALC	Galactosylceramidase	
GAS1	Growth arrest specific 1	
GAS7	Growth arrest specific 7	
GDF15	Growth differentiation factor 15	Signaling
GJA1	Gap junction protein alpha 1	Cell-cell junction
GLB1	Galactosidase beta 1	Enzyme
GLC1B	Glaucoma 1, open angle, B (adult-onset)	
GLC1C	Glaucoma 1, open angle, C	
GLC1D	Glaucoma 1, open angle, D (adult-onset)	
GLC1H	Glaucoma 1, open angle, H (adult-onset)	
GLC1J	Glaucoma 1, open angle, J (juvenile-onset)	
GLC1K	Glaucoma 1, open angle, K (juvenile-onset)	
GLC1N	Glaucoma 1, open angle, N (juvenile-onset)	
GLC3B	Glaucoma 3, primary infantile, B	
GLCCI1	Glucocorticoid induced 1	
GMDS	GDP-mannose 4,6-dehydratase	Enzyme
GRIN2B	Glutamate ionotropic receptor NMDA type subunit 2B	Ion channel
GSTK1	Glutathione S-transferase kappa 1	
GSTM1	Glutathione S-transferase mu 1	

Gene	Gene_Full_Name	Protein_Class
GSTM2	Glutathione S-transferase mu 2	
GSTP1	Glutathione S-transferase pi 1	
GSTT1	Glutathione S-transferase theta 1	
GUCY1A1	Guanylate cyclase 1 soluble subunit alpha 1	
H3P40	H3 histone pseudogene 40	
HAS2	Hyaluronan synthase 2	
HDAC6	Histone deacetylase 6	Epigenetic regulator
HES1	Hes family bHLH transcription factor 1	Transcription factor
HEYL	Hes related family bHLH transcription factor with YRPW motif like	Transcription factor
HK2	Hexokinase 2	Kinase
HLA-A	Major histocompatibility complex, class I, A	
HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	Immune response
HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	Immune response
HPGDS	Hematopoietic prostaglandin D synthase	
HSPA14	Heat shock protein family A (Hsp70) member 14	
HSPA1A	Heat shock protein family A (Hsp70) member 1A	
HSPA1B	Heat shock protein family A (Hsp70) member 1B	
HSPA4	Heat shock protein family A (Hsp70) member 4	
HSPA5	Heat shock protein family A (Hsp70) member 5	
HSPB1	Heat shock protein family B (small) member 1	
HSPB2	Heat shock protein family B (small) member 2	
HSPB3	Heat shock protein family B (small) member 3	
HSPD1	Heat shock protein family D (Hsp60) member 1	
HTC2	Hypertrichosis 2 (generalized, congenital)	
HYAL3	Hyaluronidase 3 hyaluronidase 3	Enzyme
ICA1	Islet cell autoantigen 1	
IDH3A	Isocitrate dehydrogenase (NAD(+)) 3 catalytic subunit alpha	Enzyme
IFNG	Interferon gamma	
IGF2	Insulin like growth factor 2	
IGFALS	Insulin like growth factor binding protein acid labile subunit	Receptor
IGKC	Immunoglobulin kappa constant	
IL10	Interleukin 10	
IL17B	Interleukin 17B	
IL1A	Interleukin 1 alpha	
IL1B	Interleukin 1 beta	
IL1RN	Interleukin 1 receptor antagonist	
IL2	Interleukin 2	

Gene	Gene_Full_Name	Protein_Class
IL20	Interleukin 20	
IL20RB	Interleukin 20 receptor subunit beta	Receptor
IL2RA	Interleukin 2 receptor subunit alpha	Receptor
IL6	Interleukin 6	
IL7	Interleukin 7	
IL9	Interleukin 9	
ISG20	Interferon stimulated exonuclease gene 20	
ITGA5	Integrin subunit alpha 5	
ITGAV	Integrin subunit alpha V	
ITIH4	Inter-alpha-trypsin inhibitor heavy chain 4	Enzyme modulator
ITPR3	Inositol 1,4,5-trisphosphate receptor type 3	Ion channel
KDR	Kinase insert domain receptor	Kinase
LDLR	Low density lipoprotein receptor	
LGALS14	Galectin 14	Signaling
LGTN	Ligatin	
LHCGR	Luteinizing hormone/choriogonadotropin receptor	G-protein coupled receptor
LINC02605	Long intergenic non-protein coding RNA 2605	
LMX1B	LIM homeobox transcription factor 1 beta	Nucleic acid binding
LOC110599580	CYP1B1 promoter	
LOXL1	Lysyl oxidase like 1	
LOXL2	Lysyl oxidase like 2	
LTBP2	Latent transforming growth factor beta binding protein 2	Calcium-binding protein
MAP3K1	Mitogen-activated protein kinase kinase kinase 1	Kinase
MAP3K8	Mitogen-activated protein kinase kinase kinase 8	Kinase
MARCHF8	Membrane associated ring-CH-type finger 8	
MARCHF9	Membrane associated ring-CH-type finger 9	
MBL2	Mannose binding lectin 2	Receptor
MBP	Myelin basic protein	
MFGE8	Milk fat globule-EGF factor 8 protein	Enzyme
MINDY4	MINDY lysine 48 deubiquitinase 4	
MIR182	microRNA 182	
MIR210	microRNA 210	
MIR302D	microRNA 302d	
MIR34B	microRNA 34b	
MIR630	microRNA 630	
MLXIP	MLX interacting protein	
MMP1	Matrix metallopeptidase 1	Enzyme

Gene	Gene_Full_Name	Protein_Class
MMP12	Matrix metallopeptidase 12	Enzyme
MMP2	Matrix metallopeptidase 2	Enzyme
MMP3	Matrix metallopeptidase 3	Enzyme
MMP9	Matrix metallopeptidase 9	Enzyme
MMRN1	Multimerin 1	
MPO	Myeloperoxidase	Enzyme
MPP7	Membrane palmitoylated protein 7	Enzyme
MT1A	Metallothionein 1A	
MT1B	Metallothionein 1B	
MT1E	Metallothionein 1E	
MT1F	Metallothionein 1F	
MT1G	Metallothionein 1G	
MT1H	Metallothionein 1H	
MT1IP	Metallothionein 1I, pseudogene	
MT1JP	Metallothionein 1J, pseudogene	
MT1L	Metallothionein 1L, pseudogene	
MT1M	Metallothionein 1M	
MT1X	Metallothionein 1X	
MTCO2P12	MT-CO2 pseudogene 12	
MTHFR	Methylenetetrahydrofolate reductase	
MTNR1A	Melatonin receptor 1A	G-protein coupled receptor
MUTYH	mutY DNA glycosylase	Enzyme
MVB12B	Multivesicular body subunit 12B	
MYLIP	Myosin regulatory light chain interacting protein	
MYOC	Myocilin	Cellular structure
MYOCOS	Myocilin opposite strand	
MZB1	Marginal zone B and B1 cell specific protein	
NANOS2	Nanos C2HC-type zinc finger 2	
ND2	MTND2	
NFKB1	Nuclear factor kappa B subunit 1	Transcription factor
NFKB2	Nuclear factor kappa B subunit 2	Transcription factor
NOS2	Nitric oxide synthase 2	
NOS3	Nitric oxide synthase 3	
NPPA	Natriuretic peptide A	
NPPC	Natriuretic peptide C	Signaling
NR3C1	Nuclear receptor subfamily 3 group C member 1	Nuclear receptor
NTF4	Neurotrophin 4	Signaling

Gene	Gene_Full_Name	Protein_Class
NTM	Neurotrimin	
NXF1	Nuclear RNA export factor 1	Nucleic acid binding
OAS3	2'-5'-oligoadenylate synthetase 3	Enzyme
OGG1	8-oxoguanine DNA glycosylase	
OGN	Osteoglycin	
OPA1	OPA1 mitochondrial dynamin like GTPase	Enzyme modulator
OPTC	Opticin	Receptor
OPTN	Optineurin	
PADI2	Peptidyl arginine deiminase 2	
PAH	Phenylalanine hydroxylase	
PARP1	Poly(ADP-ribose) polymerase 1	
PCOLCE2	Procollagen C-endopeptidase enhancer 2	
PDE5A	Phosphodiesterase 5A	
PDIA5	Protein disulfide isomerase family A member 5	
PEX5	Peroxisomal biogenesis factor 5	Transporter
PITX2	Paired like homeodomain 2	
PKHD1	PKHD1 ciliary IPT domain containing fibrocystin/polyductin	
PLA2G4A	Phospholipase A2 group IVA	Enzyme
PLB1	Phospholipase B1	
PLG	Plasminogen	Enzyme
PLXDC2	Plexin domain containing 2	
PLXNA2	Plexin A2	
PMEL	Premelanosome protein	Signaling
POTEKP	POTE ankyrin domain family member K, pseudogene	
POTEM	POTE ankyrin domain family member M	
PPID	Peptidylprolyl isomerase D	
PPIF	Peptidylprolyl isomerase F	
PRDM5	PR/SET domain 5	
PRKAA1	Protein kinase AMP-activated catalytic subunit alpha 1	Kinase
PRNP	Prion protein	
PRPF8	Pre-mRNA processing factor 8	Nucleic acid binding
PRS	Prieto X-linked mental retardation syndrome	
PRSS55	Serine protease 55	Enzyme
PSD	Pleckstrin and Sec7 domain containing	
PTEN	Phosphatase and tensin homolog	Enzyme
PTGFR	Prostaglandin F receptor	G-protein coupled receptor
PTGS1	Prostaglandin-endoperoxide synthase 1	Enzyme

Gene	Gene_Full_Name	Protein_Class
PTGS2	Prostaglandin-endoperoxide synthase 2	Enzyme
PTPRJ	Protein tyrosine phosphatase receptor type J	Enzyme
RAMP2	Receptor activity modifying protein 2	Receptor
RAN	RAN, member RAS oncogene family	Enzyme modulator
RBP1	Retinol binding protein 1	
RHOA	ras homolog family member A	Enzyme modulator
RHOD	ras homolog family member D	Enzyme modulator
RNR2	l-rRNA	
ROCK1	Rho associated coiled-coil containing protein kinase 1	Kinase
ROCK2	Rho associated coiled-coil containing protein kinase 2	Kinase
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase	Kinase
RPGRIP1	RPGR interacting protein 1	Enzyme modulator
RPN2	Ribophorin II	Enzyme
RTCA	RNA 3'-terminal phosphate cyclase	Enzyme
SART3	Spliceosome associated factor 3, U4/U6 recycling protein	Nucleic acid binding
SCGB1A1	Secretoglobin family 1A member 1	Signaling
SEC14L2	SEC14 like lipid binding 2	
SELENBP1	Selenium binding protein 1	Immune response
SEMA6A	Semaphorin 6A	Signaling
SERPINA3	Serpin family A member 3	Enzyme modulator
SERPINE1	Serpin family E member 1	Enzyme modulator
SFRP1	Secreted frizzled related protein 1	
SH3PXD2B	SH3 and PX domains 2B	
SHBG	Sex hormone binding globulin	
SIRT1	Sirtuin 1	Epigenetic regulator
SIX1	SIX homeobox 1	Transcription factor
SIX6	SIX homeobox 6	Transcription factor
SLC23A1	Solute carrier family 23 member 1	Transporter
SLC23A2	Solute carrier family 23 member 2	Transporter
SLC4A10	Solute carrier family 4 member 10	Transporter
SLCO6A1	Solute carrier organic anion transporter family member 6A1	Transporter
SND1	Staphylococcal nuclease and tudor domain containing 1	Transcription factor
SOAT1	Sterol O-acyltransferase 1	Enzyme
SOD1	Superoxide dismutase 1	Enzyme
SOD2	Superoxide dismutase 2	Enzyme
SPARC	Secreted protein acidic and cysteine rich	Signaling
SPOCK1	SPARC (osteonectin), cwcv and kazal like domains proteoglycan 1	Enzyme modulator

Gene	Gene_Full_Name	Protein_Class
SPP1	Secreted phosphoprotein 1	
SPRR2A	Small proline rich protein 2A	
SPZ1	Spermatogenic leucine zipper 1	
SRBD1	S1 RNA binding domain 1	Nucleic acid binding
SRL	Sarcalumenin	Enzyme modulator
SRSF3	Serine and arginine rich splicing factor 3	Nucleic acid binding
STIP1	Stress induced phosphoprotein 1	
SULT1E1	Sulfotransferase family 1E member 1	
TAP1	Transporter 1, ATP binding cassette subfamily B member	Transporter
TBK1	TANK binding kinase 1	Kinase
TEK	TEK receptor tyrosine kinase	Kinase
TGFB1	Transforming growth factor beta 1	Signaling
TGFB2	Transforming growth factor beta 2	Signaling
TGFB3	Transforming growth factor beta 3	Signaling
TGFBR3	Transforming growth factor beta receptor 3	
TGM2	Transglutaminase 2	Enzyme
THBS1	Thrombospondin 1	
THBS2	Thrombospondin 2	
TIMP1	TIMP metallopeptidase inhibitor 1	Enzyme modulator
TIMP2	TIMP metallopeptidase inhibitor 2	Enzyme modulator
TIMP3	TIMP metallopeptidase inhibitor 3	Enzyme modulator
TIMP4	TIMP metallopeptidase inhibitor 4	Enzyme modulator
TLR2	Toll like receptor 2	
TLR4	Toll like receptor 4	
TMCO1	Transmembrane and coiled-coil domains 1	
TMTC2	Transmembrane O-mannosyltransferase targeting cadherins 2	
TNF	Tumor necrosis factor	Signaling
TNNT1	Troponin T1, slow skeletal type	Cellular structure
TP53	Tumor protein p53	Transcription factor
TP53BP2	Tumor protein p53 binding protein 2	Enzyme modulator
TPX2	TPX2 microtubule nucleation factor	Cellular structure
TRPM5	Transient receptor potential cation channel subfamily M member 5	Ion channel
TXNRD2	Thioredoxin reductase 2	Enzyme
UROD	Uroporphyrinogen decarboxylase	
USO1	USO1 vesicle transport factor	Transporter
VAV2	Vav guanine nucleotide exchange factor 2	
VAV3	Vav guanine nucleotide exchange factor 3	

Gene	Gene_Full_Name	Protein_Class
VDR	Vitamin D receptor	Nuclear receptor
VEGFA	Vascular endothelial growth factor A	Signaling
VEGFC	Vascular endothelial growth factor C	Signaling
WDR36	WD repeat domain 36	
XRCC1	X-ray repair cross complementing 1	
ZNF410	Zinc finger protein 410	Transcription factor
ZNF469	Zinc finger protein 469	
ZP4	Zona pellucida glycoprotein 4	

Literature reports that the potential therapeutic targets based on the molecular and cellular alterations caused by MYOC, OPTN and TBK1 mutations. Additionally, GWAS study performed in adult-onset glaucoma have identified novel loci for POAG (primary open-angle glaucoma) in CAV1/CAV2, CDKN2BAS, TMCO1, SIX6, 8q22(NTG), ABCA1, AFAP1, GMDS, PMM2, TGFBR3, FNDC3B, ARHGEF12, GAS7, FOXC1, ATXN2, TXNRD2, OPTC, MPP7 genes. Additionally, Single SNPs in the MYOC, COL8A2, COL1A1 and ZNF469 gene regions were reported by the study conducted in South Africa in POAG subjects.

Table 6.
Primary open angle glaucoma associated genes.

Gene	Variant	Chr	Position	Consequence	Alleles	Class
ABCB1	rs74315329	7	87509329	Synonymous variant	A/G;T	snv
ABO	rs28939688	9	133262254	Intron variant	C/T	snv
ADAMTS10	rs75654767	19	8589505	Missense variant	C/T	snv
ADRB2	rs1057519378	5	148826910	Stop gained	G/C;T	snv
ADRB2	rs1346865805	5	148827322	Missense variant	C/T	snv
AGER	rs137854858	6	32183666	Missense variant	C/T	snv
APBB2	rs137854860	4	40995241	Intron variant	T/C	snv
APEX1	rs137854863	14	20456995	Missense variant	T/A;C;G	snv
ASB10	rs139006752	7	151181233	Synonymous variant	G/A	snv
ASB10	rs1553534421	7	151181278	Synonymous variant	G/A	snv
ASB10	rs1555954284	7	151181173	Synonymous variant	C/A;G;T	snv
ATOH7	rs1564354968	10	68231992	5 prime UTR variant	T/G	snv
ATOH7	rs200148764	10	68232096	5 prime UTR variant	A/G	snv
B4GALT3;PPOX	rs200710076	1	161175160	Missense variant	C/T	snv
BIRC6	rs201794655	2	32545090	Intron variant	A/T	snv
C14orf39;SIX6	rs373425395	14	60509819	Missense variant	C/A;G	snv
C14orf39;SIX6	rs750643216	14	60509783	Missense variant	G/A	snv
C1orf112;SELE	rs878854408	1	169728058	Missense variant	C/A;T	snv
CARD10	rs1217691063	22	37516037	Missense variant	C/A;T	snv
CARD10	rs2165241	22	37508609	Missense variant	G/A	snv
CARD10	rs33912345	22	37508568	Missense variant	C/T	snv

Gene	Variant	Chr	Position	Consequence	Alleles	Class
CARD10	rs3825942	22	37492794	Missense variant	G/A	snv
CARD10	rs1048661	22	37506365	Missense variant	G/A	snv
CAT	rs566289099	11	34438684	Upstream gene variant	C/T	snv
CAT	rs1063192	11	34461361	Synonymous variant	C/T	snv
CAT	rs11258194	11	34438925	Upstream gene variant	A/T	snv
CAV1	rs74315330	7	116550415	Intron variant	G/A	snv
CAV2	rs1042522	7	116508316	3 prime UTR variant	T/C;G	snv
CD48	rs12994401	1	160681172	Frameshift variant	C/-;CC;CCC	delins
CD48	rs137853277	1	160681173	Frameshift variant	-/T	ins
CDKN2B;CDKN2B-AS1	rs2149356	9	22003368	3 prime UTR variant	G/A;T	snv
CDKN2B-AS1	rs4986791	9	22056500	Intron variant	G/A	snv
CDKN2B-AS1	rs74315337	9	22033367	Non coding transcript exon variant	C/T	snv
CDKN2B-AS1	rs10120688	9	22062135	Intron variant	G/T	snv
CDKN2B-AS1	rs1131691014	9	22055049	Intron variant	A/G;T	snv
CDKN2B-AS1	rs145285325	9	22019130	Intron variant	A/G	snv
CDKN2B-AS1	rs2157719	9	22028802	Intron variant	A/G	snv
CNTNAP4	rs2234926	16	76307609	Intron variant	A/G	snv
COL8A2	rs25487	1	36099217	Missense variant	C/G;T	snv
COX1;COX2	rs367923973	MT	6150	Missense variant	G/A	snv
COX2;COX1	rs4898	MT	6253	Missense variant	T/C	snv
COX2;COX1;ATP8	rs4986790	MT	6480	Missense variant	G/A	snv
CYP1B1	rs74315328	2	38071060	Missense variant	G/C	snv
CYP1B1	rs74315332	2	38071007	Missense variant	A/G;T	snv
CYP1B1	rs74315339	2	38070996	Missense variant	T/C;G	snv
CYP1B1;CYP1B1-AS1	rs781662103	2	38075034	Missense variant	C/A	snv
CYP1B1;CYP1B1-AS1	rs878854066	2	38075247	Missense variant	G/C	snv
CYP1B1;CYP1B1-AS1	rs1001179	2	38076389	Non coding transcript exon variant	G/A	snv
CYP1B1;CYP1B1-AS1	rs10202118	2	38075148	Missense variant	A/T	snv
CYP1B1-AS1;CYP1B1	rs1056827	2	38074704	Missense variant	C/T	snv
CYP46A1	rs11656696	14	99691630	Non coding transcript exon variant	A/G	snv
DCLK1	rs1279683	13	36078480	Intron variant	T/C	snv
DDX3X	rs1533428	X	41346607	Missense variant	C/T	snv
EDNRA	rs16947	4	147542688	3 prime UTR variant	G/A;C	snv
ENO4	rs17576	10	116864069	Intron variant	G/A	snv
ESR1	rs1799750	6	151929945	Intron variant	C/A	snv

Gene	Variant	Chr	Position	Consequence	Alleles	Class
ESR1	rs1799983	6	151970431	Intron variant	C/A	snv
ESR2	rs180040	14	64279461	Intron variant	G/A;T	snv
ESR2	rs1900004	14	64292158	Intron variant	C/T	snv
FASLG	rs199752860	1	172658358	Upstream gene variant	C/T	snv
FASTKD1	rs2234927	2	169531449	Missense variant	A/T	snv
FDXR	rs267606929	17	74872110	Stop gained	G/A;C	snv
FDXR	rs3219489	17	74863112	Missense variant	C/A;G;T	snv
FNDC3B	rs369410616	3	172315221	Intron variant	C/G	snv
FNDC3B	rs3918188	3	172274597	Intron variant	G/A	snv
GAS7	rs397507444	17	10130362	Intron variant	C/A	snv
GCM1	rs74315334	6	53258320	Regulatory region variant	T/C	snv
GPX4	rs74315336	19	1101993	Upstream gene variant	A/G	snv
GSTP1	rs74315338	11	67585218	Missense variant	A/G	snv
HSP90AA1	rs754203	14	102083827	Missense variant	T/C	snv
IL20RA	rs754237376	6	137008718	Missense variant	G/A	snv
IL20RB-AS1;IL20RB	rs10012	3	136982255	Missense variant	C/T	snv
INKA2;DDX20; LOC101928718	rs10038177	1	111754860	Non coding transcript exon variant	A/T	snv
KCNQ4	rs10063949	1	40814886	Intron variant	C/T	snv
KLC3;ERCC2	rs1011970	19	45351661	Stop gained	T/A;G	snv
LINC02640	rs1042714	10	68241124	Intron variant	C/T	snv
LOC102724808;OPA1	rs10451941	3	193647160	Missense variant	A/G	snv
LOC105376196	rs1045642	9	104933567	Downstream gene variant	G/A	snv
LOC107986513;GMDS	rs104886478	6	1707020	Intron variant	C/T	snv
LOC112268121;EDNRB-AS1	rs1051993	13	77800045	Intron variant	A/T	snv
LOC730100	rs1052133	2	51845108	Intron variant	C/T	snv
LOC730100	rs1052990	2	51723186	Intron variant	C/T	snv
LOC730100	rs1056836	2	51732120	Intron variant	T/A;C	snv
LOC730100	rs1056837	2	51725011	Intron variant	G/A	snv
LOXL1;LOXL1-AS1	rs11125375	15	73927241	Missense variant	G/A;C;T	snv
LOXL1-AS1;LOXL1	rs111698934	15	73929861	Intron variant	T/C	snv
LOXL1-AS1;LOXL1	rs11241095	15	73927205	Missense variant	G/T	snv
LTBP2	rs112983858	14	74551266	Missense variant	C/A;T	snv
LTBP2	rs1130409	14	74502911	Missense variant	C/G;T	snv
LTBP2	rs1135840	14	74505102	Missense variant	T/C	snv
MIR182;LOC105375501	rs11536889	7	129770387	Non coding transcript exon variant	C/G;T	snv

Gene	Variant	Chr	Position	Consequence	Alleles	Class
MIR34C;BTG4;MIR34B; LOC728196	rs11568658	11	111511840	Intron variant	T/C	snv
MMP9	rs11669977	20	46011586	Missense variant	A/G	snv
MPP7	rs1171063544	10	28116482	Intron variant	G/C;T	snv
MTHFR	rs11720822	1	11796309	Missense variant	A/G	snv
MTHFR	rs11771443	1	11794407	Missense variant	T/G	snv
MUL1	rs12025126	1	20503285	Missense variant	C/T	snv
MUTYH	rs12154178	1	45331833	Missense variant	C/A;G	snv
MUTYH	rs121909194	1	45329400	Missense variant	C/T	snv
MYOC	rs12377632	1	171652476	Stop gained	G/A;C;T	snv
MYOC	rs1255428605	1	171652385	Missense variant	C/T	snv
MYOC	rs1256031	1	171652468	Missense variant	C/A	snv
MYOC	rs1268656	1	171652578	Missense variant	C/G	snv
MYOC	rs1270841723	1	171652341	Stop gained	G/A	snv
MYOC	rs12789379	1	171652139	Missense variant	C/G;T	snv
MYOC	rs1279386	1	171652539	Missense variant	A/G	snv
MYOC;MYOCOS	rs1315538274	1	171636338	Stop gained	G/A	snv
MYOC;MYOCOS	rs13181	1	171636382	Missense variant	G/A	snv
MYOC;MYOCOS	rs13186912	1	171636131	Missense variant	A/G	snv
MYOC;MYOCOS	rs14035	1	171636143	Missense variant	A/G	snv
MYOC;MYOCOS	rs1428758	1	171636161	Missense variant	C/T	snv
MYOC;MYOCOS	rs143413116	1	171636302	Missense variant	C/G	snv
MYOC;MYOCOS	rs144249808	1	171636185	Missense variant	T/C	snv
MYOC;MYOCOS	rs145437203	1	171636010	Missense variant	A/C;T	snv
MYOC;MYOCOS	rs1463461589	1	171636686	Missense variant	C/T	snv
MYOC;MYOCOS	rs1466441587	1	171636542	Missense variant	C/T	snv
MYOCOS;MYOC	rs146737847	1	171636329	Missense variant	A/G	snv
MYOCOS;MYOC	rs166850	1	171636310	Missense variant	G/A	snv
MYOCOS;MYOC	rs1695	1	171636331	Missense variant	G/A	snv
MYOCOS;MYOC	rs16984299	1	171636000	Missense variant	G/T	snv
MYOCOS;MYOC	rs1799782	1	171638703	Missense variant	G/A;C	snv
MYOCOS;MYOC	rs1800440	1	171636341	Missense variant	C/T	snv
MYOCOS;MYOC	rs1800779	1	171636173	Missense variant	T/C	snv
MYOCOS;MYOC	rs1800888	1	171638675	Missense variant	C/T	snv
MYOCOS;MYOC	rs184561087	1	171636028	Missense variant	T/C	snv
MYOCOS;MYOC	rs185815146	1	171635999	Missense variant	G/A	snv
NCKAP5	rs1884054	2	133605461	Regulatory region variant	T/A;C;G	snv

Gene	Variant	Chr	Position	Consequence	Alleles	Class
ND2;RNR2;ND1	rs1926320	MT	3010	Non coding transcript exon variant	G/A	snv
NDUFA6-DT;CYP2D6	rs1927911	22	42127941	Missense variant	G/A;T	snv
NDUFA6-DT;CYP2D6	rs197388	22	42126611	Missense variant	C/G	snv
NOS3	rs199476128	7	150999023	Missense variant	T/A;G	snv
NOS3	rs199746824	7	151005693	Intron variant	C/A;T	snv
NOS3	rs200165736	7	150990599	Upstream gene variant	C/T	snv
NOS3	rs200547613	7	150992855	Intron variant	G/A;C	snv
NOS3	rs2070600	7	150998107	Intron variant	G/A	snv
NOS3;ATG9B	rs2156323	7	151012483	3 prime UTR variant	G/T	snv
NRP1	rs2253592	10	33221802	Missense variant	A/G	snv
NTF4	rs2383204	19	49060867	Non coding transcript exon variant	A/G	snv
NTF4	rs2472493	19	49061660	Missense variant	A/G	snv
NTF4	rs2567206	19	49061735	Missense variant	G/A	snv
NTF4	rs2754511	19	49061453	Missense variant	G/A	snv
NTM	rs2801219	11	131422069	Intron variant	A/G;T	snv
OGG1	rs28358580	3	9756778	Missense variant	C/T	snv
OGG1;CAMK1	rs2842980	3	9757089	Missense variant	C/G	snv
OPA1	rs34551253	3	193637313	Intron variant	T/A;C	snv
OPA1	rs34595252	3	193637285	Splice region variant	T/A;C	snv
OPTN	rs3766355	10	13109270	Missense variant	G/A	snv
OPTN	rs3793342	10	13136766	Missense variant	G/A	snv
OPTN	rs3801994	10	13110416	Missense variant	G/C	snv
OPTN	rs386741044	10	13109279	Frameshift variant	-/AGCT	delins
OPTN	rs3928306	10	13109198	Missense variant	C/A;G;T	snv
OPTN	rs4880	10	13132122	Missense variant	A/G	snv
OPTN	rs4938723	10	13110400	Missense variant	T/A	snv
OPTN	rs523096	10	13132098	Missense variant	A/G	snv
OPTN	rs523747	10	13110394	Missense variant	G/A;T	snv
OPTN	rs5335	10	13124076	Missense variant	G/A;C	snv
OPTN	rs537516822	10	13124076	Missense variant	G/A;C	snv
PBX2;AGER	rs547984	6	32185657	3 prime UTR variant	C/A	snv
PDIA5	rs554235897	3	123150194	Intron variant	C/T	snv
PRPF8	rs571448378	17	1684534	Missense variant	G/A	snv
PRPF8	rs5743704	17	1684498	Missense variant	A/G	snv
PTGFR	rs5746136	1	78491756	Intron variant	C/A;T	snv
RAN	rs576499843	12	130876696	3 prime UTR variant	C/T	snv
RERE	rs5773704	1	8699495	Intron variant	T/C	snv

Gene	Variant	Chr	Position	Consequence	Alleles	Class
RFTN1;OXNAD1	rs57865060	3	16354161	Intron variant	C/G;T	snv
RHOA	rs59892895	3	49363049	Intron variant	T/C	snv
RNR2;ND1	rs61732310	MT	2416	Non coding transcript exon variant	T/C	snv
SEC14L2	rs61854782	22	30406040	Intron variant	C/A;G;T	snv
SLC23A1	rs6445055	5	139383837	Intron variant	T/C	snv
SLC23A2	rs690037	20	5002446	Intron variant	G/A;C	snv
SNORD13G;ABCC4	rs6917589	13	95210754	Missense variant	C/A	snv
SOD2	rs693421	6	159679084	3 prime UTR variant	A/T	snv
SOD2	rs6994076	6	159692840	Missense variant	A/G	snv
SOD2	rs7037117	6	159682052	3 prime UTR variant	C/T	snv
SOD2	rs7049105	6	159678228	3 prime UTR variant	T/C	snv
STIP1	rs7159462	11	64195658	Missense variant	C/A;G	snv
STIP1	rs735860	11	64203143	Missense variant	A/G	snv
SYNE2;ESR2	rs737723	14	64180928	Intron variant	T/G	snv
TIMP1;SYN1;MIR4769	rs74315331	X	47585586	Synonymous variant	T/C	snv
TLR2	rs74315341	4	153704799	Missense variant	C/A	snv
TLR4	rs746418406	9	117711921	Intron variant	T/G	snv
TLR4	rs746702110	9	117713324	Missense variant	C/T	snv
TLR4	rs747058633	9	117713024	Missense variant	A/G;T	snv
TLR4	rs747782	9	117715853	3 prime UTR variant	G/C	snv
TLR4	rs7481514	9	117710452	Intron variant	T/A;C	snv
TLR4	rs748621461	9	117707776	Intron variant	A/G	snv
TLR4	rs748899944	9	117721385	3 prime UTR variant	A/G	snv
TMTC2	rs751417985	12	82698057	Intron variant	G/A	snv
TP53	rs751497460	17	7676154	Missense variant	G/C;T	snv
TP53	rs754829637	17	7676154	Frameshift variant	-/C	ins
TP53	rs755246983	17	7676153	Missense variant	GG/AC	mnv
TRPM5	rs757228	11	2415234	Missense variant	C/A;T	snv
TTPA	rs75864656	8	63087002	Upstream gene variant	A/T	snv
TXNRD2	rs7588567	22	19876070	3 prime UTR variant	T/C	snv
VAV2	rs761875612	9	133855699	Intron variant	G/A	snv
VAV3	rs763068244	1	107874935	Missense variant	G/A	snv
VAV3	rs763110	1	107959790	Intron variant	C/A	snv
VAV3	rs76481776	1	107617607	Missense variant	A/C;G	snv
WDR36	rs766147142	5	111100751	Intron variant	C/T	snv
WDR36	rs769217	5	111103810	Missense variant	A/C;G	snv
WDR36	rs782006965	5	111121006	Synonymous variant	A/T	snv

Gene	Variant	Chr	Position	Consequence	Alleles	Class
WDR36	rs7830	5	111092362	Missense variant	T/C	snv
WDR36	rs7916697	5	111119021	Missense variant	A/G	snv
WTAPP1;MMP1	rs7916852	11	102797141	Synonymous variant	A/G	snv
WTAPP1;MMP1	rs7943316	11	102799765	Intron variant	C/-	delins
XRCC1	rs7961953	19	43551574	Missense variant	T/C	snv
XRCC1	rs8176693	19	43553422	Missense variant	G/A	snv
	rs879053914	15	97027933	Intergenic variant	T/C	snv
	rs9282671	1	237933586	Intergenic variant	A/C	snv
	rs9503012	1	237935790	Downstream gene variant	T/A;G	snv
	rs974495	11	47919373	Intergenic variant	T/C	snv

Table 7.
Variants associated with primary open angle glaucoma.

Gene	Gene_Full_Name	Protein_Class
ABCA1	ATP binding cassette subfamily A member 1	Transporter
ABCC5	ATP binding cassette subfamily C member 5	Transporter
ACD	ACD shelterin complex subunit and telomerase recruitment factor	
AKR1C4	Aldo-keto reductase family 1 member C4	Enzyme
APOE	Apolipoprotein E	
AQP1	Aquaporin 1 (Colton blood group)	Ion channel
ATOH7	Atonal bHLH transcription factor 7	Enzyme
BIRC6	Baculoviral IAP repeat containing 6	
BRCA1	BRCA1 DNA repair associated	Enzyme
C10orf53	Chromosome 10 open reading frame 53	
C3	Complement C3	Enzyme modulator
CALCRL	Calcitonin receptor like receptor	G-protein coupled receptor
CAT	Catalase	Enzyme
CCL2	C-C motif chemokine ligand 2	Signaling
CCN2	Cellular communication network factor 2	Signaling
CDC42	Cell division cycle 42	Enzyme modulator
CDR1	Cerebellar degeneration related protein 1	
CHAT	Choline O-acetyltransferase	Enzyme
CIAO3	Cytosolic iron-sulfur assembly component 3	Enzyme
COL11A1	Collagen type XI alpha 1 chain	
COL1A1	Collagen type I alpha 1 chain	

Gene	Gene_Full_Name	Protein_Class
CST3	Cystatin C	
CTSD	Cathepsin D	Enzyme
CYP1B1	Cytochrome P450 family 1 subfamily B member 1	Enzyme
CYP2B6	Cytochrome P450 family 2 subfamily B member 6	
DBN1	Drebrin 1	Cellular structure
DCN	Decorin	
DPM2	Dolichyl-phosphate mannosyltransferase subunit 2, regulatory	
EIF2D	Eukaryotic translation initiation factor 2D	Receptor
ELN	Elastin	
EPDR1	Ependymin related 1	
F2	Coagulation factor II, thrombin	Enzyme
FAM102A	Family with sequence similarity 102 member A	
FBLN7	Fibulin 7	
FERMT2	Fermitin family member 2	
GLIS3	GLIS family zinc finger 3	
GSTM1	Glutathione S-transferase mu 1	
HGF	Hepatocyte growth factor	Enzyme
HLA-DPA1	Major histocompatibility complex, class II, DP alpha 1	Immune response
HSPA4	Heat shock protein family A (Hsp70) member 4	
HTR3C	5-hydroxytryptamine receptor 3C	Ion channel
HTR3D	5-hydroxytryptamine receptor 3D	Ion channel
IL1A	Interleukin 1 alpha	
IL1B	Interleukin 1 beta	
KDR	Kinase insert domain receptor	Kinase
KERA	Keratocan	
LGTN	Ligatin	
LOC110599580	CYP1B1 promoter	
LOX	Lysyl oxidase	
LOXL1	Lysyl oxidase like 1	
LOXL2	Lysyl oxidase like 2	
MFRP	Membrane frizzled-related protein	Enzyme
MINDY4	MINDY lysine 48 deubiquitinase 4	
MMP1	Matrix metallopeptidase 1	Enzyme
MMP9	Matrix metallopeptidase 9	Enzyme
MTHFR	Methylenetetrahydrofolate reductase	
MYOC	Myocilin	Cellular structure

Gene	Gene_Full_Name	Protein_Class
NEB	Nebulin	
NOS3	Nitric oxide synthase 3	
NT5E	5'-nucleotidase ecto	Enzyme
NTF4	Neurotrophin 4	Signaling
OGG1	8-oxoguanine DNA glycosylase	
OPA3	Outer mitochondrial membrane lipid metabolism regulator OPA3	
OPTN	Optineurin	
PACC1	Proton activated chloride channel 1	
PARL	Presenilin associated rhomboid like	Enzyme
PCMTD1	Protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 1	Enzyme
PDE5A	Phosphodiesterase 5A	
PDIA5	Protein disulfide isomerase family A member 5	
PLEKHA7	Pleckstrin homology domain containing A7	
PLXNA2	Plexin A2	
PRSS56	Serine protease 56	
RAC1	Rac family small GTPase 1	Enzyme modulator
RUNX1T1	RUNX1 partner transcriptional co-repressor 1	Transcription factor
SFRP4	Secreted frizzled related protein 4	
SOD2	Superoxide dismutase 2	Enzyme
SPARC	Secreted protein acidic and cysteine rich	Signaling
SPP1	Secreted phosphoprotein 1	
ST18	ST18 C2H2C-type zinc finger transcription factor	Transcription factor
TGFB1	Transforming growth factor beta 1	Signaling
TGFB2	Transforming growth factor beta 2	Signaling
THBS1	Thrombospondin 1	
TMCO1	Transmembrane and coiled-coil domains 1	
TP53	Tumor protein p53	Transcription factor
TXNRD2	Thioredoxin reductase 2	Enzyme
VSX2	Visual system homeobox 2	
ZNRF3	Zinc and ring finger 3	

The inheritance pattern of angle closure causing mutations in COL18A1 *was autosomal dominant. PACG (primary angle-closure glaucoma (EPDR1, CHAT, GLIS3, FERMT2, DPM2-FAM102); and exfoliation syndrome (XFS) glaucoma (CACNA1A). Additionally, it has been reported that the most significant GWAS in the Asian population were identified in SNPs of rs11024102 (PLEKHA7; 11p15.1), rs3753841 (COL11A1; 1p21.1), and rs1015213 (8q11.23).*

Table 8.
Genes associated with primary angle closure glaucoma.

Gene	Variant	Chr	Position	Consequence	Alleles	Class
ABCC5	rs1132776	3	183978614	Synonymous variant	A/G	snv
ABCC5	rs939336	3	183967746	Stop gained	A/G;T	snv
BIRC6	rs2754511	2	32545090	Intron variant	A/T	snv
C10orf53	rs1258267	10	49687724	Intron variant	G/A	snv
CALCRL; LOC105373786	rs1157699	2	187394177	Intron variant	C/G;T	snv
CAT	rs1001179	11	34438684	Upstream gene variant	C/T	snv
COL11A1	rs3753841	1	102914362	Missense variant	G/A	snv
COL11A1	rs12138977	1	102927901	Intron variant	C/T	snv
COL11A1	rs1676486	1	102888582	Missense variant	A/G;T	snv
DPM2;FAM102A	rs3739821	9	127940198	Non coding transcript exon variant	A/G	snv
EPDR1;SFRP4	rs3816415	7	37948709	Intron variant	G/A	snv
FERMT2	rs7494379	14	52944673	Intron variant	C/G;T	snv
GLIS3	rs736893	9	4217028	Intron variant	G/A;C	snv
HGF	rs17427817	7	81735119	Intron variant	C/A;G; T	snv
HGF	rs12540393	7	81734871	Intron variant	C/T	snv
HGF	rs3735520	7	81771623	Upstream gene variant	G/A;T	snv
HGF	rs5745718	7	81718232	Intron variant	T/G	snv
HSPA1L;HSPA1A	rs1043618	6	31815730	5 prime UTR variant	G/A;C; T	snv
HTR3D	rs12493550	3	184034985	Intron variant	G/A	snv
LINC02640	rs1900004	10	68241124	Intron variant	C/T	snv
LOC105373786; CALCRL	rs6759535	2	187373374	Intron variant	T/C	snv
LOC105373786; CALCRL	rs840617	2	187365606	Intron variant	A/T	snv
LOC107985096	rs1676484	1	102839465	Intron variant	A/C	snv
LOXL1;LOXL1-AS1	rs3825942	15	73927241	Missense variant	G/A;C; T	snv
LOXL1-AS1;LOXL1	rs2165241	15	73929861	Intron variant	T/C	snv
MMP1;WTAPP1	rs756459094	11	102795237	Missense variant	T/A;C; G	snv
MMP9	rs17576	20	46011586	Missense variant	A/G	snv
MMP9	rs2664538	20	46011586	Missense variant	A/G	snv
MMP9	rs3918249	20	46009497	Intron variant	T/C	snv
MTHFR	rs1217691063	1	11796309	Missense variant	A/G	snv
MYOC	rs183532	1	171640341	Intron variant	T/A;C	snv
MYOC	rs235875	1	171644616	Intron variant	C/T	snv
MYOC	rs235913	1	171649516	Intron variant	T/C;G	snv

Gene	Variant	Chr	Position	Consequence	Alleles	Class
NOS3	rs3793342	7	150998107	Intron variant	G/A	snv
NTF4	rs11669977	19	49060867	Non coding transcript exon variant	A/G	snv
NTF4	rs61732310	19	49061735	Missense variant	G/A	snv
PDIA5	rs11720822	3	123150194	Intron variant	C/T	snv
PLEKHA7	rs11024102	11	16987058	Intron variant	T/C	snv
PLEKHA7	rs216489	11	16802189	Intron variant	G/A;T	snv
SLC12A5-AS1;MMP9	rs2250889	20	46013767	Missense variant	G/C;T	snv
SLC12A5-AS1;MMP9	rs17577	20	46014472	Missense variant	G/A;C	snv
SLC38A4	rs983667	12	46769523	Intron variant	C/T	snv
SOD2	rs4880	6	159692840	Missense variant	A/G	snv
TP53	rs1042522	17	7676154	Missense variant	G/C;T	snv
TP53	rs1131691014	17	7676154	Frameshift variant	-/C	ins
TP53	rs878854066	17	7676153	Missense variant	GG/AC	mnv
TXNRD2	rs3788317	22	19902302	Intron variant	G/T	snv
VAV2	rs2156323	9	133855699	Intron variant	G/A	snv
VAV3	rs1466441587	1	107874935	Missense variant	G/A	snv
VAV3	rs2801219	1	107959790	Intron variant	C/A	snv
VAV3	rs576499843	1	107617607	Missense variant	A/C;G	snv
WTAPP1;MMP1	rs1799750	11	102799765	Intron variant	C/-	delins
ZNRF3	rs7290117	22	29054868	3 prime UTR variant	C/G;T	snv
	rs1015213	8	51974981	Intron variant	C/T	snv
	rs4656461	1	165717968	TF binding site variant		G/A

Table 9.
Variants associated with primary angle closure glaucoma.

8. Conclusions

Glaucoma genetics and genomics have to be assessed with the larger picture of visual impairment, disease prevalence, comorbidities, genetics, genomics, disease mechanisms, mechanical stress, neuroprotection, neurodegeneration, apoptosis, and immune imbalance. Few single causative genes, but multiple genes' dysregulated expressions at several tissues' sites of the eye like ciliary body, trabecular meshwork, lamina cribrosa, retina and optic nerve determine the spectrum of phenomics in glaucoma (**Figure 1**). This has led to the identification of neurotrophic factors, and anti-apoptotic molecules to prevent further neurodegeneration of RGCs and loss of vision. The complex nature of the disease and the discovery of several hundred genes and molecules is a boon and a bane at the same time. This status needs further research to focus and identify a battery of few molecules that could be used, individually or as a cocktail, in a majority of patients with glaucoma. However, it looks like the field may move towards a cocktail of molecular therapy based on personalised medicine and the individuals' genetic signature pattern and phenomics.

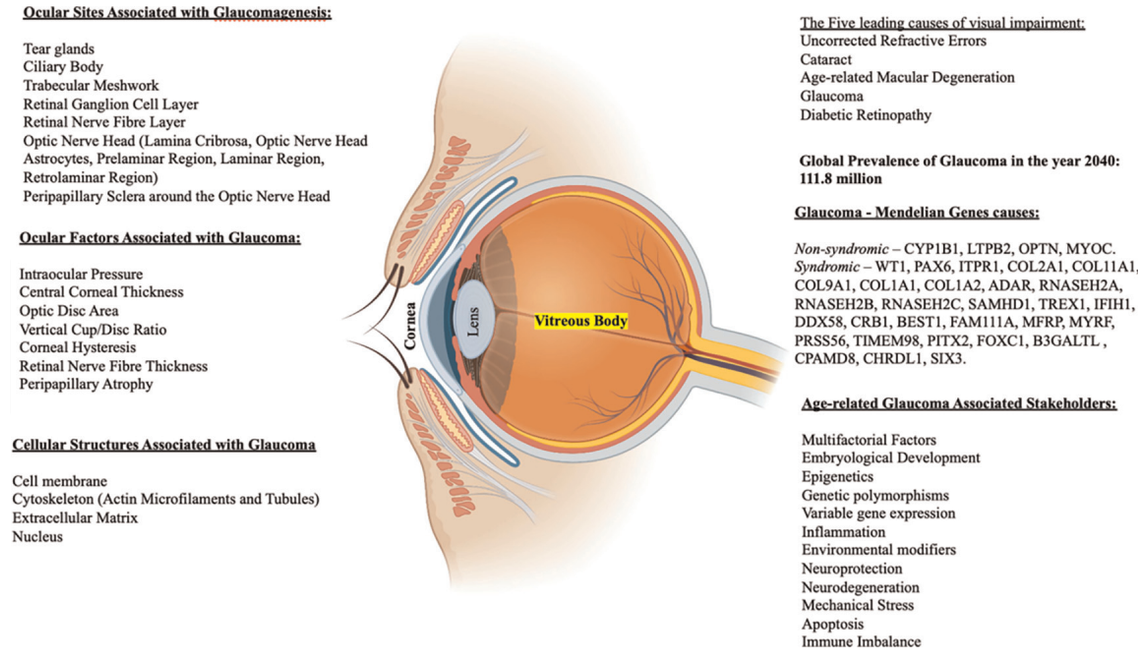

Figure 1.
The ocular tissues, genomics and biomechanisms of glaucoma.

Author details

Govindasamy Kumaramanickavel[1*], Siddhita Jadhav[1,2], Sugirdhana Parthiban Ramsait[1] and Pinakin Gunvant Davey[3]

1 Counselling in Medical Genetics Unit, GenVams Trust, GenVamsalya, Chennai, India

2 University Eye Clinic Maastricht, Maastricht University Medical Center, Maastricht, The Netherlands

3 College of Optometry, Western University of Health Sciences, Pomona, California, United States of America

*Address all correspondence to: gkumarmvel@gmail.com

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