REVIEW ARTICLE

Molecular complexity of primary open angle glaucoma: current concepts

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Abstract

Glaucoma is a group of heterogeneous optic neuropathies with complex genetic basis. Among the three principle subtypes of glaucoma, primary open angle glaucoma (POAG) occurs most frequently. Till date, 25 loci have been found to be linked to POAG. However, only three underlying genes (*Myocilin, Optineurin* and *WDR36*) have been identified. In addition, at least 30 other genes have been reported to be associated with POAG. Despite strong genetic influence in POAG pathogenesis, only a small part of the disease can be explained in terms of genetic aberration. Current concepts of glaucoma pathogenesis suggest it to be a neurodegenerative disorder which is triggered by different factors including mechanical stress due to intra-ocular pressure, reduced blood flow to retina, reperfusion injury, oxidative stress, glutamate excitotoxicity, and aberrant immune response. Here we present a mechanistic overview of potential pathways and crosstalk between them operating in POAG pathogenesis.

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Introduction

Glaucoma is a heterogenous group of optic neuropathies with a complex genetic basis. It reduces vision, often without any symtoms and warning. It is the second largest blinding disorder after cataract. Recent report estimates that there will be 60.5 million people with primary glaucoma in 2010 and 79.6 million by 2020 resulting in bilateral blindness in 8.4 and 11.2 million people by the corresponding years, respectively (Quigley and Broman 2006). Almost all types of glaucoma share some common clinical features, which include specific abnormal appearance of the optic nerve head, characteristic loss of visual field and chronic painless progression. Furthermore, the condition is frequently associated with increased intraocular pressure (IOP), which is neither necessary nor sufficient for onset or progression of the disease (Ray *et al*. 2003). Glaucoma could be classified according to etiology (primary versus secondary), anatomy of the anterior chamber (open angle versus closed angle) and time of onset (infantile versus juvenile versus adult). In general, glaucoma is broadly classified into three major groups: (i) primary open angle glaucoma (POAG); (ii) primary acute closed angle glaucoma; and (iii) primary congenital glaucoma. Among those subtypes POAG is the most common form of the glaucoma (Quigley 1993; Shields *et al*. 1996). Here we present an update of the present knowledge of the molecular basis of primary open angle glaucoma.

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Candidate genes and beyond

Till date, 25 loci have been found to be linked with POAG (table 1) but only three underlying genes have been identified so far, viz. *Myocilin* (Stone *et al*. 1997), *Optineurin* (Rezaie *et al*. 2002) and *WDR36* (Monemi *et al*. 2005). Although *CYP1B1* was primarily implicated in PCG, mutations in this gene are also reported in POAG cases. In addition, genetic evidence has been provided to suggest that mutations in this gene alone can cause POAG by autosomal-recessive mode of inheritance (Acharya *et al*. 2006; Bayat *et al*. 2008). Here, we briefly discuss the involvement of each of these candidate genes in POAG and other modifying loci.

Myocilin gene (MYOC)

Myocilin was the first gene found to be linked to POAG (Stone *et al*. 1997) and is the most studied one. It is located in chromosome 1 and contains three exons (Kubota *et al*. 1998).

Table 1. Genetic loci linked to glaucoma.

Locus	Chromosomal location	OMIM no.	Gene	GenBank accession no.	Reference
GLC1A(JOAG1)	1q 21-31	137750	*Myocilin*	NM 000261	Sheffield *et al*. 1993
GLC1B	2cen-q31	606689	-	-	Stoilova *et al*. 1996
GLC1C	3q 21-24	601682	-	-	Wirtz *et al*. 1997
GLC1D	8p 23	602429	-	-	Trifan *et al*. 1998
GLC1E	10p 15-14	602432	*Optineurin*	NM_021980	Sarfarazi *et al*. 1998
GLC1F	7q 35-q36	603383	-	-	Wirtz *et al*. 1999
GLC1G	5q 22.1	609887	*WDR36*	NM_139281	Monemi *et al*. 2005
GLC1H	14q11-q13	611276	-	-	Suriyapperuma *et al*. 2007
GLC1I	15q11-13	609745	-	-	Allingham *et al*. 2005
GLC1J (JOAG2)	9q22	608695	-	-	Wiggs *et al*. 2004
GLC1K (JOAG3)	20p12	608696	-	-	Wiggs *et al*. 2004
GLC1L (JOAG4)	3p21-22	137750	-	-	Baird *et al*. 2005
GLC1M (JOAG5)	5q22.1-q32	610535	-	-	Pang *et al*. 2006
GLC1N (JOAG6)	15q22-q24	61274	-	-	Wang *et al*. 2006b
-	19q12	-	-	-	Wiggs *et al*. 2000
-	17q25.1-17q25.3-	-	-	-	Wiggs *et al*. 2000
-	14q11.1-14q11.2-	-	-	-	Wiggs *et al*. 2000
-	14q21.1-q21.3	-	-	-	Wiggs *et al*. 2000
-	17p13	-	-	-	Wiggs *et al*. 2000
-	10p12.33-p12.1	-	-	-	Nemesure *et al*. 2003
-	2q33.1-q33.3	-	-	-	Nemesure *et al*. 2003
-	2p14	-	-	-	Wiggs *et al*. 2000
-	2p15-16-	-	-	-	Lin *et al*. 2008
-	1p 32	-	-	-	Charlesworth *et al*. 2005
-	10q 22	-	-	-	Charlesworth *et al*. 2005

The protein is mainly comprised of an N-terminal coiled coil region and a C-terminal olfactomedin domain (Abderrahim *et al*. 1998; Fingert *et al*. 1998). This is largely an extracellular matrix (ECM) protein but its function is still not well elucidated. Although a large number of olfactomedin domain containing proteins have been found to be involved in developmental pathways (Tomarev and Nakaya 2009), myocilin null mice neither have any decipherable defect in development nor does it develop any glaucomatous phenotype (Kim *et al*. 2001). Mutations in myocilin largely have their effect by dominant negative gain of function mechanism (Lam *et al*. 2000). A total of 66 point mutations are listed in the HGMD database (www.hgmd.cf.ac.uk/ac/index.php) but a more comprehensive overview is provided in the myocilin mutation database (www.myocilin.com) (Hewitt *et al*. 2008), where till date 74 disease causing mutations are listed. Myocilin mutations are generally associated with juvenile or early-adult form of POAG. This genetic form of glaucoma is typically associated with high intraocular pressure and frequently requires surgical intervention for controlling the disease. In adult POAG populations, the prevalence of myocilin mutations varies between 3–5% making it the most common form of inherited glaucoma currently known (Allingham *et al*. 2009). Among the three exons of myocilin most of the diseases causing mutations have been found in the third exon of myocilin, a few in the 1st exon but none in the second exon. The third exon of myocilin mostly codes for olfactomedin domain and clustering of most of the myocilin mutations in this region indicates the functional importance of the region in POAG pathogenesis. Bio-informatics analysis also indicated that the olfactomedin domain is largely conserved across the species and any variation is naturally deleterious (Mukhopadhyay *et al*. 2002). It may be possible that myocilin may essentially be a remnant of the evolutionary process. Like the vestigial organs of the body it remains as a vestigial genomic region; only to cause harm in case of any perturbance.

Till date, published literature indicates that mutations in myocilin have their pathogenic effect largely because of inability of the protein to fold properly. When misfolded, this mutated protein forms aggregates in the endoplasmic reticulum (ER) (also called Russell bodies) as well as in the cytoplasm (also called aggresomes). This misfolded or unfolded protein ultimately results in unfolded protein response (UPR) in the cells and activates a mitochondria-independent apoptosis pathway which ultimately leads to cell death and breakdown of trabecular meshwork (TM) cell structure, obstruction of aqueous humor outflow pathway, ocular hypertension and glaucoma (Zhou and Vollrath 1999; Jacobson *et al*. 2001; Joe *et al*. 2003; Liu and Vollrath 2004; Jia *et al*. 2009). Protein aggregates in cells are also the hallmark of many neurodegenerative disorders e.g. Alzheimer's dis-

ease, Parkinson's disease, multiple sclerosis etc. It is reported that myocilin is expressed in optic nerve head (Clark *et al*. 2001) and astrocytes (Noda *et al*. 2000). It is possible that myocilin, when mutated, could impair optic nerve function. However, direct evidence for all the hypothesis is still lacking. Myocilin was found to be upregulated in glial scars and inhibit neurite growth (Jurynec *et al*. 2003). Mutation in myocilin was also found to cause mitochondrial membrane depolarization, decreased ATP generation and generation of reactive oxygen species. Therefore, in addition to mitochondria-independent apoptosis, mitochondria-mediated apoptosis cannot be ruled out (Tamm and Russell; Sakai *et al*. 2007; Wang *et al*. 2007; He *et al*. 2009).

It has been shown that myocilin is cleaved in ER by calpain II, a Ca^{++} dependent enzyme, into two fragments; a 20 kDa N-terminal fragment and a C-terminal 35 kDa olfactomedin containing fragment. The 35-kDa fragment and the full length myocilin have been shown to be excreted into the extra cellular matrix (ECM), and thus hypothesized to maintain a normal ECM structure. Mutations in myocilin perturb this cleavage and results in breakdown of ECM structure in TM which ultimately results in higher IOP and glaucoma (Aroca-Aguilar *et al*. 2005; Sanchez-Sanchez *et al*. 2007).

It has been hypothesized that myocilin could control the adhesive properties of the cell. It is reported to be a modulator of *Wnt* signalling pathway (Kwon *et al*. 2009) and also affects the TM adhesion properties through Rho GTPase and cAMp/protein kinase A signalling pathways (Shen *et al*. 2008). Overexpression of myocilin leads to the abolition of actin stress fibers and have a de-adhesive effect. If overexpression of wild-type myocilin is found to have a de-adhesive effect, the mutant form will give a more stiff and resistant phenotype. And this may lead to an increase in the IOP (Resch and Fautsch 2009). In cultured cells mutated myocilin was found to show increased sensitivity towards trypsin digestion (He *et al*. 2009). Thus it may be concluded that mutated myocilin is responsible for the breakdown of TM cell structure through altering its adhesion properties and interaction with other ECM proteins (Joe *et al*. 2005; Peters *et al*. 2005).

Overexpression of wild-type myocilin is also believed to be involved in glaucoma pathogenesis. But still there are some conflicting opinions about it. It is believed that in case of steroid-induced glaucoma, overexpression of myocilin is one of the triggering factors for glaucoma causation. It is well known that myocilin contain several GRE in its promoter region and myocilin overexpression was observed in TM cell line upon treatment with dexamethason, a glucocorticoid. Thus, myocillin is also known as TIGR (trabecular meshwork inducible glucocorticoid response element) (Polansky *et al*. 1997; Nguyen *et al*. 1998). In short, current studies suggest that myocillin can affect the structural integrity of TM on overexpression of the protein or on aberration caused by acquired mutations. The structural defect in TM possibly damages the optic nerve through a multitude of mechanisms leading to the glaucomatous pathogenesis. The involvement of myocilin in glaucoma pathogenesis has been recently reviewed (Resch and Fautsch).

Optineurin gene (OPTN)

In 1998, Sarfarazi *et al*. (1998) reported linkage of a normal-tension glaucoma phenotype in a large British family to a locus (p15-14) on chromosome 10 (GLC1E). In 2002, the same group (Rezaie *et al*. 2002) reported characterization of the underlying gene for the GLC1E with identification of sequence variations in optineurin gene (OMIM # 602432) in the original GLC1E family as well as eight other families with NTG. A total of 16.7% of the 52 families in their report were found to have putative disease-causing *OPTN* variations with an additional attributable risk factor of 13.6% in both familial and sporadic cases. These families all included at least one member with NTG.

Following this discovery, a large number of studies were undertaken to identify the defects in *OPTN* causal to NTG and POAG but only a few mutations have been reported (Alward *et al*. 2003; Aung *et al*. 2003; Baird *et al*. 2004; Toda *et al*. 2004; Mukhopadhyay *et al*. 2005; Hauser *et al*. 2006b). One such study screened 1,048 patients for variations in *OPTN* and identified one of the previously reported mutation (E50K) in one individual with familial NTG but found another mutation (R545Q) in controls suggesting the variant to be polymorphic and unrelated to the disease (Alward *et al*. 2003). Similarly, other reports have made conflicting claims regarding association of specific allelic variant of *OPTN* with POAG and/or NTG (Mukhopadhyay *et al*. 2005; Liu *et al*. 2008; Yen *et al*. 2008; Caixeta-Umbelino *et al*. 2009). It is interesting to note that despite discovery of *OPTN* as a glaucoma causing gene, the HGMD database (http://www.hgmd.cf.ac.uk) do not yet include any additional entry for defects in the gene other than those from the discovery paper. Although studies have been undertaken to decipher the effects of missense mutations in OPTN at molecular level, current knowledge of genetic studies suggests that the gene might not have any major role in causation of POAG in general.

OPTN spans ~37-kb genomic region and contains three non-coding exons in the 5′-region and 13 exons that code for a 577-amino acid protein. Alternative splicing generates at least three different isoforms. It is possible that an imbalance in the expression of these isoforms leads to glaucoma. However, any conclusive evidence for imbalance of splice variants of *OPTN* is still lacking and remains a possible testable hypothesis.

Multiple interacting partners of optineurin have been reported viz huntingtin, myosin VI, rab8, TBK1(TANK binding kinase.) etc (Anborgh *et al*. 2005; Chibalina *et al*. 2008; Morton *et al*. 2008; del Toro *et al*. 2009). Optineurin was found to be localized in golgi apparatus and upon apoptotic stimuli it translocates to the nucleus. This translocation is mediated via a GTpase rab8, an interactor of optineurin (De

Marco *et al*. 2006). It was also found that optineurin protects the cell from oxidative damage and blocks the release of cytochrome c from mitochondria. A well documented mutation of optineurin, E50K, was found to impair the trafficking of optineurin to the nucleus and also it can cause oxidative stress to the cells which can lead to apoptosis. (De Marco *et al*. 2006; Chalasani *et al*. 2007). Optineurin can mediate this action through the antiapoptotic affect of NFk-B. It is known that optineurin negatively regulates NFk-B by competing with NEMO, a subunit of protein kinase IKK complex involved in NFk-B regulation. IKK sequesters NFk-B in the cytoplasm and, upon ubiquitin-mediated destruction of IKK, it translocates to the nucleus and induces the expression of many anti-apoptotic genes. By competing with NEMO optineurin prevents the NFk-B translocation to the nucleus (Zhu *et al*. 2007; Wagner *et al*. 2008; Fenner *et al*. 2009). Upon apoptotic signal, its translocation to the nucleus can alleviate its negative regulation of NFk-B and infer a protection from cell death. But again NFk-B positively regulates optineurin (Sudhakar *et al*. 2009) and upon release from apoptotic stress it can quickly render the NFk-B to its inactive state. It can be said that optineurin maintain the cell heath by its expression pattern (Park *et al*. 2006) .The regulatory regions of this gene can be scanned for probable POAG causing mutations.

Park *et al*. (2007) has recently shown that overexpression of OPTN in TM cells results in prolonged turnover rate of *MYOC* mRNA but had little effect on *MYOC* promoter activity (Park *et al*. 2007). The authors have speculated the interaction through control of mRNA stability. Again, as discussed earlier, overexpression of myocilin can lead to glaucoma. Optinuerin also interacts with metabotropic glutamate receptors (mGluR) and selectively inhibit mGluR1a (Anborgh *et al*. 2005).

As eluded earlier, it is intriguing that so much functional studies have been reported to unravel the role of OPTN in ocular cells but its relevance to POAG is not entirely persuasive for lack of enough genetic evidence for its major role in pathogenesis of the disease.

WD Repeat Domain 36 gene (WDR36)

Another locus for POAG, designated as GLC1G, was identified in chromosome 5q22.3 using linkage analysis in two large Caucasian families (Monemi *et al*. 2005). Further, the underlying gene associated with the disease was characterized as *WDR36* which is expressed in human ocular and non-ocular tissues. The gene spans about 34.7-kb genomic region and contains 23 exons, expressed predominantly as two transcripts (5.9 kb and 2.5 kb). The full length protein contains 950aa (M_r ~105 kD) harbouring four conserved domains: (a) nine WD40 repeat domain; (b) Utp21 domain; (c) AMP-dependant synthetase and ligase domain, and (d) cytochrome cd1-nitrite reductase-like domain.

Monemi *et al*. (2005) identified four mutations in the *WDR36* gene among 17 unrelated POAG subjects, 11 with high-pressure and six with low-pressure glaucoma. The mutations were absent in a minimum of 200 normal control chromosomes and the residues were conserved between *WDR36* orthologs in mouse, rat, dog, chimpanzee and human. Specific ocular expressions and observed mutations were consistent with a role for *WDR36* in the etiology of both high and low-pressure glaucoma (Monemi *et al*. 2005).

Recently, another JOAG locus has been identified in close proximity of *GLC1G* but not overlapping it (Pang *et al*. 2006). Mutation screening in the family where JOAG segregates with the novel locus does not bear any mutation in the coding region or splicing junctions of *WDR36* and observed sequence variant in intron and promoter could not be correlated with the disease.

Most of the studies on *WDR36* were done in Caucasian populations. Hauser *et al*. (2006a) reported probable disease causing variants in 17% of the patients, but the distribution of *WDR36* variants in the pedigrees did not show consistent segregation with the disease. They found *WDR36* sequence variants to be more frequent in patients with more severe disease. They concluded that defect in *WDR36* is not sufficient for POAG causation rather *WDR36* act as a modifier locus for POAG (Hauser *et al*. 2006a). Studies on German POAG and NTG patients concluded that WDR36 play a minor role in OAG pathogenesis (Weisschuh *et al*. 2007; Pasutto *et al*. 2008). A case–control study in Australian population with one of the predominant *WDR36* mutations (i.e. D658G) in Caucasians revealed the presence of this mutation in both patient and control groups questioning its role in OAG pathogenesis (Hewitt *et al*. 2006). Also, study by Fingert *et al*. did not find any association of *WDR36* with POAG (Fingert *et al*. 2007). As far as Asian populations are concerned, only two studies have been published so far — one from Japanese population (Miyazawa *et al*. 2007) and another from Chinese population (Fan *et al*. 2009). These two studies have identified one disease causing variant each viz.S664L and I713V, respectively (Miyazawa *et al*. 2007; Fan *et al*. 2009)). Also, two SNPs (I264V and c1965-30A>G) were found to be associated with high tension glaucoma in Japanese cohort and a single SNP (c.1965-30A>G) was found to be associated with HTG in Chinese cohort (Miyazawa *et al*. 2007; Fan *et al*. 2009)). Our limited study in Indian POAG cohort did not reveal any disease causing mutation in *WDR36* coding exons but a single intronic SNP was found to be associated with HTG (S. Mookherjee and K. Ray, unpublished data); the lead is being investigated further.

This gene was previously reported to be uniquely involved in T-cell activation and highly coregulated with interleukin 2. Recent study by Skarie *et al*. (2008) provides an insight into the functionality of the protein. This study reveals WDR36 is a multifunctional protein. WDR36 is required for ribosomal rRNA processing and maintaining the proper nucleolar morphology. The protein is also important

for proper development of brain, eye and gut. It has also been noted that loss of WDR36 function in mouse leads to an activation of the p53 stress–response pathway (Skarie *et al*. 2008).

Recently Footz *et al*. (2009) have developed a yeast model to test the functionality of *WDR36* mutations. They have introduced the probable POAG causing sequence variants to *UTP21*, the yeast homolog of *WDR36*, and found that these variants by themselves could not produce any effect on rRNA processing or cell viability but when present along with disruption of *STI1* (which interacts with *UTP21*), five of the 11 tested variants had increased or decreased cell viability which corresponded with reduced or elevated levels of pre-rRNA, respectively. This observation indicates that *WDR36* mutations can alter cellular phenotype when present in a permissible genetic background and support the role of *WDR36* as a modifier locus in polygenic POAG (Footz *et al*. 2009).

CYP1B1 (cytochrome P450 family 1 subfamily B polypeptide 1)

CYP1B1 was primarily identified to cause primary congenital glaucoma (PCG) in autosomal recessive mode of inheritance (Sarfarazi *et al*. 1995; Stoilov *et al*. 1997). Mutations in this gene has also been found in Peters anomaly (Vincent *et al*. 2001), Axenfield Reiger syndrome (Chavarria-Soley *et al*. 2006) and in POAG patients as well. Involvement of *CYP1B1* in glaucoma has been extensively covered in a review by Vasiliou and Gonzalez (2008). Earlier, this gene was reported to be a modifier locus for POAG, i.e., mutation in this gene along with myocilin mutation was found to hasten up the disease onset and progression (Vincent *et al*. 2002; Melki *et al*. 2004). But later, it was observed that in rare cases mutation in this gene also cause early onset POAG in autosomal recessive mode of inheritance (Acharya *et al*. 2006; Bayat *et al*. 2008). But mostly, mutations in *CYP1B1* were found in heterozygous state in POAG cases.

CYP1B1 belongs to cytochrome p450 group of proteins and is functionally diverse. It is involved in drug metabolism, fatty acid metabolism and steroid metabolism. CYP1B1 is a membrane bound enzyme and has a role in iredocorneal angle development of the eye. CYP1B1 null mice have grossly normal phenotype but develop focal malformation of the iredocorneal angle (Libby *et al*. 2003; Jiang *et al*. 2008). In the affected region, the malformation can include hypoplastic trabecular meshwork, abnormally located basal lamina in the trabecular meshwork and iridocorneal adhesions. Developmental malformation as seen in some PCG cases with *CYP1B1* mutations resembles that of CYP1B1 null mouse (Gould *et al*. 2004). CYP1B1 has been proposed to be involved in a yet unknown biologically active process for development. Mutation in *CYP1B1* may affect the production/activation, degradation/deactivation of a key biological molecule involved in anterior segment development of eye. One possibility is that, it is involved in retinoic acid signaling pathway; CYP1B1 oxidizes all-trans-retinol to all-trans-retinal which is a rate-limiting step in retinoic acid biosynthesis (Chen *et al*. 2000). But the exact role of CYP1B1 in ocular development is still lacking.

Recent study suggests mutation in *CYP1B1* can alter its enzymatic activity but this protein has multiple enzymatic activities, alteration of one activity may not be responsible for other one. Direct evidence of *CYP1B1* mutation dependent alteration of retinoic acid catabolism activity is still lacking. But studies from our lab (M. Acharya, S. Mookherjee and K. Ray, unpublished data) and others suggest that mutations in *CYP1B1* alters its steroid metabolism either by perturbing the structure of the protein (Achary *et al*. 2006; Achary and Nagarajam 2008) or by decreasing its stability (Jansson *et al*. 2001; Bagiyeva *et al*. 2007; Chavarria-Soley *et al*. 2008; Choudhary *et al*. 2008). We observed that Leu432Val polymorphism is associated with POAG with Val432 acting as a risk factor for the disease. By functional analysis we showed that Val432 bearing CYP1B1 increases the susceptibility towards POAG by increasing the reactive oxygen species (ROS) generation (Bhattacharjee *et al*. 2008).

Recently we have observed that CYP1B1 mediated estrogen metabolism can alter the expression of myocilin. We found that putative ERE elements in the myocilin promoter are active and myocilin expression can be induced by 17β estradiol treatment. Any mutation in *CYP1B1* that affects its estrogen metabolism activity could upregulate myocilin expression by prolonging the presence of estrogen in the cells. Wit the help of three mutation of CYP1B1, that have lower estrogen metabolism activity, we observed that these mutants have the ability to upregulate myocilin expression (M. Acharya, S. Mookherjee and K. Ray, unpublished data), and overexpression of myocilin can lead to POAG.

Other genes associated with glaucoma

In addition to the candidate genes, many other genes have been proposed to be associated with POAG (table 2). Most of the studies demonstrate association in single population groups and in some cases conflicting results have been published in multiple studies done on the same population. Therefore, it is difficult to judge whether the variations of the association study results are due to population difference, sample size, study design or clinical heterogeneity between different cohorts of patients. The involvement of such predisposing factors can be better elucidated with studies done on large sample size, study design applied to multiple cohorts of patient samples and/or functional studies deciphering the molecular basis of pathogenesis.

Recently a genome wide association study has identified six SNPs which can act as candidate gene markers for POAG (Nakano *et al*. 2009). Four markers viz. rs547984, rs540782, rs693421, rs2499601 were identified near *ZP4* gene, one near *PLXDC2* gene i.e. rs7081455 and one in the intronic region of *DKFZp762A217* gene i.e. rs7961953.

The interactions between different SNPs among the genes had also been implicated in POAG pathogenesis.

Table 2. Genes reported to be associated with POAG.

Gene symbol	Gene name	OMIM no.	Chromosomal location	Reference
AGTR2	Angiotensin II receptor, type 2	300034	Xq22-q23	Hashizume *et al*. 2005
APOE	Apolipoprotein E	107741	19q13.2	Copin *et al*. 2002
IL1A	Interluekin 1 alpha	147760	2q14	Wang *et al*. 2006a
EDNRA	Endothelin receptor, type A	131243	4q31.2	Ishikawa *et al*. 2005
GSTM1	Glutathione S-transferase, mu-1	138350	1p13.3	Juronen *et al*. 2000
IGF2	Insulin-like growth factor II	147470	11p15.5	Tsai *et al*. 2003
IL1B	Interluekin 1 beta	147720	2q14	Lin *et al*. 2003b
MTHFR	5,10- methylenetetra-hydrofolate reductase	607093	1p36.3	Junemann *et al*. 2005
NOS3	Nitric oxide synthase 3	163729	7q36	Tunny *et al*. 1998
NPPA	Natriuretic peptide precursor A 108780	1p36.2		Tunny *et al*. 1996
OCLM	Oculomedin	604301	1q31.1	Fujiwara *et al*. 2003
OLFM2	Olfactomedin 2	-	19p13.2	Funayama *et al*. 2006
OPA1	Optic atrophy 1	605290	3q28-q29	Aung *et al*. 2002
TAP1	Transporter, ATP-binding cassette, major histocompatibility complex,	1170260	6p21.3	Lin *et al*. 2004
TNF	Tumour necrosis factor	191160	6p21.3	Lin *et al*. 2003a
TP53	Tumour protein p53	191170	17p13.1	Lin *et al*. 2002
OPTC	Opticin	605127	1q32.1	Acharya *et al*. 2007
CYP2D6	Cytochrome P450, Subfamily IID, Polypeptide 6	124030	22q13.1	Yang *et al*. 2009
PON1	Paraoxonase 1	168820	7q21.3	Inagaki *et al*. 2006a
CDH-1	Cadherin 1	192090	16q22.1	Lin *et al*. 2006
LMX1B	Lim Homeobox Transcription Factor 1	602575	9q34.1	Park *et al*. 2009
ANP	Atrial natriuretic polypeptide	108780	1p36.2	Tunny *et al*. 1996
P21	P21	116899	6p21.2	Tsai *et al*. 2004
HSPA1A	Heat shock 70 kDa protein 1A	140550	6p21.3	Tosaka *et al*. 2007
TLR4	Toll-like receptor 4	603030	9q32-q33	Shibuya *et al*. 2008
CYP46A1	Cytochrome P450, Family 46, Subfamily A, Polypeptide 1	604087	14q32.1	Fourgeux *et al*. 2009
PAI-1	plasminogen activator inhibitor-1	173360	7q21.3-q22	Mossbock *et al*. 2008
ADRB1	beta-adrenergic receptors 1	109630	10q24-q26	Inagaki *et al*. 2006b
ADRB2	beta-adrenergic receptors 2	109690	5q32-q34	Inagaki *et al*. 2006b

An interaction was observed between *TNF*-α −863A/C and *OPTN* 603A/T (Met98Lys) polymorphisms (Funayama *et al*. 2004). Eventually it was found that *TNF*-α induces *OPTN* expression through NFk-B and their role in POAG has also been described (Sudhakar *et al*. 2009). There is also report of possible interactions between *MYOC* and *OPTN* SNPs with APOE SNPs (Fan *et al*. 2005). They observed two sets of interaction for HTG patients of *OPTN* IVS15+10G/A and *OPTN* IVS5+38T/G with *MYOC* Thr353Ile and *APOE* −491A/T respectively and three sets of interaction for NTG patients of *OPTN* Arg545Gln with *APOE* ϵ2/ϵ3/ϵ4, *MYOC* -83G/A with *APOE* ϵ2/ϵ3/ϵ4 and *MYOC* IVS2+35A/G and *APOE* −219T/G. Another interaction was also found between OPTN and OLFM2 in POAG pathogenesis (Funayama *et al*. 2006). Incidentally, OLFM2 or olfactomedin2 was predicted to be a probable candidate gene of POAG by bioinformatics analysis from our lab (Mukhopadhyay *et al*. 2004).

Apart from association studies, microarray expression studies (Hernandez *et al*. 2002; Ishibashi *et al*. 2002; Miyahara *et al*. 2003; Ahmed *et al*. 2004; Yang *et al*. 2004; Steele *et al*. 2006; Johnson *et al*. 2007; Kirwan *et al*. 2009) and proteomic studies (Zhao *et al*. 2004; Bhattacharya *et al*. 2005; Tezel *et al*. 2005; Bhattacharya *et al*. 2006; Miyara *et al*. 2008; Zhang *et al*. 2008) done in different tissues and cells (e.g., trabecular meshwork cell and tissue, retina, optic nerve head astrocytes, retinal ganglion cells, retinal glial cells etc.) have identified a large number of differentially expressed genes. Although the role of these genes in POAG is largely unknown, such a repertoire of genes provides a good resource to select candidate genes for identification of glaucoma genes in known genetic loci or selection of possible glaucoma-related genes in case–control association studies.

Involvement of mitochondrial genome in glaucoma pathogenesis

The list of optic neuropathies currently associated with mitochondrial abnormalities includes LHON, certain patients with optic neuritis and multiple sclerosis, Wolfram's syndrome, dominant optic atrophy (DOA) and NAION (nonarteritic anterior ischemic optic neuropathy). There is limited information available for involvement of mitochondrial

genome in glaucoma. The only report available so far is from Saudi Arabian population. Abu-Amero *et al*. (2006) screened the whole mitochondrial genome in a cohort of 27 POAG patients and identified a total of 34 novel non-synonymous mtDNA sequence changes spanning the mitochondrial coding region; 17 (50%) were in complex I, 2 (5.9%) in complex III, 9 (26.5%) in complex IV, 5 (14.7%) in complex V and 1 (2.9%) in tRNA glycine. Among these 34 changes, seven non-synonymous mtDNA changes were detected in both patients with POAG and control subjects and were predicted to be benign. Twenty-seven of these changes were detected in patients with POAG but not in control subjects, among which 22 altered moderately or highly conserved amino acids and were predicted to be damaging to the corresponding protein structure and/or function. However, the higher preponderance of transversion type of changes pointed towards the involvement of oxidative stress in mitochondrial DNA damage in POAG cases. The relative mitochondrial DNA content of the patients did not differ significantly from that of control subjects. However, the patients were seen to have lower mitochondrial respiratory activity than that of the control group (Abu-Amero *et al*. 2006).

In two other reports, the same group attempted to elucidate the role of mitochondrial genome in PACG and pseudoexfoliating glaucoma. In both the cases, they failed to identify any significant involvement of mitochondrial genome (Abu-Amero *et al*. 2007, 2008a). In another study, it has been reported that while there is no association of POAG or pseudoexfoliating glaucoma with specific haplogroup of mitochondria, PACG is associated with a specific ('preHV') haplotype of mitochondria (Abu-Amero *et al*. 2008b).

Glaucoma as a neurodegenerative disorder

Recent observations suggest that, in addition to RGC, glaucoma patients contain neurodegenerative lesions deep into the brain supporting the speculation of its being a neurodegenerative disorder.

There are certain degree of similarity between the common neurodegenerative disorders and glaucoma which includes: (i) loss of specific neuronal population of brain, (ii) trans-synaptic spreading of neurodegeneration from RGC to deep into the brain, (iii) deposition of protein aggregates in glaucomatous RGC as observed in other neurodegenerative disorders like Alzheimer's disease, Parkinson disease etc., (vi) drugs administered in neurodegenerative disorder like Alzheimer disease and Parkinson disease treat glaucoma.

A common feature shared between the neurodegenerative disorders is the loss of specific groups of neurons. For example, (i) loss of cortical and hippocampal neurons in the Alzheimer disease can be correlated with the loss of memory and cognitive function; and (ii) in Parkinson's disease loss of dopaminergic nigrostriatal neurons can be correlated with gradual movement disorder (Lang and Lozano 1998a,b). Similarly, in glaucoma a progressive degeneration in the visual centre of the brain is observed along with the degeneration of RGC (Yucel *et al*. 2000, 2001; Harwerth and Quigley 2006). After exiting from the eye, the axons of RGC cross each other at optic chiasma and terminate at lateral geniculate nucleus (LGN). The LGN of each hemisphere represents the contrallateral half of the visual field. The LGN is primarily composed of six layers; interneurons are confined within the LGN and the relay neurons communicate with visual cortex. There are three types of the relay neurons viz. magnocellular (covey motion information), Parvocellular (convey red–green colour information) and Koniocellular (convey blue–yellow signal) type. Ventral layers 1 and 2 constitutes the Magnocellular neurons, four dorsal layers constitutes the parvocellular neurons and koniocellular neurons are located within and between the principal layers (Yucel *et al*. 2003).

Definite degenerative changes were observed in the optic tracts, in the brains of the glaucomatous patients and in the lateral geniculate nucleus (LGN). Also axonal loss was found in the intracranial optic tract. The size of the LGN was found to be reduced in glaucomatous patients with the loss of neurons. Visual cortex was also found to be affected with neuronal loss. So, similar to other neurodegenerative disorders a loss of specific group of neurons involved in vision was observed in the glaucoma patients. (Weber *et al*. 2000; Yucel *et al*. 2000, 2001; Gupta *et al*. 2006, 2009).

In neurodegenerative disorders, the mode of disease spreading is from sick neuron to healthy neurons through the synaptic connection along the functional and anatomical neural pathway. The process is called *trans*-synaptic degeneration. Such degeneration is well known in Alzheimer disease (Su *et al*. 1997) and has also been found in human and experimental glaucoma cases (Gupta and Yucel 2001).

Like other neurodegenerative disorders, deposition of unfolded or misfolded proteins aggregates has been found in RGC of glaucoma patients (Wax *et al*. 1998; Janciauskiene and Krakau 2001; Vemuganti and Mandal 2002; Bhattacharya *et al*. 2005; Gupta *et al*. 2008; Wang *et al*. 2008; Wostyn *et al*. 2008; Yin *et al*. 2008). Deposition of cochlin, which is primarily associated with deafness has also been observed in glaucomatous TM cells (Bhattacharya *et al*. 2005). Abnormal Tau protein, AT8 which is a hallmark of many neurodegenerative disorders like Alzheimer disease, corticobasal degeneration, Pick's disease, agrylophilic grain disease, frontotemporal dementia, Parkinson disease etc. has also been reported in glaucomatous RGC (Gupta *et al*. 2008). In addition, there are indications that β-amyloid can also be involved in glaucoma pathogenesis (Janciauskiene and Krakau 2001; Vemuganti and Mandal 2002; Wang *et al*. 2008; Wostyn *et al*. 2008; Yin *et al*. 2008).

Perhaps the most striking similarity between glaucoma and neurodegenerative disorder lies in their treatment regime. Memantine, an NMDA open-channel blocker, which has been used for long time in the treatment of Parkinson disease and Alzheimer disease, was found to be effective in glaucoma

treatment (Yucel *et al*. 2006; Cheung *et al*. 2008; Hare and Wheeler 2009; Osborne 2009). Memantine along with other IOP lowering drugs was found to control the progressive neurodegeneration in glaucoma more effectively than only with IOP lowering treatment. Recently, Guo *et al*. (2007) showed that the compound which is used to reduce β-amyloid deposits in Alzheimer's disease can be equally effective in treating glaucomatous neurodegeneration. On treating glaucomatous rat by β-secretase inhibitor antibody against amyloid β-proteins and congo red they observed that a combinatorial treatment is better than single treatment in controlling the RGC death.

Cause of neurodegeneration in glaucoma

Till date, several theories have been put forward to explain the loss of RGC in the POAG patients. The following factors have been proposed to influence the RGC loss which are mentioned here along with the recent reviews that have dealt the issues in depth: (i) mechanical stress due to increased intraocular pressure and withdrawal of trophic factors (Whitmore *et al*. 2005), (ii) reduced blood flow in retina (Mozaffarieh *et al*. 2008a), reperfusion injury, oxidative stress (Mozaffarieh *et al*. 2008b), glutamate excitotoxicity (Dreyer and Grosskreutz 1997; Dreyer 1998), (iii) and autoimmunity (Wax and Tezel 2009). Some or all of these factors may operate to cause glaucomatous RGC loss.

Increased IOP is believed to be one of the major factors responsible for glaucomatous cell death. The axons of the optic nerve exit through the fenestrated collageneous barrier called lamina cribrosa through a twisty tervy way before entering the brain. It has been proposed that increased IOP causes a mechanical stress to the lamina cribrosa, which in turn exerts pressure on the axon that passes through it. This pressure might block the trafficking of the essential material through the axons; which would lead to a slow degeneration of the axons of the RGC. With increased IOP, gradual withdrawal of trophic factor from RGC has been observed in mouse model (Johnson *et al*. 2000). Also apoptosis was observed to be a much delayed process in RGC in such scenario (Johnson *et al*. 2000). It was, thus, proposed that with increased IOP and mechanical stress on lamina cribrosa, axons of RGC are lost much earlier than the cell body of the RGC. Thus RGCs become ineffective in their visual function much earlier than actual phenotypic changes are observed in retina/optic disc, as they are incapable of sending visual signals to the visual center of the brain (Whitmore *et al*. 2005).

However, increased IOP alone cannot account for all the POAG cases. Also, subjects with ocular hypertension do not necessarily develop glaucoma. Again in NTG cases, RGC loss occurs in spite of IOP being in normal range.

Ocular blood flow in various tissues (e.g. retina, iris, optic nerve and choroids) was found to be reduced in glaucoma patients (Flammer and Prunte 1991; Flammer and Orgul 1998; Flammer *et al*. 2002). The blood flow reduction was more pronounced in NTG patients (Flammer and Orgul 1998; Doyle *et al*. 2005; Selbach *et al*. 2005; Mozaffarieh *et al*. 2008a). Interestingly, reduction of blood flow was also observed in the nail-fold capillaries of fingers in glaucoma patients (Usui and Iwata 1992); suggesting that the reduction of blood flow is not due to increased IOP or an epiphenomenon of glaucoma, but a global vascular dysregulation is involved in POAG especially in NTG cases. This regulation of the blood flow in differs in different ocular tissues. The retinal vascular regulation is similar to that of the brain except the fact that it has no autonomic innervations. Thus, blood flow of the retina is largely regulated by the endothelial cell derived substances that are collectively known as endothelium derived vasoactive compounds (EDVCs) (Haefliger *et al*. 2001), acting both abluminally and intraluminally. Patients with primary vascular dysregulation often have high level of endothelin-1 (ET-1) (Flammer *et al*. 2001; Cleary *et al*. 2005) and matrixmetalloproteinase such as MMP-9 (Golubnitschaja *et al*. 2004). ET-1 has the capability of vasoconstriction (Orgul *et al*. 1999; Haefliger *et al*. 2001) and also interferes with vascular permeability. By increasing the vascular permeability it can result in retinal hemorrhage that has also been observed in glaucoma patients, especially in NTG cases (Grieshaber and Flammer 2007). The vascular leakage can facilitate the diffusion of harmful materials to cross the incomplete blood brain barrier in the retina (Grieshaber and Flammer 2007). Apart from vasoconstriction, ET-1 also regulates the blood brain barrier, by upregulating the prostaglandin E2 which in turn reduces the endothelial tight junction complex (Grieshaber and Flammer 2007). ET-1 cause ischemic stress not only by inducing vasoconstriction but also by altering the activity of ATP dependent Na+/K+ pump (Petzold *et al*. 2003).

Autoimmunity which is often found to be associated with PAOG, especially with NTG cases can increase the level of MMP-9 in circulation (Yan *et al*. 2000; Agapova *et al*. 2001; Xu *et al*. 2009). MMP-9 is an endo-peptidase which has a capability to digest the extracellular matrix; in particular it digests basement membrane of the vascular wall (Grieshaber and Flammer 2007). Together these could open up a channel of communication between the eye and brain; a potential source responsible for spreading of neurodegeneration from retina to visual centre in the brain.

A repeated reperfusion injury to the tissue due to vascular dysregulation was demonstrated to cause oxidative stress to the tissue. Thus oxidative stress, which arises by reperfusion injuries, could be responsible for RGC cell death. In normal condition the super-oxide species are scavenged by various antioxidants. In eye, there is high level of ascorbic acid or vitamin C, which is an excellent antioxidant (Giblin *et al*. 1984; Richer and Rose 1998; Rose *et al*. 1998). In addition, reduced glutathione, super-oxide dismutase and catalase convert the ROS to harmless substances (Green *et al*. 1990; Riley 1990; Izzotti *et al*. 2006). But studies revealed that the antioxidant levels were decreased significantly in glaucoma

patients (Yang *et al*. 2001b; Gherghel *et al*. 2005). So the replenishment of the antioxidants can be one of the treatment regimens of glaucoma especially for the aged person whose innate defense system against ROS has diminished. In addition, ROS can react with nitric oxide (NO), which is secreted by the endothelial cells, to produce peroxynitrate (ONOO-) a highly reactive and potent neurotoxic species. The peroxynitate species is responsible for nitration of the proteins especially the tyrosine residue. The presence of nitrotyrosine in the vascular lining of retinal blood vessels in glaucoma patients indicates a potent oxidative damage to the vascular system by oxidative stress. So, by reperfusion injury-induced-oxidative stress, which damages the retinal blood vessels further increases the chance of oxidative damage by reducing the blood flow to retina, thus inducing a cyclic process of damage (Feilchenfeld *et al*. 2008).

NO, as suggested by the vascular pathogeneses theory of glaucoma, is responsible for counter-balancing the vessel-tone increase (Flammer *et al*. 1999; Grieshaber *et al*. 2007a,b). But it also plays an important role in neuronal physiology by acting as a second messenger and by modulating the cellular sodium pump. Through these mechanisms, NO increases the production of glutamate and other intercellular messengers, which in turn cause a marked and prolonged alteration in activity of the ATP dependent, Na+/K+ pump, a mechanism implicated in various degenerative diseases (Petzold *et al*. 2003), including glaucoma (Sacca 2002; Saccr 2002; Toda and Nakanishi-Toda 2007).

Glutamate excitotoxicity is also believed to be one of the reasons for glaucomatous neurodegeneration. In fact, increased buildup of the glutamate was observed at the posterior aspect of the glaucomatous eye in monkeys with elevated IOP and in human glaucoma patients (Dreyer and Grosskreutz 1997). Glutamate, a neurotransmitter released from the pre-synaptic membrane, binds to the glutamate receptors in the post-synaptic membrane. This in turn induces the rapid build up of cytosolic Ca^{++} levels (Pin and Duvoisin 1995). Prolonged activation of glutamate receptors by increased level of glutamate would lead to high Ca^{++} level in the cytosol and thus can facilitate the opening of mitochondrial PTPC (permeability transition pore complex) (Crompton 1999). Opening of the PTPC will lead to passage of cytochrome C, AIF, endonuclease G, caspase activators, IAP inhibitors to the cytosol and starts the cascade of apoptotic cell death (Kroemer *et al*. 2007). In glaucoma patients, it has been already documented that mitochondrial DNA is damaged by oxidative stress and the patients have diminished mitochondrial respiratory activity (Abu-Amero *et al*. 2006). Thus, glutamate excitotoxicity is predicted to have more effect on oxidative stress induced sick mitochondria. Mitochondria are the power house of the cell and retinal nerve cells has prodigious energy demand (Schober *et al*. 2008). Sick mitochondria produce energy less efficiently, thus energy starvation of the nerve cells is possible. Opening of PTPC will lead to a decrease in mitochondrial (Kroemer *et al*. 2007; Wojda *et al*. 2008) membrane potential and thus will decrease the proton-motive force required to generate ATP. This may lead to decreased functionality of the nerve cells and an 'energy stress' to the nerve cells. Experimental evidence suggests that level of ATP at least in part plays a role in the mode of cell death (Choi and Rothman 1990; Crompton 1999). So it is necessary to elucidate whether in animal models of glaucoma as well as in humans there is decreased ATP level.

Immunity, aberrant immune response and auto-immunity also play a role in glaucomatous neurodegeneration. Immune system plays a beneficial role in the body by removing the extraneous challenges like bacteria and viruses. But aberrant stress induced immune response is harmful to the body (Young and Elliott 1989; van Noort 1996; Tezel *et al*. 2003; Tezel and Wax 2003; Ziyal *et al*. 2004). Oxidative stress caused by the reperfusion injuries give rise to various proteins that are damaged by ROS. When these damaged proteins are recognized by the immune system, antibodies are generated against them, which can cross react with the intact proteins as well. Antibody levels against some of the self proteins e.g. anti-NSE antibody (Ikeda *et al*. 2002), antibodies to heat shock proteins (Tezel *et al*. 198), and beta 2 glycoproteins (Latalska *et al*. 2004) have been reported to be significantly higher in glaucoma patients. Also, deposition of the immunoglobulin molecules has been found in the retina of the glaucoma patients (Wax *et al*. 1998). Antibodies to the various proteins of the neurons can lead to mislabeling of the self neuron as foreign and can cause severe degenerative changes in the neurons. Although immune privileged, T-cells can cross the blood brain barrier and can enter the brain and eye as a part of immune-surveillance mechanism of the body. Build up abnormal population of the T-cells in the eye of glaucoma patient has also been reported (Yang *et al*. 2001a; Tezel *et al*. 2007). Those abnormal antigen stimulated T-cells can be directly cytotoxic to the RGC mostly by Fas/FasL mediated pathway (Tezel *et al*. 2007). So, abnormal T-cell population build up in eyes of the glaucoma patients indicates towards the failure and/or the inability of the aberrant self antigen activated T-cell population controlling mechanism in the eye. Pro-inflammatory cytokines like *TNF*-α, which is produced in the brain and in eye by microglial cells, was proposed to play an important role in glaucomatous neurodegeneration (Yan *et al*. 2000; Tezel *et al*. 2001). In cultured RGC cell it was observed that treatment with *TNF*-α leads to an apoptotic cell death. Increased expression of *TNF*-α and its receptor were observed in the optic nerve heads of the glaucoma patients. *TNF*-α induces the production of NO which can be cytotoxic to the RGC as described before (Tezel and Wax 2000). Perhaps the most compelling evidence towards the involvement of the immune system in glaucoma comes from the observation that immunization of the mouse with antibodies specific to the HSPs results in the RGC loss similar to that was observed in glaucoma patients (Wax *et al*. 2008).

In conclusion, glaucoma is a multifactorial disease where multiple genetic, systemic and environmental factors interact to precipitate the disease. Based on the information available on the involvement of different genes and pathways, we summarized the unfolding network of events in POAG in figure 1. The pathways given in the figure e.g. genetic factors, immune system, oxidative stress, vascular dysregulation, glutamate excitotoxicity and their interconnection are

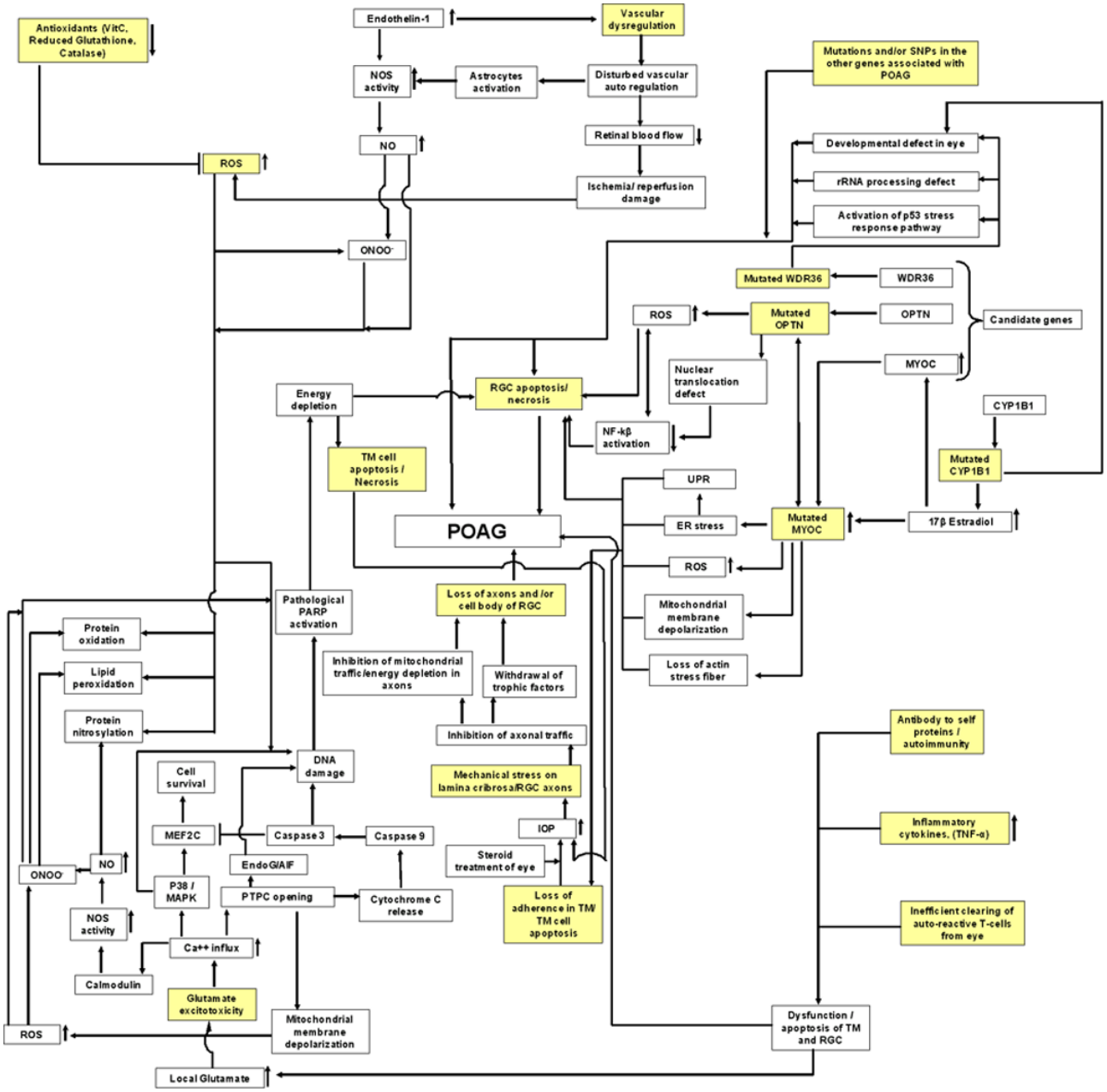

Figure 1. Schematic overview of potential involvement of different pathways in POAG pathogenesis. The scheme presented summarizes the unfolding network of events in primary open angle glaucoma (POAG) and has been created based on the information available on the involvement of different genes and pathways in its pathogenesis. The major nodes in the network i.e., mutation in the candidate gene(s) or in the modifier genes, associated SNPs, reduced antioxidants and rise in ROS generation, vascular dysregulation, glutamate excitotoxicity, immune dysregulation, mechanical stress which ultimately leads TM cell dysfunction and RGC loss are highlighted in yellow. Abbreviations used: ROS reactive oxygen species; NOS, nitric oxide synthetase; UPR, unfolded protein response; NO, nitric oxide; ONOO, peroxy-nitrate species; AIF, apoptosis inducing factor; MEF2C, MADS box transcription enhancer factor 2, polypeptide C; RGC, retinal ganglion cells.

described in detail the text. Incidentally, a recent report has identified a potential regulatory network operating in astrocytes-mediated neurotoxicity in case of glaucomatous neurodegeneration (Nikolskaya *et al*. 2009). Their data on genetics, gene expression and proteomics provide a more detail network of genes involved in glaucomatous neurodegeneration and have led to the identification of some key network hubs involved in astrocytes-mediated neurotoxicity in glaucoma. Their analyses too have indicated the involvement of immune system, oxidative stress, alteration in the ECM structure and glutamate excitotoxicity in glaucomatous neurodegeneration. Moreover, it was found that over two third of the genes linked to glaucoma by genetic analysis can be functionally interconnected into one epistatic network via experimentally-validated interactions. The key biological network modules they have identified can be potential targets for anti-glaucomatous drugs.

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