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Review

Mitochondrial dysfunction in glaucoma: Understanding genetic influences ☆

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ABSTRACT

Glaucoma is the leading cause of irreversible blindness worldwide. This review aims to provide a greater understanding of the complex genetic influences that may lead to mitochondrial dysfunction and increase susceptibility to retinal ganglion cell (RGC) loss in primary open angle glaucoma (POAG), and thus elucidate potentially important pathophysiological pathways amenable to therapeutic intervention. Emerging evidence from genome wide association and other genetic studies suggests that changes in the mitochondrial DNA (mtDNA) and in nuclear DNA genes that encode mitochondrial proteins may influence mitochondrial structure and function and, therefore, contribute to the pathogenesis of POAG. We propose that a variety of genes (OPA1, MFN1, MFN2, CYP1B1, PARL, SOD2, SRBD1, GST, NOS3, TNFa and TP53) may each confer a background susceptibility to POAG in different populations having one common link: mitochondrial dysfunction. The relationship between polymorphisms in these genes and increasing risk for POAG is presented and the limitations of the available current knowledge are discussed.

Contents

Abbreviations: RGC, retinal ganglion cell; POAG, primary open angle glaucoma; mtDNA, mitochondrial DNA; IOP, intraocular pressure; ADOA, autosomal dominant optic atrophy; LHON, Leber's hereditary optic neuropathy; ROS, reactive oxygen species; OXPHOS, oxidative phosphorylation; SNP, single nucleotide polymorphism; NTG, normal tension glaucoma; HTG, high tension glaucoma; HRT, Heidelberg retina tomography; OPA-1, optic atrophy 1; MFN, mitofusin; CYP1B1, cytochrome P450 superfamily, subfamily I, polypeptide 1; PARL, presenilin associated rhomboid-like; SOD2, superoxide dismutase 2; SRBD1, S1 RNA-binding domain; GST, Glutathione S-transferase; NOS3, nitric oxide synthase 3; TNFa, Tumour necrosis factor alpha; TP53, Tumour Protein p53.

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1. Introduction

Mitochondrial dysfunction has been implicated in retinal ganglion cell (RGC) loss in experimental animal models of glaucoma (Ju et al., 2008; Mittag et al., 2000) and in transformed ganglion cell cultures (Ju et al., 2007). Pre-existing mitochondrial dysfunction, either congenital or acquired, can increase the vulnerability of RGC to stress from other risk factors, including raised intraocular pressure (IOP), vascular insufficiency and light exposure (Kong et al., 2009). This review aims to support the increasingly popular concept of mitochondrial dysfunction in the pathogenesis of human glaucoma (Lee et al., 2011; Tezel, 2009) by highlighting the emerging evidence from genetic studies in glaucoma that show changes in the mitochondrial and nuclear genes which encode mitochondrial proteins, thus influencing mitochondrial structure and function.

2. The role of mitochondria in retinal ganglion cells

RGCs, because of their high energy requirement, are heavily dependent on mitochondria for survival and function. Mitochondria play a pivotal role in the maintenance of cellular homeostasis regulating death signalling pathways (Kroemer and Reed, 2000; Naoi et al., 2009) and various metabolic functions that include oxidative energy metabolism, intracellular pH maintenance, calcium signalling (Pozzan and Rizzuto, 2000) and neuronal excitability (Chan, 2006; Schapira, 2006). Mitochondria are involved in the control of synaptic transmission and the production of reactive oxygen species (ROS) that promote and regulate apoptosis (Halliwell and Gutteridge, 1999). Significantly, retinal ganglion cell axons are unmyelinated within the ocular globe and have mitochondria-enriched axon varicosities (Barron et al., 2004; Wang et al., 2003), which are interpreted as functional sites with local high-energy demand, critical for maintaining normal signal transmission along the axon (Carelli et al., 2004). It is therefore clear that alteration in the functional status of these ganglion cell axon mitochondria may influence ganglion cell survival in a disease like glaucoma (Osborne, 2008). RGCs are thought to die by apoptosis at varying rates depending on, for example, the ganglion cells' receptor profile (Osborne et al., 1999) and other factors, such as the number and spatial distribution of the RGC mitochondria (Yu-Wai-Man et al., 2005) and their axonal length and position within the globe (Osborne, 2010). This may explain why the preferential loss of RGCs in glaucoma is also a key pathological feature found in the two most common inherited mitochondrial optic neuropathies, Leber hereditary optic neuropathy (LHON; MIM#535000) and autosomal dominant optic atrophy (DOA; MIM#165500) (Yu-Wai-Man et al., 2009). It is also interesting that murine RGCs have been found to be more sensitive to the downstream events of mitochondrial fragmentation and pro-apoptotic stimuli than other neuronal populations (Kamei et al., 2005), thus emphasising the potential importance of mitochondrial integrity in preventing or delaying glaucomatous optic neuropathies.

3. Overview of mitochondrial genetics

Mitochondria have a functional genome separate from that of nuclear DNA (Leonard and Schapira, 2000) which is indispensable to the function of the eukaryotic cell. In 1981, Anderson et al. published the sequence and organisation of the human mitochondrial genome, which was 16,569 bp long (Anderson et al., 1981). The mitochondrial DNA (mtDNA) is a closed circular molecule organised in hundreds of punctate structures, called nucleoids, which contain 2–8 mtDNA molecules each and are distributed throughout the mitochondrial compartment (Legros et al., 2004). The human mtDNA contains 37 genes, all of which are essential for normal mitochondrial function (Fig. 1). Thirteen of these genes encode enzymes, which form vital components of the oxidative phosphorylation (OXPHOS) pathway, essential for the production of the majority of cellular ATP (Andrews et al., 1999; Chomyn et al., 2007). Each oxphos unit consists of five complexes, which are derived from both nuclear and mtDNA, with the exception of complex II that is entirely derived from nuclear DNA. ROS are produced primarily from electron leakage of complexes I and III of the oxphos pathway (Cadenas and Davies, 2000) leading to oxidative stress and cell death via oxidation of macromolecules, such as proteins (Brand et al., 2004; Butterfield et al., 1997; Goto et al., 1999; Münch et al., 2010), lipids (Praticò, 2002; Sagai and Ichinose, 1980), mtDNA (Jarrett et al., 2008; Wei et al., 1998) and nuclear DNA (Halliwell and Dizdaroglu, 1992; Sohal et al., 1994). Importantly, the mtDNA is particularly vulnerable to oxidative stress (Richter et al., 1988; Sastre et al., 2000) due to its proximity to oxphos enzymes, limited DNA repair mechanisms and lack of protective histones (Croteau et al., 1999), while oxidative stress-induced apoptosis in neurons has been shown to correlate with the level of mtDNA repair pathway imbalance (Harrison et al., 2005).

4. Mitochondrial DNA and ageing

A major risk factor for the prevalence (Mitchell et al., 1996; Varma et al., 2004) and incidence (Mukesh et al., 2002) of POAG is increasing age and it is likely that mitochondrial dysfunction may serve as one of the links between ageing and glaucoma. In post-mitotic non-

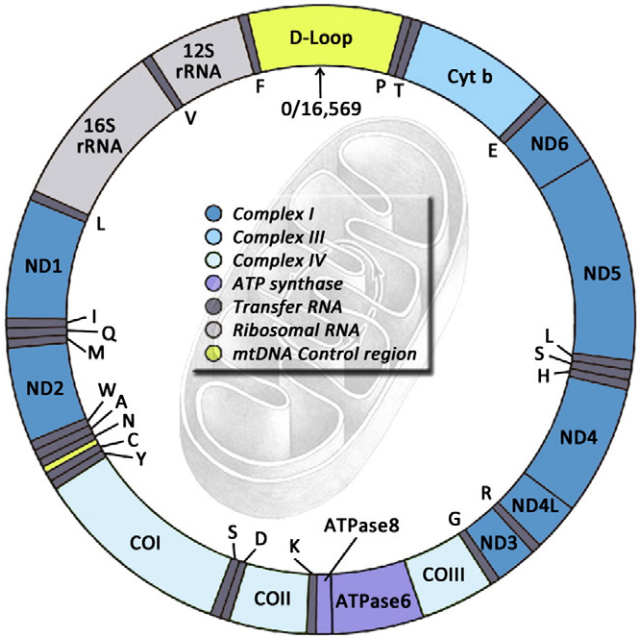

Fig. 1. Gene map of the human mitochondrial DNA. Loci are indicated by functional grouping. The non-coding D-Loop is shown at the top of the map and nucleotide position 1 is at twelve o'clock. Transfer RNA loci are designated by the single letter code of their specific amino acid.
Figure adapted from MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2010 (courtesy of M. Stamboli). ND: NADH Dehydrogenase, CO: Cytochrome c Oxidase.

replicating cells, including the neurons of the retina, the mtDNA in contrast to the nuclear DNA is continuously replicated as mitochondria are turned over, increasing the likelihood of ongoing replication errors and mtDNA mutations. Therefore, mtDNA changes are considered relevant to the mitochondrial theory of ageing (Druzhyna et al., 2008; Harman, 1972; Moosmann and Behl, 2008) particularly as somatic mutations can be propagated during replacement of mitochondria (Liang and Godley, 2003). Indeed, mtDNA mutations have been shown to accumulate with age (Wei, 1992), a phenomenon which may in part be a consequence of the age-related diminishment of autophagic activity (Terman, 1995), the process that sequesters and degrades organelles and macromolecular constituents of cytoplasm for cellular restructuring and repair. Moreover, mitophagy (the autophagic destruction of mitochondria) may be important for the elimination of dysfunctional mitochondria and mutated mtDNA (Weber and Reichert, 2010); certain mtDNA mutations decrease recognition signals for mitophagy and, therefore, accumulate with age (Lemasters, 2005). Also, emerging data suggest that the inherent error rate of mtDNA polymerase gamma may be responsible for many somatic mtDNA mutations (Larsson, 2010).

Age-associated mtDNA mutations include large-scale deletions and point mutations (Corral-Debrinski et al., 1992; Lin et al., 2002a,b), as well as oxidative modification with the formation of 8-hydroxy-2′-deoxyguanosine (Wei, 1998a). mtDNA mutations are maternally inherited, while large-scale deletions tend to develop in the maternal germ-line and are transmitted to the embryo (Wei et al., 1998). The mutant mtDNA often coexists with the wild-type mtDNA in affected tissues, a condition termed heteroplasmy (Lightowlers et al., 1997). The clinical severity of glaucoma may therefore be correlated with the proportion of the mutant mtDNA in the target tissue, the type of mutations, the pattern of distribution of the mutant mtDNA and the energy demand of the RGCs. These parameters could be important in determining the pathological outcome of the mtDNA mutations in POAG, especially in the context of the high energy requirements of RGCs, particularly in the pre-laminar region.

5. Mitochondrial DNA changes in POAG

A maternal family history of POAG is more likely than a paternal family history, suggesting a possible mitochondrial genetic influence (Charliat et al., 1994; Mitchell et al., 2002; Nemesure et al., 1996; Shin et al., 1977). This is unexpected, as there is no sex predilection to POAG prevalence and there is no maternal influence on IOP, and so Mendelian inheritance cannot explain these epidemiological differences. However, a study from the North East of England has failed to show an association between mitochondrial haplogroups and POAG in Caucasian patients (Andrews et al., 2006). Similarly, a recent study from the same group involving 137 POAG patients has not found an association between the mtDNA haplogroups H, T, J and U and either normal tension glaucoma (NTG) or high tension glaucoma (HTG), although there was a tendency for haplogroup J to be over-represented amongst the NTG group compared with controls (Yu-Wai-Man et al., 2010). This is an interesting observation considering the link between haplogroup J and increased risk of visual loss in Caucasian LHON mutation carriers (Hudson et al., 2007) and also the role of mtDNA background in modulating the assembly kinetics of oxphos complexes (Pello et al., 2008). Recently, the mtDNA haplogroups have been implicated in the pathogenesis of other types of glaucoma, with haplogroups T and L2 conferring susceptibility to pseudoexfoliation glaucoma in the Saudi Arabian population (Abu-Amero et al., 2011) and haplogroup U being associated with a reduced risk for pseudoexfoliation glaucoma in the German population (Wolf et al., 2010).

Other groups have screened glaucoma cohorts for mitochondrial mutations implicated in LHON. In one study involving 551 Japanese POAG patients and 284 controls, 5 LHON-associated mitochondrial DNA mutations were identified in the glaucoma group, whereas no such mutations were found in the control group. However, the difference was not statistically significant and the study was not conclusive as to whether these mtDNA mutations were a risk factor for POAG (Inagaki et al., 2006). Equally, in a Swiss population, no mtDNA mutations at nucleotides 11778, 3460 and 14484, typically associated with LHON, were identified amongst 54 unselected patients with NTG (Opial et al., 2001).

Somatic and age-associated mutations in mitochondria could also contribute to glaucoma pathogenesis. Indeed, in a study by Abu-Amero et al., 27 different novel non-synonymous mtDNA changes were found in patients with POAG with none found in control subjects, while 22 of the identified mutations were potentially pathogenic (Abu-Amero et al., 2006). Unlike patients with LHON, these POAG patients had a high frequency of mtDNA transversion mutations implying oxidative stress. A decrease was also noted in the mitochondrial mean respiratory activity in 24 of the 27 POAG patients, further supporting a role for oxidative stress and mitochondrial dysfunction contributing to the pathogenesis of POAG. Interestingly, the same group was unable to show significant mtDNA derangements in primary angle closure glaucoma (Abu-Amero et al., 2007), consistent with the idea that anatomic factors may be more important determinants for primary angle closure than mitochondrial genetics. Moreover, in primary congenital glaucoma patients from the Indian subcontinent, 8 (22.85%) of 35 patients had potentially pathogenic mtDNA sequence variants (Tanwar et al., 2010). It is important to note that these studies have been performed on mtDNA isolated from peripheral blood leucocytes, while tissue specific mutations in the trabecular meshwork, RGC compartment and optic nerve head may contribute more significantly to glaucoma pathogenesis. Indeed, mtDNA deletion has been shown recently to be increased more than 5-fold in the trabecular meshwork of POAG patients comparing to controls, accompanied by a significant decrease in the number of mitochondria per cell and by cell loss (Izzotti et al., 2010).

6. Nuclear DNA changes affecting mitochondrial function in POAG (Table 1)

6.1. OPA1

Alexander et al. (2000) and Delettre et al. (2000) independently identified the optic atrophy-1 gene (OPA1; MIM#605290; chr3q28-q29) that encodes a polypeptide with homology to dynamin-related GTPases. In patients with autosomal dominant optic atrophy, mutations in the OPA1 gene have been reported (Cohn et al., 1992; Furhmann et al., 2009; Pesch et al., 2001; Toomes et al., 2001) and defective oxidative phosphorylation has been demonstrated using phosphorus magnetic resonance spectroscopy (Lodi et al., 2004). OPA1 is involved in fusion of the mitochondrial inner membrane (Meeusen et al., 2004; Meeusen et al., 2006; Wong et al., 2000) and is required for the maintenance of cristae integrity (Olichon et al., 2003; Olichon et al., 2007; Zanna et al., 2008). OPA1 is also known to regulate apoptosis by controlling cristae remodeling and cytochrome c redistribution (Arnoult et al., 2005; Frezza et al., 2006). In the retina, OPA1 is expressed in the outer plexiform layer, the inner nuclear layer (Ju et al., 2005) and the inner plexiform layer (Aijaz et al., 2004), while in the ganglion cell layer (Pesch et al., 2004) OPA1 is predominantly expressed in RGCs, supporting its potential role in neuronal loss in glaucoma.

Aung et al. (2002) suggested that polymorphisms in the OPA1 gene are associated with NTG in Caucasians and may be a marker for the disease. In a cohort of 83 NTG patients and a second cohort of 80 NTG patients an intronic single nucleotide polymorphism (SNP), IVS8+4C/T, was strongly associated with the occurrence of NTG. A second SNP, IVS8+32T/C, appeared to be associated with the disease in the first cohort, but this finding could not be replicated in a second cohort. In the combined cohort, the compound at-risk genotype IVS8+4C/T, +32T/C was shown to be strongly associated with the occurrence of NTG. In

Table 1
Nuclear genes potentially implicated in mitochondrial dysfunction in POAG.

Gene symbol	Gene name	MIM ID	Chromosomal location	References
OPA1	Optic atrophy 1	605290	3q28–q29	Aung et al. (2002)
MFN1	Mitofusin1	608506	3q25–q26	Wolf et al. (2009)
MFN2	Mitofusin 2	608507	1p36.2	Wolf et al. (2009)
CYP1B1	Cytochrome P450, subfamily I, polypeptide 1	601771	2p22–p21	Vincent et al. (2002)
PARL	Presenilin associated rhomboid-like	607858	3q27	Wolf et al. (2009)
SOD2	Superoxide dismutase 2	147460	6q25.3	Ferreira et al. (2004)
SRBD1	S1 RNA binding domain 1	n/a	2p21	Meguro et al. (2010)
GSTT1	Glutathione S transferase theta 1	600436	22q11.2	Unal et al. (2007)
GSTM1	Glutathione S transferase Mu 1	138350	1p31	Juronen et al. (2000)
NOS3	Nitric oxide synthase 3	163729	7q35–36	Tunny et al. (1998)
TNFa	Tumour necrosis factor alpha	191160	6p21.3	Lin et al. (2003)
TP53	Tumour protein p53	191170	17p13.1	Lin et al. (2002a,b)

a second publication by the same group, unlike NTG, the OPA1 genotype IVS8+4C/T, +32T/C was not significantly associated with HTG, suggesting genetic heterogeneity between these conditions (Aung et al., 2002). Interestingly, another study by Powell et al. only supported an association of the IVS8+32T/C genotype with Caucasian NTG (Powell et al., 2003), for which no independent association was seen by the Aung group. Moreover, a recent study on 137 POAG patients from the North East of England, including 67 HTG and 70 NTG patients, confirmed a strong association between the CT/TT compound genotype at IVS8+4 and IVS8+32 with NTG, but not HTG (Yu-Wai-Man et al., 2010). In Japan, Mabuchi et al. found a significant association of NTG (n = 194) with the IVS8+32T/C SNP, but not with the IVS8+4C/T SNP. Importantly, although there was no significant difference in the OPA1 IVS 8+32T/C genotype frequency between the HTG patients (n = 191) and control subjects (n = 185), the age at the time of diagnosis in the HTG patients with the OPA1 IVS 8 + 32C allele was significantly younger than that in the HTG patients without C allele (Mabuchi et al., 2007).

The study by Mabuchi et al. was the first to suggest that an OPA1 gene polymorphism can influence the HTG phenotype, although the association between OPA1 and HTG was only marginal and could not be replicated in other populations; Caucasian (279 cases, 227 controls), African-American (193 cases, 97 controls), and Ghanaian (170 cases, 138 controls) populations (Liu et al., 2007), as well as the African-Caribbean population of Barbados (48 cases, 48 controls) (Yao et al., 2006). Nevertheless, it may be important to note that OPA1 polymorphisms are thought to act as non-IOP related genetic factors of glaucomatous optic neuropathy and may, therefore, be more likely to be relevant in patients with lower IOP rather than HTG patients (Mabuchi et al., 2007). Other studies have also failed to show a relationship between OPA1 and NTG in Japan (Kumaramanickavel et al., 2005; Sato et al., 2003), Singapore (Kumaramanickavel et al., 2005), India (Kumaramanickavel et al., 2005), Germany (Wolf et al., 2009), China (Fan et al., 2010), Korea (Woo et al., 2004) and Barbados (Yao et al., 2006). A possible explanation offered for the lack of association in many of these studies was the relatively small cohort size. It is also notable that the IVS8+4C/T polymorphism is far more common in Caucasians, accounting for about 30% of genotypes in Caucasians with NTG and 12.4% to 33.9% in Caucasian controls (Aung et al., 2002; Powell et al., 2003), than in the African-Caribbean population, where it contributed less than 5.0% of genotypes in either affected individuals or unaffected controls in the Barbados study (Yao et al., 2006). Furthermore, no association has been found between OPA1 polymorphisms and NTG clinical phenotype, including IOP, cup-to-disc ratio, visual field global indices and progression, and HRT (Heidelberg retinal tomography) parameters (Aung et al., 2003). This lack of association between OPA1 and NTG severity is also supported by the study by Yu-Wai-Man et al., where the CT/TT compound genotype at IVS8+4 and IVS8+32 was not associated with either higher pre-treatment IOPs or worse optic disc cupping (Yu-Wai-Man et al., 2010).

6.2. MFN-1 and MFN-2

NTG has recently been associated in a German population with a number of mutations in genes encoding mitochondrial proteins, including mitofusin 1 (MFN1; (MIM#608506)) and mitofusin 2 (MFN2; MIM#608507) (Wolf et al., 2009). In this study 98 SNPs were investigated in 285 NTG patients and 282 controls. A nominally significant association of NTG was identified with one SNP in the MFN1 gene (rs2111534) and three almost consecutive SNPs in the MFN2 gene (rs873458, rs2295281 and rs11588779), while the association with MFN2 was further confirmed by multimarker haplotype-based association testing (Wolf et al., 2009). Mitofusins (MFNs) are known to mediate the fusion of mitochondria (Bossy-Wetzel et al., 2003; Chen et al., 2005; Westermann, 2003) and thereby contribute to the dynamic balance between fusion and fission that determines mitochondrial structure (Eura et al., 2006; Koshiba et al., 2004; Santel et al., 2003). MFN1 was first cloned in Santel and Fuller (2001) and the deduced 741-amino acid protein is thought to show functional overlap with OPA1 (Song et al., 2009). Chen et al. (2003) mapped the mouse MFN1 gene to the proximal end of mouse chromosome 3, a region syntenic to human 3q25-26. Cipolat et al. (2004) demonstrated interdependence between OPA1 and MFN1 in promoting mitochondrial elongation. Human MFN2 shares 60% identity with human MFN1 and is located on chromosome 1 at 1p36.2 (Nagase et al., 1996; Santel et al., 2003). MFN2 enhances mitochondrial metabolism by influencing oxphos expression (Bach et al., 2003) through signals independent of its role in mitochondrial fusion (Pich et al., 2005) and is enriched at the endoplasmic reticulum–mitochondria interface, thus regulating efficient mitochondrial calcium uptake (De Brito and Scorrano, 2008). Interestingly, apart from NTG, MFN2 has also been linked to other neurodegenerative and neurological diseases, including the Charcot–Marie–Tooth disease type 2A (Casasnovas et al., 2010; Guillet et al., 2010; Kijima et al., 2005; Züchner et al., 2004), axonal neuropathy with optic atrophy (Züchner et al., 2006) and early-onset stroke (Chung et al., 2008).

6.3. PARL

In addition to MFN1 and MFN2, common variants of another nuclear encoded mitochondrial gene — PARL (presenilin associated rhomboid-like; MIM#607858) have also been shown to be associated with NTG in a German population (Wolf et al., 2009). Two neighbouring SNPs in PARL (rs1000002 and rs1402003) were found to be associated with NTG and this relationship was confirmed by multimarker haplotype-based association testing. Interestingly, although all the above genes (MFN1, MFN2, PARL) are known to be functionally involved in common mitochondrial pathways, the study by Wolf et al. did not detect any significant interaction based on a SNP × SNP epistasis test between any of these genes. PARL encodes a processing protease for OPA1 (Pellegrini and Scorrano, 2007) and has been suggested to influence apoptotic processes (McQuibban et al., 2003) by

regulation of cytochrome c release via OPA1-dependent cristae remodeling (Cipolat et al., 2006). The role of PARL in mitochondrial function is further emphasised by a recent genome-wide linkage scan and association study in Thailand showing a strong association with Leber hereditary optic neuropathy (LHON) (Phasukkijwatana et al., 2010). This association was not confirmed in Chinese LHON patients (Zhang et al., 2010), but nevertheless PARL remains one of the first nuclear genes, together with OPA1 (Abu-Amero et al., 2010) to be implicated in the pathogenesis of this classic and extensively studied mitochondrial disorder.

6.4. CYP1B1

CYP1B1 (MIM#601771), located on chromosome 2p21 at the GLC3A locus, encodes a 543-amino-acid dioxin inducible member of the cytochrome P450 gene superfamily of monooxygenases, subfamily I, polypeptide 1 (Sutter et al., 1994; Tang et al., 1996). The enzyme encoded by the CYP1B1 gene localises to the endoplasmic reticulum and is widely known for its role in the metabolism of a variety of substrates, including steroids and retinoids (Chambers et al., 2007), in xenometabolic detoxification (Nebert and Dalton, 2006), vascular development and homeostasis (Fleming, 2001; Zhao et al., 1998), and eye development during embryogenesis (Choudhary et al., 2007). Lack of CYP1B1 has been shown to lead to increased intracellular oxidative stress (Tang et al., 2009), while in HL-60 cells suppression of CYP1B1 can lead to the activation of mitochondrial death signaling pathways, as evidenced by Bax translocation and cytochrome c release (So et al., 2008). Mutations in the CYP1B1 gene have been linked to the autosomal recessive form of primary congenital glaucoma (Bejjani et al., 1998; Bejjani et al., 2000; Martin et al., 2000; Mashima et al., 2001; Plasilova et al., 1999; Stoilov et al., 1997; Stoilov et al., 1998), juvenile open angle glaucoma (Acharya et al., 2006; Bayat et al., 2008; Vincent et al., 2002) and anterior segment dysgenesis, including Peter's anomaly (Vasiliou and Gonzalez, 2008; Vincent et al., 2006). Interestingly, in the study by Vincent et al. CYP1B1 mutations were shown to expedite disease onset in a Canadian family with autosomal dominant open-angle glaucoma when present alongside a myocilin (MYOC) mutation, suggesting a role for CYP1B1 as a modifier gene of MYOC (Vincent et al., 2002), a well recognised POAG gene (Alward et al., 1998; Baird et al., 2003; Fingert et al., 1999; Sheffield et al., 1993; Suzuki et al., 1997; Tamm, 2002; Wiggs et al., 1998).

A common sequence variant (Leu432Val) in the CYP1B1 gene has been proposed to act as a risk factor for the development of POAG in a study involving 264 unrelated Indian POAG patients and 95 controls (Bhattacharjee et al., 2008). Importantly, CYP1B1 Val432 was estimated to generate higher reactive oxygen species in transfected RPE cells compared to its allelic variant (Leu432) suggesting that this high risk allelic variant may predispose to POAG via the induction of apoptotic pathways. CYP1B1 mutations have also been detected in almost 5% of 236 unrelated French Caucasian early-onset POAG patients (Melki et al., 2004), while another study from the same group suggested that a common coding CYP1B1 polymorphism (Asn453Ser) may influence clinical features like optic disc cupping and visual field deterioration in POAG patients (Melki et al., 2005). Interestingly, in the study by Wolf et al. (2009) on German NTG patients, it has not been possible to confirm the significant association between POAG and either the Leu432Val CYP1B1 variant (rs1056836) (Bhattacharjee et al., 2008) or the Asn453-Ser CYP1B1 variant (rs1800440) (Melki et al., 2005). This may be attributed to the phenotypic differences, such as IOP level, between NTG and POAG, as well as the large variability of the CYP1B1 allele frequency amongst different populations and the modest proportion of controls amongst the total number of samples in the previous studies (Wolf et al., 2009). Similarly, a recent study in a Chinese population did not show an association between POAG and CYP1B1, with the authors suggesting that the allele G of rs1800440 was very rare in their Chinese sample (Fan et al., 2010). Furthermore, four different CYP1B1 mutations (Glu229Lys, Arg368His, Pro193Leu and Met292Lys) have been reported in almost 11% of 251 Indian adult-onset POAG patients, of which the last two mutations were not found in control subjects (Kumar et al., 2007). Most importantly, a recent study using in vitro functional analysis has identified seven heterozygous CYP1B1 mutations with absent or reduced relative enzymatic activity in 3.6% of 399 unrelated German POAG patients and in only 0.2% of 376 control subjects (Pasutto et al., 2010). Similarly, in another recent functional study involving 245 unrelated Spanish POAG patients and 326 control subjects, heterozygous hypomorphic CYP1B1 mutations were found in 17 (6.7%) patients and in only seven controls (2.1%), suggesting that these mutations are associated with an increased risk of POAG (López-Garrido et al., 2010).

6.5. SOD2

The SOD2 gene (superoxide dismutase-2; MIM#147460), mapped to the gene locus 6q25.3 (Church et al., 1992; Creagan et al., 1973), encodes the manganese-dependent superoxide dismutase that acts as a primary scavenger of reactive oxygen species in the mitochondrion (Bastaki et al., 2006; Macmillan-Crow and Cruthirds, 2001; Melov et al., 1999). Increased expression of the SOD2 gene was observed in the aqueous humour of POAG patients (Ferreira et al., 2004; Ghanem et al., 2010) and in the ciliary processes and iris tissue of subjects with pseudoexfoliation glaucoma (Zenkel et al., 2007). Interestingly, in the study by Wolf et al. (2009) no association was found between NTG and SOD2 sequence variants.

6.6. SRBD1

The S1 RNA-binding domain is found in a large number of RNA-binding proteins, such as polynucleotide phosphorylase (PNPase) (Bycroft et al., 1997), whose overexpression is thought to inhibit cell growth (Leszczyniecka et al., 2002; Schnier et al., 1986), stimulate proinflammatory cytokine production (Sarkar et al., 2004) and induce apoptosis (Sarkar et al., 2003), thus potentially leading to ganglion cell loss in NTG. In the context of this review, it is interesting to note that human PNPase also plays a crucial role in maintaining mitochondrial homeostasis (Chen et al., 2006). A recent genome-wide association study of patients with NTG and healthy controls in a Japanese population has observed a strong association for a SNP (rs3213787) in the S1 RNA binding domain 1 (SRBD1) gene on chromosome 2p21 (Meguro et al., 2010). An additional seven SNPs (rs6719211, rs4455206, rs3755076, rs10205197, rs17033745, rs17033801, and rs11884064) in SRBD1 showed less strong, but still significant, disease association. Importantly, the most strongly NTG-associated risk allele (rs3213787 A) correlated with enhanced expression of SRBD1 in white blood cells (Meguro et al., 2010).

7. Glutathione S-transferase (GST)

GST enzymes comprise a large supergene family and catalyse the conjugation of glutathione (GSH) to a wide range of potential toxins as the first step in detoxification (Baars and Breimer, 1980; Hayes et al., 2005). These multifunctional enzymes are divided, in humans, into several classes (Mannervik, 1985; Strange et al., 2001), including alpha (A), mu (M), pi (P), theta (T), kappa (K), omega (O) and zeta (Z), and are thought to protect mitochondria from oxidative stress (Gallagher et al., 2006; Goto et al., 2009; Raza et al., 2002). Oxidative stress has been shown to induce ATP, NADPH and GSH depletion, while GST ablation augments cytotoxicity by reactive oxygen species (Vaillancourt et al., 2008). Decreased GST function might interfere with the metabolism of oxidative intermediates and exacerbate the damaging effects of oxidative stress on the optic nerve, thus contributing to glaucomatous neurodegeneration. Polymorphisms for GSTM1, mapped to 1p31 (DeJong et al., 1988; Zhong et al., 1992), and GSTT1, mapped to 22q11.2 (Webb et al., 1996), have been described in 107 Arab glaucoma patients,

including POAG, pseudoexfoliation glaucoma and primary angle closure glaucoma (Abu-Amero et al., 2008). GSTM1 positive and GSTT1 null genotypes have also been associated with increased risk of developing POAG in a Turkish population (Unal et al., 2007), while only the GSTM1 positive genotype was identified as a risk factor for POAG in an Estonian population (Juronen et al., 2000). Interestingly, there have even been studies showing a reversed association, in which the null GSTM1 genotype was more common in POAG patients in a Turkish (Yildirim et al., 2005) and Italian population (Izzotti et al., 2003). In the latter study, GSTM1 gene deletion was suggested to predispose to more severe oxidative DNA damage in POAG patients, as shown by significantly higher levels of 8-hydroxy-2′-deoxyguanosine (8-OH-dG) in the trabecular meshwork of GSTM1-null comparing to GSTM1-positive subjects (Izzotti et al., 2003). Importantly, a recent study from the same group found that POAG patients bearing the GSTM1-null genotype showed increased amounts of mtDNA deletion and a decreased number of mitochondria per cell, as compared with GSTM1-positive subjects (Izzotti et al., 2010). Nevertheless, a Swedish study reported no association between this genotype and POAG (Jansson et al., 2003), which may represent a population specific effect caused by differences in the genetic background between various populations. Similarly, a recent study in a Chinese population showed no association of either GSTM1 or GSTT1 with POAG (Fan et al., 2010).

7.1. NOS3

The human NOS3 gene (or eNOS, endothelial NOS; MIM#163729) localised to 7q35-q36 (Marsden et al., 1993; Robinson et al., 1994) regulates the release of the gaseous second messenger nitric oxide (NO) following direct phosphorylation and activation of the eNOS by the protein kinase Akt (Dimmeler et al., 1999; Fulton et al., 1999). Importantly, NO is known to trigger mitochondrial biogenesis in cells as diverse as brown adipocytes and 3T3-L1, U937 and HeLa cells (Nisoli et al., 2007). This effect of NO was dependent on cGMP and was mediated by the induction of PPARGC1 (peroxisome proliferator-activated receptor gamma, co-activator 1; MIM#604517) (Esterbauer et al., 1999), a master regulator of mitochondrial biogenesis (Stefan et al., 2007; Wu et al., 1999). Moreover, NOS3 deficiency has been shown recently to impair the ability of the mitochondria to produce ATP in mice, due in part to reduction in the mitochondrial respiratory chain complex I activity (Bougaki et al., 2010). Interestingly, NO has been found to inhibit complexes I and IV (Cleeter et al., 2001), while excess plasma NO-mediated neurotoxicity (Liu and Neufeld, 2003) and elevated levels of NOS activity have been implicated in glaucomatous optic neuropathy in humans (Neufeld et al., 1997) and in animal glaucoma models (Franco-Bourland et al., 1998). A variant in the promoter region of the eNOS gene (rs3918226) was first reported in 1998 to be associated with POAG in an Australian population (Tunny et al., 1998). Nevertheless, another promoter SNP (rs2070744) of NOS3 was not associated with POAG in two other studies (Lin et al., 2005; Logan et al., 2005), while in a third study in a Chinese population no association was found between two NOS3 SNPs (rs2070744 and rs1799983) and POAG (Fan et al., 2010). Furthermore, the A allele in an intron 4 polymorphism of eNOS has been shown to be significantly associated with POAG in the Pakistani population (Ayub et al., 2010), but not in the Chinese population (Lin et al., 2005). Importantly, functional analyses have shown that the A allele in homozygous form is strongly correlated with plasma NO levels twice as high as in the B allele homozygous form, indicating the eNOS underlying potential for excess NO-related pathogenicity (Malek et al., 1999). Furthermore, another study in Caucasian populations demonstrated that three SNPs of NOS3 (rs3918188, rs2070744 and rs1800779) were significantly associated with HTG amongst women, but not amongst men (Kang et al., 2010). This gender-dependent association was not identified for two other NOS3 SNPs (rs1799983 and rs7830) in the same study (Kang et al., 2010), as well as for the NOS3 SNPs rs2070744 and rs1799983 in a Chinese population (Fan et al., 2010).

7.2. TNFa

Tumour necrosis factor alpha (TNFa or TNF; MIM#191160) is a multifunctional pro-inflammatory cytokine, whose gene in humans has been mapped to 6p21.3 (Carroll et al., 1987; Nedwin et al., 1985). TNFa impairs mitochondrial biogenesis and function in different animal models (Mariappan et al., 2009) by down-regulating eNOS expression (Valerio et al., 2006) and interferes with mitochondrial morphology and dynamics (Chen et al., 2010) to induce apoptosis (Djavaheri-Mergny et al., 2003; Paintlia et al., 2011). Intriguingly, an up-regulation of TNFa has been implicated in RGC apoptosis in animal glaucoma models (Nakazawa et al., 2006; Tezel et al., 2001) and the human glaucomatous optic nerve head (Tezel, 2008; Yuan and Neufeld, 2000). In 2003, TNF was reported to be associated with POAG in a Chinese population with the A allele frequency of the promoter SNP rs1800629 (−308 G>A) being higher in POAG patients than in controls (Lin et al., 2003). This association with the A allele was replicated in an Iranian population (Razeghinejad et al., 2009) and, interestingly, this A allele has been shown to increase TNF production in a study of lipopolysaccharide-stimulated whole blood cell cultures in healthy humans (Louis et al., 1998). However, in a recent study in another Chinese population the G allele frequency was higher in HTG patients than in controls, while the A allele appeared to have a protective effect (Fan et al., 2010). This difference was attributed by the authors of the latter study to the much lower allele A frequency than that reported in the initial Chinese study. Moreover, an Austrian study did not reveal any significant association between two promoter SNPs of TNF (−308 G>A and −238 G>A) and POAG (Mossbock et al., 2006). Similarly, a Japanese study showed no significant association between three promoter SNPs of TNF (−308 G>A, −857 C>T and −863 C>A) and POAG, while statistical analyses in the same cohort suggested a possible interaction between polymorphisms in the optineurin (OPTN) and TNF genes that would enhance the risk for the development and progression of POAG (Funayama et al., 2004).

7.3. TP53

The TP53 gene (Tumour Protein p53; MIM#191170) mapped to the human chromosome 17p13.1 (Isobe et al., 1986; McBride et al., 1986) encodes the transcription factor p53 known to regulate target genes involved in cell cycle arrest (Toledo and Wahl, 2006), changes in cellular metabolism (Vousden and Lane, 2007), senescence (Levine, 1997) and DNA repair (Artandi and Attardi, 2005). p53 has also been shown to cause apoptosis through transcriptional stimulation of redox-related genes, formation of ROS (Hussain et al., 2004) and oxidative degradation of mitochondrial components (Polyak et al., 1997). Originally, in 2002, TP53 was shown to be associated with POAG in a Chinese population, with the C allele frequency of the nonsynonymous SNP rs1042522 being higher in POAG patients than in controls (Lin et al., 2002a,b). Two studies in Caucasian populations also revealed a significant association between POAG and both rs1042522 and rs17878362 (Daugherty et al., 2009; Ressiniotis et al., 2004). In contrast to the original study in Chinese, in which the C allele of rs1042522 was more frequent in POAG patients than in controls, the study by Daugherty et al. (2009) and a recent Chinese study from a different group (Fan et al., 2010) found that the G allele frequency was higher. This difference was again attributed by the authors of the latter study to the much lower G allele frequency than that in the original Chinese study (Fan et al., 2010). Most importantly, SNP rs1042522 has been shown to occur in the proline-rich domain of p53, which is necessary for the protein to fully induce apoptosis (Jeong et al., 2010) by localising to the mitochondria and causing the release of cytochrome c into the cytosol (Dumont et al., 2003). The G allele

of rs1042522 is known to have increased apoptotic ability compared to the C allele (Dumont et al., 2003) and thus may confer increased susceptibility to POAG by leading to RGC apoptosis. This different apoptotic potential has also been found to increase with age (Bonafé et al., 2004), which may be relevant to age-related neurodegenerative diseases like POAG. It is interesting to note that the study by Daugherty et al. (2009) reported an even higher frequency of the allele G in NTG compared to POAG patients, suggesting that apoptosis may have a greater role in NTG compared to HTG. Nevertheless, no significant association was noted between rs1042522 and POAG in various studies in Turkish (Saglar et al., 2009), Japanese (Mabuchi et al., 2009), Brazilian (Silva et al., 2009), Indian (Acharya et al., 2002) and Australian (Dimasi et al., 2005) populations, with the latter two studies also showing lack of association with rs17878362 (Acharya et al., 2002; Dimasi et al., 2005).

8. Discussion

The currently identified POAG genes account for only a small percentage of the disease (Fan et al., 2006). This review presents the increasing body of evidence from genetic studies that the bioenergetic consequences of mtDNA and nuclear DNA derangements (summarised schematically in Fig. 2), with the associated mitochondrial dysfunction, may contribute to the development of POAG. This may be particularly relevant in the context of the 'common disease–common variant' hypothesis, where multiple variants may each contribute a small additive or multiplicative effect to the glaucomatous phenotype. Despite the lack of evidence from many studies as to whether the identified mitochondrial and nuclear DNA changes in POAG are inherited or acquired, it is likely that such changes could create a background genetic susceptibility for the development of glaucoma in the affected individuals. In the case of acquired mutations, these tend to accumulate with age, possibly influencing mitochondrial function (Kujoth et al., 2005; Navarro and Boveris, 2007) and providing a link between ageing and glaucoma.

This review focuses on a variety of genes (OPA1, MFN1, MFN2, CYP1B1, PARL, SOD2, SRBD1, GST, NOS3, TNFa and TP53) many of which had not previously been linked with mitochondrial dysfunction, especially in the context of glaucoma. It is now widely recognised that POAG is likely caused by interactions of multiple genes and environmental factors (Wiggs, 2007). It is interesting to note that, to date, most association studies for POAG have investigated only single genes or single gene variants without accounting for the role of gene–gene and gene–environment interactions. This, together with ethnic differences, could explain to some extent the conflicting results from some of the genetic studies presented. Small sample sizes may also have contributed to poor representation of the study populations and reduced the study power to detect genuine associations in replication studies. Moreover, many of the currently available replication studies have not used exactly the same inclusion criteria with the original study in the same population, while in a few studies included in this review the reported polymorphisms have not been shown to result necessarily in altered gene expression. Nevertheless, this review provides an insight into the emerging role of mitochondrial genetics in the pathogenesis of POAG and further supports the role of mitochondrial dysfunction in the disease process.

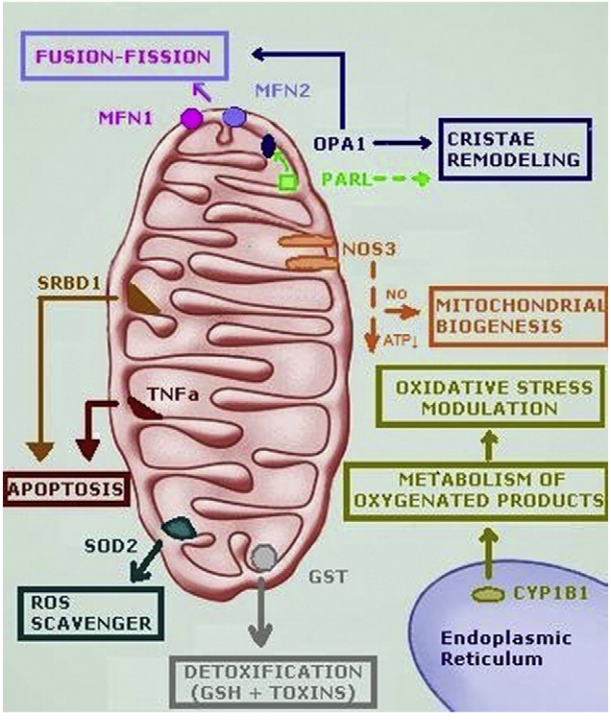

Fig. 2. Schematic diagram summarising the interplay between the different nuclear DNA gene products and mitochondrial dysfunction.

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