Mutation Research 778 (2015) 26–40

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

# The role of base excision repair in the development of primary open angle glaucoma in the Polish population

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ARTICLE INFO

*Article history:*
Received 23 December 2014
Received in revised form 1 April 2015
Accepted 9 May 2015
Available online 19 May 2015

*Keywords:*
Primary open angle glaucoma
Gene polymorphism
BER
HRT
Oxidative DNA damage

ABSTRACT

Glaucoma is a leading cause of irreversible blindness in developing countries. Previous data have shown that progressive loss of human TM cells may be connected with chronic exposure to oxidative stress. This hypothesis may suggest a role of the base excision repair (BER) pathway of oxidative DNA damage in primary open angle glaucoma (POAG) patients. The aim of our study was to evaluate an association of BER gene polymorphism with a risk of POAG. Moreover, an association of clinical parameters was examined including cup disk ratio (c/d), rim area (RA) and retinal nerve fiber layer (RNFL) with glaucoma progression according to BER gene polymorphisms.

Our research included 412 patients with POAG and 454 healthy controls. Gene polymorphisms were analyzed by PCR-RFLP. Heidelberg Retinal Tomography (HRT) clinical parameters were also analyzed.

The 399Arg/Gln genotype of the *XRCC1* gene (OR 1.38; 95% CI 1.02–1.89 $p = 0.03$) was associated with an increased risk of POAG occurrence. It was indicated that the 399Gln/Gln *XRCC1* genotype might increase the risk of POAG progression according to the c/d ratio (OR 1.67; 95% CI 1.07–2.61 $P = 0.02$) clinical parameter. Moreover, the association of VF factor with 148Asp/Glu of *APE1* genotype distribution and POAG progression (OR 2.25; 95% CI 1.30–3.89) was also found. Additionally, the analysis of the 324Gln/His *MUTYH* polymorphism gene distribution in the patient group according to RNFL factor showed that it might decrease the progression of POAG (OR 0.47; 95% CI 0.30–0.82 $P = 0.005$).

We suggest that the 399Arg/Gln polymorphism of the *XRCC1* gene may serve as a predictive risk factor of POAG.

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## 1. Introduction

Glaucoma rates are second after cataracts among the proximate causes of blindness. The most recent epidemiological studies have shown that up to 60 million people may suffer from glaucomatous neuropathy [1,2]. Moreover, approximately 9 million people have gone blind as a result of the progressive degeneration of retinal ganglion cells (RGC) [1,2]. Additionally, Quigley et al. noted that the most frequent type of glaucoma is primary open angle glaucoma (POAG), which constitutes 75% of all diagnosed cases [3]. The genetic background of glaucoma development has yet to be completely understood. The main risk factors for POAG development and progression are intraocular pressure increases (IOP), aging (increased risk over 40), gender (men are more likely to develop

*Abbreviations:* POAG, primary open angle glaucoma; hTM, human trabecular meshwork; RGC, retinal ganglion cell; BER, base excision repair; ROS, reactive oxygen species; IOP, increase intraocular pressure; CNS, central nervous system; AP site, the apurinic/apyrimidinic (AP) site; OGG1, 8-Oxoguanine DNA glycosylase; MUTYH (MYH), A/G-specific adenine DNA glycosylase; APE1, mammalian apurinic/apyrimidinic endonuclease Ape1; XRCC1, X-ray repair cross complementing group 1; *APDRT*, gene (poly (ADP-ribose) polymerase 1; c/d, cup disk ratio; VF, visual field; RNFL, retinal nerve fiber layer; RA, rim area; NFL, nerve fiver layer; SNP, Single Nucleotide Polymorphism.

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http://dx.doi.org/10.1016/j.mrfmmm.2015.05.003
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glaucoma [4]), race [5], family history and diabetes mellitus type 2 [6]. Moreover, ocular parameters including myopic refractive error, optic disk shape, and corneal thickness are considered to be additional risk factors for glaucoma development [7,8]. Furthermore, oxidative stress is also perceived as an important risk factor in glaucoma pathogenesis. The occurrence of oxidative stress may play an important role in RGC death [9]. Reactive oxygen species (ROS) are generated during normal cellular metabolism, during exposure to ionizing radiation and resulting from other environmental factors [10]. Gilgun-Sherki et al. found that glial cells and neurons, which are post-mitotic cells, are very sensitive to free radical impacts [11]. Additionally, in the brain, a low level of antioxidant enzymes is observed; thus, neuronal cells are especially susceptible to giving rise to oxidative DNA lesions [12]. Izzotti et al. noted that the level of oxidative DNA damage in the human trabecular meshwork (hTM) as well as retinal cells is significantly higher among POAG patients compared to the control group. Additionally, they postulated that a progressive loss of hTM cells may be associated with long-term ROS exposure [13,14]. Moreover, an increased level of IOP and loss of the visual field correlates with elevated levels of oxidative DNA damage in hTM. Sacca et al. indicated an increased level of oxidative DNA damage in circulating lymphocytes of POAG patients [15].

The human genome possesses several mechanisms that prevent cells from accumulating DNA damage and from passing the DNA lesions to offspring cells. Recent data demonstrate that DNA repair mechanisms may play a significant role in protecting brain cell viability and nervous system function [12,16]. A strong relationship between altered DNA repair pathways and neurodegenerative disease development was observed [17]. Base excision repair (BER) is the first DNA repair mechanism that protects cells from small base modifications including alkylation, deamination and oxidation. In addition, it is expected that BER is active during all stages of the cell cycle; therefore, it may be essential for both dividing and non-dividing cells [16]. There are some results suggesting that BER may play an essential role in the development and maintenance of the central nervous system (CNS) [18].

BER follows a pathway that consists of recognition and excision of the modified base, incision of the DNA backbone, formation of AP sites (apurinic/apyrimidinic sites), creation of 3′OH groups and 5′P ends and repair synthesis and ligation [12]. In the first step, the specialized DNA glycosylase recognizes and removes the modified base. 8-Oxoguanine DNA glycosylase (OGG1) is a major human glycosylase, which causes cleavage of the glycosylic bond between the oxidase base and the sugar. This results in formation of the apurinic/apyrimidinic (AP) site [19]. It is extensively emphasized that polymorphism in the *OGG1* gene may alter glycosylase function, which in turn decreases the ability to repair DNA lesions [20]. Khono et al. indicated that individuals carrying the hOGG1-Cys326 protein have a significantly reduced ability to repair 8-OHdG compared to ones carrying the hOGG1-Ser326 protein [21]. Another important DNA glycosylase is MUTYH (MYH) (A/G-specific adenine DNA glycosylase) with the crucial role of preventing oxidative DNA damage [22]. It prevents adenine from forming mismatched bonds with 8-oxoG. Changes in the *MUTYH* gene may compromise its function, leading to a decrease in the DNA repair capacity [23]. AP sites that are formed in this manner may be repaired by endonuclease APE1 (mammalian apurinic/apyrimidinic endonuclease Ape1). APE1 incises the phosphodiester backbone of the DNA – 5′ to the lesion, leaving behind the strand break with the normal 3′-hydroxyl group and a non-conventional 5′-abasic terminus [24]. It was shown that individuals carrying the 148Glu allele may have changes in DNA binding efficiency resulting from the lower ability of APE1 to interact with other BER proteins [25]. Thus, the presence of the Glu allele may lead to increased vulnerability to ionizing radiation [26]. The X-ray repair cross complementing group 1 (XRCC1) gene encoding XRCC1 – scaffold protein has no known enzymatic activity. It interacts with DNA ligase III, DNA polymerase β, APE1 and ADPRT [27]. Cappelli et al. suggested that absence of *XRCC1* may lead to a decreased level of DNA ligase III [28]. Moreover, multiple studies have shown that the presence of 399Arg/Gln and 399Gln/Gln genotypes of the *XRCC1* gene is associated with lower DNA repair capacity and increased genomic instability [29,30]. The main function of ADPRT is binding to the DNA strand breaks and recruiting the XRCC1-Lig3α complex. Deficiency in its function may be linked to the 762Val/Ala polymorphism. Moreover, the presence of the Ala allele leads to decreased poly ADP-ribosylation activity [26]. Additionally, altered activity of ADPRT is symptomatic of ailments including inflammation diseases, diabetes and neurodegeneration [31].

It is worthwhile to note that the presence of Single Nucleotide Polymorphisms (SNPs) in DNA repair genes may change the function of the proteins. It may cause genetic instability and increase the risk of developing certain diseases [32]. To the best of our knowledge, the genetic background of the BER mechanism has not yet been widely studied in relation to POAG development. Therefore, the aim of this study is to confirm the hypothesis that oxidative DNA damage and lower efficiency of its repair play an essential role in the pathogenesis of POAG.

## 2. Materials and methods

### 2.1. Characteristics of patients

A total of 412 patients with confirmed POAG (275 females and 148 males, mean age 73 ± 9 years) who were hospitalized in the Department of Ophthalmology, Medical University of Warsaw, and 454 (260 females and 194 males) age-matched controls (mean age 71 ± 12 years), who were selected from subjects without glaucoma symptoms, were enrolled in the present study. All patients and control subjects were Caucasian. The characteristics of the patients are presented in Table 1. The correct volume of IOP is indicated from the applied therapy. At the time of the study, POAG patients were treated topically with one or a combination of typical anti-glaucoma medications including beta blockers (e.g., Timolol), prostaglandin analogs (e.g., Latanoprost), carbonic anhydrase inhibitors (e.g., Dorzolamide) and alpha2 agonists (e.g., Brimonidine). The aim of the therapy is to reduce the IOP to a level that will not lead to further damage of the optic nerve. All patients with POAG were tested by Heidelberg Retinal Tomography (HRT). In this study, we focused on the following clinical parameters: disk ratio (c/d), rim area (RA), Retinal Nerve Fiber Layer (RNFL) and visual field (VF) and nerve fiber layer (NFL). To analyze the progression of POAG according to the above-mentioned clinical parameters, all POAG patients were divided into appropriate groups. RA parameter patients were divided into the following groups: early POAG changes (1.26–1.39 $mm^2$), middle-advanced glaucomatous loss (0.87–1.26 $mm^2$) and advanced glaucomatous loss (<0.81 $mm^2$). Each group was compared to a normal RA parameter value (1.39–1.78 $mm^2$). To assess the relationship between progression of POAG and the RNFL parameter, the patients were also categorized into appropriate groups: early glaucomatous loss (0.181–0.210 mm), middle-advanced glaucomatous loss (0.130–0.180 mm) and advanced glaucomatous loss (<0.13 mm). Each group was compared with the normal range of the RNFL (>0.20 mm). We also combined middle-advanced glaucomatous loss and advanced glaucomatous loss compared to early glaucomatous loss. In relation to changes in the optic nerve disk, all POAG patients were divided into two groups. In the first group, patients had a c/d volume between 0.3 and 0.7 (early POAG changes), and in the second group, the volume of the c/d ratio was between

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