The role of the 148 Asp/Glu polymorphism of the *APE1* gene in the development and progression of primary open angle glaucoma in the Polish population

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Glaucoma is an ocular disorder that is characterized by progressive degeneration of the optic nerve and loss of visual field (VF). Recent data have suggested that the level of oxidative DNA damage in human trabecular meshwork is significantly increased in glaucomatous patients as compared to controls. It was also noted that progressive loss of visual field may by connected with elevated levels of oxidative DNA lesions. This hypothesis may suggest the role of an inefficient base excision repair pathway in primary open angle glaucoma (POAG) pathogenesis. The aim of the study was to evaluate the association of the 148 Asp/Glu *APE1* gene polymorphism with the risk of POAG development. One hundred fifty patients with POAG and 190 controls were enrolled in our study. Gene polymorphisms were analyzed by PCR-CTPP. We did not observe a statistically significant difference between the frequencies of alleles and genotypes of the 148 Asp/Glu *APE1* gene polymorphism in POAG patients and controls. However, the presented study indicated that 148 Asp/Glu of the *APE1* gene was associated with decreased risk of progression of POAG with reference to the parameter VF. We suggest that the 148 Asp/Glu *APE1* gene polymorphism may decrease the risk of POAG progression.

Key words: glaucoma, BER, genetic polymorphism, APE1, HRT.

Introduction

Glaucoma is one of the main causes of blindness that is characterized by progressive loss of retinal ganglion cells (RGC) and damage of the visual field [1]. It is estimated that 68 million people may suffer from glaucoma, among them over 7 million people are blindness. Additionally, the World Health Organization (WHO) has postulated that the most frequent type of glaucoma is primary open angle glaucoma (POAG) and it represents over 50% glaucoma cases [2]. This report is supported by a Polish epidemiological statement which indicated that 1.6% of the population (> 40 years old) has glaucoma and it is also observed that the risk of glaucoma development may increase with age (4.6% of the population aged above 70 years). It was also noted that primary open angle glaucoma represents about 90% of diagnosed cases of glaucoma among the Polish population [3]. Glaucoma is a multifactorial disease. It is thought that the crucial risk factor for POAG pathogenesis is an elevated level of intraocular pressure (IOP) but other coexisting risk factors that play an important role in optic nerve neurodegeneration are age, race, sex, diabetes mellitus type 2, vascular alteration and oxidative DNA damage [1]. It is suggested that oxidative stress may be associated with increased levels of IOP. Same data have shown that oxidative DNA lesions are significantly more frequent in human trabecular meshwork (TM) cells among glaucomatous patients as compared to controls. Moreover, there was also reported an

association between increased level of IOP, loss of visual field and elevated level of oxidative DNA damage [4, 5].

Human cells are permanently exposed to many endogenous (reactive oxygen species) and exogenous (mutagens and radiation) agents that may lead to genomic instability and malignant transformation. In order to protect cells against these factors organisms have developed several DNA repair pathways. It is suggested that DNA repair deficiency may be associated with increased risk of development of various diseases such as cancers or neurodegenerative disorders [6, 7]. It is worth mentioning that the brain is composed of non-proliferating neuronal cells so it is particularly susceptible to defective DNA repair that may cause accumulation of unrepaired DNA damage. It is also suggested that some parts of the brain are more susceptible to oxidative DNA damage. Accumulation of DNA lesions may be one of the main risk factors for neurodegenerative disorders. It is also suggested that an age may plays important role in progressive neurodegeneration [8, 9]. The free radical theory of aging postulated that accumulation of oxidative lesions may correlate with age-related degeneration. According to this theory, Weismann *et al.* have suggested that deficiencies in the repair of oxidative DNA damage may be associated with development of neurodegenerative diseases among the aged population [10]. Additionally, a low level of antioxidant enzymes in the human brain was observed. Therefore, it is postulated that defects in DNA repair pathways may lead to accumulation of oxidative DNA damage, thereby leading to development of neurodegenerative diseases [7]. Among the most common DNA lesions are single strand breaks (SSBs) that may be the result of reactive oxygen species (ROS) activity. Cells have developed special mechanisms to remove this type of DNA damage [11]. Base exaction repair (BER) is the crucial pathway for removing oxidative DNA lesions. Not only cellular metabolism but also environmental agents such as UV light, ionizing radiation and pollution may be the source of ROS [10].

In this paper, we evaluate the effect of genetic polymorphism in a gene encoding one of the main protein of the BER pathway. APE1 (endonuclease 1) is a crucial enzyme that participates in the BER pathway. The studied gene is located on chromosome 14q11.2-q12. There have been known 18 polymorphic variants of the *APE1* gene but the best-studied genetic variant of the *APE1* gene is amino acid alterations at codon 148 (Asp/Glu) in exon 5. It is suggested that this polymorphism may have a relationship with hypersensitivity to ionizing radiation [12]. One of the best known roles of this endonuclease is to protect the cell against generating AP sites that may accumulate in DNA. APE1 also has the function of hydrolyzing 3'-blocking fragments from oxidized DNA and this enzyme participates in the creation of 3'-hydroxyl nucleotide termini that are crucial for DNA repair synthesis and ligation at single- or double-strand breaks. Moreover, it is postulated that APE1 is a transcriptional co-activator for many transcription factors that take part in development of cancer [13, 14].

The aim of this study was to evaluate the association of the 148 Asp/Glu *APE1* gene polymorphism with clinical parameters and the risk of POAG development in the Polish population.

Material and methods

Characteristics of patients

One hundred fifty patients with POAG (96 women and 64 men, main age 72.3 ±7.34) hospitalized in the Department of Ophthalmology, Medical University of Warsaw, and 190 (120 women and 70 men age 67 ±14) sex- and age-matched controls, who were selected from subjects without glaucoma symptoms, were enrolled in this study. All patients and controls were Caucasian. The characteristics of POAG patients including age, mean intraocular pressure (mm Hg), average value of cup disk ratio, rim area (RA), visual fields, retinal nerve fiber layer in the right and the left eye, sex, family history of POAG, vascular disease, diabetic mellitus type 2 and cigarette smoking are summarized in

Table I. Clinical parameters of POAG patients

PATIENTS	AGE (YEARS)	INTRAOCULAR PRESSURE, IOP (MM HG)	CUP DISK RATIO (C/D) RIGHT EYE/ LEFT EYE	RIM AREA (RA) RIGHT EYE/ LEFT EYE	RETINAL NERVE FIBER LAYER (RNFL) RIGHT EYE/LEFT EYE	VISUAL FIELD (VF) RIGHT EYE/ LEFT EYE
Mean ± SD	72.3 ±7.34	13.1 ±1.8	0.71 ±0.15/ 0.71 ±0.15	1.23 ±0.43/ 1.26 ±0.37	0.18 ±0.09/ 0.22 ±0.24	9.06

	GENDER MALE/ FEMALE (150)	HYPERTENSION*	POAG IN FAMILY MEMBERS	VASCULAR DISEASE	DIABETES MELLITUS TYPE 2	CIGARETTE SMOKING IN THE PAST/ PRESENT
Number	64/96	81	39	76	30	73/21

Systolic pressure ≥ 140; Diastolic pressure ≥ 90 mm Hg

Table I. Mean value of intraocular pressure that is shown in Table I is at the right IOP level. The normal range of IOP is associated with the therapy. The aim of the therapy is to reduce the IOP to a level that will not lead to further damage to the optic nerve.

In this study the association of clinical parameters with risk and POAG progression was also evaluated. The Heidelberg Retinal Tomography (HRT) test was used for the analysis of clinical parameters such as disk ratio (c/d), rim area (RA), retinal nerve fiber layer (RNFL) and visual field (VF).

In order to analyze the POAG progression according to clinical parameters all patients were assigned to groups. For the rim area (RA) parameter the patients were divided into the following groups: early POAG loss (1.26-1.39), middle-advanced glaucomatous loss (0.87-1.26), and advanced glaucomatous loss (< 0.87). Each group was compared with normal clinical parameters for the RA parameter. Also advanced glaucomatous loss and middle-advanced glaucomatous loss were combined and compared to the group with early glaucomatous loss. In the case of the RNFL parameter the POAG patients were also assigned to suitable groups: early glaucomatous loss (0.187-0.21), middle-advanced glaucomatous loss (0.187-0.13), and advanced glaucomatous loss (< 0.13). Each group was compared with the normal range of these parameters (0.21-0.31). Middle-advance glaucomatous loss and advanced glaucomatous loss were also combined and compared to early glaucomatous loss. The changes in the optic nerve disc are thought to be early stage POAG (0.3-0.7) and advanced stage POAG (0.7-1.0). In the case of the c/d parameter advanced stage of POAG was compared to early glaucomatous loss. For the VF parameter the patients were compared between three groups: early (MD > –6), moderate (–6 > MD > –12) and advanced (MD < –12) glaucomatous loss. In this study the moderate and advanced glaucomatous loss groups were compared with the early glaucomatous loss group. There were also combined studies of moderate and advanced glaucomatous loss compared with the early glaucomatous loss group.

All subjects underwent ophthalmic examination, including best-corrected visual acuity, intraocular pressure, slit-lamp examination, gonioscopy and fundus examination using non-contact and contact fundus lenses with a slit lamp. In the group of glaucomatous patients, the diagnosis of POAG was made prior to enrolment in accordance with the guidelines of the European Glaucoma Society (Terminology and Guidelines for Glaucoma 2nd Edition, Dogma, Savona 2003, Italy). The diagnosis of glaucoma is determined on the basis of level of intraocular pressure, optic disc appearance and loss of visual field. Additionally, the medical history included the following information about the patient: age, family history.

Medical history was obtained from all subjects, and no one reported present or former cancer or any genetic disease.

The study protocol was reviewed and approved by the Local Ethics Committee of the Medical University of Warsaw and the Local Ethics Committee of the Medical University of Lodz. Written consent was obtained from each participant before enrolment in the study.

Genotype determination

Genomic DNA was isolated from peripheral blood leukocytes using the QIAamp DNA Blood Mini Kit for isolation of high-molecular-weight DNA (Qiagen, Chatsworth, CA, USA). The genotype of the 148 Asp/Glu *APE1* gene polymorphism was determined by PCR-CTPP. The PCR reactions were carried out in 20 µl volume. Each sample contained 10 ng genomic DNA, 1.25 U Taq polymerase (Qiagen, Chatsworth, CA, USA) in $1 \times$ PCR buffer (100 mM Tris- HCl, pH 8.3, 500 mM KCl, 11 mM $MgCl_2$, 0.1% gelatin), 1.5 mM $MgCl_2$, 50 mM dNTPs, and 250 nM each primer. The primer sequences for the 148 Asp/Glu APE1 gene polymorphism have the following sequence: F1: 5'-GAT-ACGGCATAGGTGAGACC-3', F2: 5'-TCTGTTTCA TTTCTATAGGCGAT-3'; R1: 5'TCCTGTCATGCT CCTCC-3' and R2: 5'-GTCAATTTCCTTCATGT-GTGCCA-3'.

Thermal cycling conditions for the 148 Asp/Glu polymorphism of the *APE1* gene were as follows: initial denaturation step at 95°C for 1 min, 30 cycles at 95°C for 60 s and 60 s at the 58°C annealing temperature, and at 72°C for 60 s. The final extension was performed at 72°C for 5 min. More than 10% of the samples were repeated and the results were 100% concordant. The amplifications were performed as described previously [15] with minor modifications.

Data analysis

Student's t-test was used to compare differences in age and sex between the control group and cases. Distribution of genotypes and alleles was compared between groups using the χ^2 test. The odds ratios (ORs) and 95% (95% CI) confidence intervals for estimating the associations between genotypes of the *APE1* gene and the risk of POAG were calculated by using a logistic regression model. Hardy-Weinberg equilibrium was tested using the χ^2 test to compare the observed genotype frequency with the expected frequency among the control group. P-values of less than or equal to 0.05 were considered to represent statistical significance. If all expected cell frequencies were less than 5, one-tailed Fisher's exact probability test was used. All analyses were performed using STATISTICA 6.0 software (StatSoft, Tulsa, OK, USA).

Results

Statistical analyses of patients

There was no difference in average age or sex of the patients and the controls (p > 0.05). The results of the

medical examination showed that among 81 patients with POAG hypertension was diagnosed. Vascular disease was diagnosed among 76 patients with POAG, while diabetes mellitus type 2 was diagnosed in 30 glaucoma cases. The medical history demonstrated that POAG was diagnosed in the family of 39 patients. In the case of cigarette smoking, 73 patients smoked in the past and 21 patients currently smoke.

Polymorphism distribution analyses

The observed genotype frequency of the 148 Asp/Glu *APE1* gene polymorphism in the control group was not in agreement with Hardy-Weinberg equilibrium (HWE) (p = 48.03, χ^2 = 0.0001). The genotype and allele distributions of the 148 Asp/Glu *APE1* gene polymorphism are summarized in Table II. We did not observe a statistically significant difference in the frequencies of alleles and genotypes of the 148 Asp/Glu *APE1* gene polymorphism between POAG patients and controls. However, in this study the genotype and allele distributions in POAG patients were also analyzed according to the following clinical parameters: cup disk (c/d), rim area (RA), retinal nerve fiber layer (RNFL) and visual field (VF). Distributions of genotype and allele frequencies of gene polymorphism with regard to clinical parameters are presented in Tables III, IV. Each patient was analyzed for the right eye and left eye separately and the mean values of clinical parameters were calculated according to the genotype distribution.

The present study involved patients with early glaucoma stage, middle-advanced glaucoma stage and advanced glaucoma changes. It was found that the 148 Asp/Glu genotype (OR 0.46; 95% CI: 0.22-0.96) of the *APE1* gene was associated with decreased risk of progression of POAG with reference to the VF parameter. The results are shown in Table IV.

For the parameters RA, c/d and RNFL there was no relationship between these factors and POAG progression. The results of the investigation are shown in Tables III, V, VI.

Discussion

Age, diabetic mellitus type 2, sex, genetic predisposition, oxidative DNA lesions and elevated level of IOP may be distinguished as POAG risk factors [4]. Epidemiological studies have shown that the risk of glaucoma development increases with age, and therefore age may be one of the main risk factors for POAG pathogenesis. This fact may by supported by the free radical theory of aging. It is noticeable that among older patients there is age-dependent accumulation of oxidative DNA damage and instability of the genome [5]. Many reports have postulated that ROS may participate in glaucoma development. This hypothesis was supported by Alvarado *et al.*, who reported elevated level of oxidative damage in glaucomatous TM cells in comparison to controls [17]. Nizankowska and Kacz-

Table II. Genotype distribution, allele frequencies and odds ratios of the 148 Asp/Glu *APE1* gene polymorphism in POAG patients and controls

GENOTYPE/ ALLELE	PATIENTS		CONTROLS		OR (95% CI)	P-VALUE
	NUMBER (N = 150)	FREQUENCY	NUMBER (N = 190)	FREQUENCY		
Asp/Asp	36	0.24	60	0.31	1	
Asp/Glu	111	0.74	129	0.68	1.43 (0.88-2.33)	0.01
Glu/Glu	3	0.02	1	0.01	5 (0.50-49.98)	0.16
Asp	183	0.61	249	0.65	1	
Glu	117	0.39	131	0.35	1.21 (0.89-1.66)	0.13

Table III. Genotype distribution, allele frequencies and odds ratios of 148 Asp/Glu *APE1* gene polymorphism in POAG patients according to cup/disc index (c/d) for each eye counted

GENOTYPE/ ALLELE	C/D 0.7-1.0 NUMBER (N = 163) FREQUENCY	C/D 0.3-0.7 NUMBER (N = 155) FREQUENCY	OR (95% CI)*	P-VALUE
Asp/Asp	28 (0.22)	31 (0.24)	1	
Asp/Glu	97 (0.76)	100 (0.76)	1.07 (0.60-1.92)	0.81
Glu/Glu	2 (0.02)	0	–	
Asp	153 (0.60)	162 (0.62)	1	
Glu	101 (0.40)	100 (0.38)	0.94 (0.66-1.33)	0.71

Table IV. Genotype distribution, allele frequencies and odds ratios of the 148 Asp/Glu *APE1* gene polymorphism in POAG according to visual field (VF) for each eye counted

Genotype/ Allele	VF MA < −12 dB	VF −6 > MD > −12 dB	VF MD > −6 dB	VF < −6 dB	OR (95% CI)*	P-value	OR (95% CI)**	P-value	OR (95% CI)***	P-value
	Number (n = 57) (Frequency)	Number (n = 67) (Frequency)	Number (n = 124) (Frequency)	Number (n = 111) (Frequency)						
Asp/Asp	18 (0.32)	15 (0.22)	33 (0.27)	19 (0.17)	1				1	
Asp/Glu	39 (0.68)	49 (0.73)	88 (0.71)	90 (0.81)	0.46 (0.22-0.96)	0.03	0.69 (0.32-1.47)	0.22	0.56 (0.28-1.06)	0.05
Glu/Glu	0	3 (0.03)	3 (0.02)	2 (0.02)	–		–		0.86 (0.13-5.64)	0.61
Asp	75 (0.66)	79 (0.59)	154 (0.62)	128 (0.58)	1		1		1	
Glu	39 (0.34)	55 (0.41)	94 (0.38)	94 (0.42)	0.71 (0.44-1.13)	0.09	0.95 (0.61-1.46)	0.45	0.83 (0.57-1.20)	0.19

Table V. Genotype distribution, allele frequencies and odds ratios of the 148 Asp/Glu *APE1* gene polymorphism in POAG patients according to rim area (RA) for each eye counted

Genotype/ Allele	RA 1.39-1.26	RA 1.261-0.87	RA < 0.87	RA < 1.261	RA 1.20-1.78	OR (95% CI)*	P-value	OR (95% CI)**	P-value	OR (95% CI)***	P-value	OR (95% CI)****	P-value
	Number (n = 31) (Frequency)	Number (n = 68) (Frequency)	Number (n = 32) (Frequency)	Number (n = 100) (Frequency)	Number (n = 48) (Frequency)								
Asp/Asp	9 (0.29)	14 (0.20)	6 (0.19)	20 (0.20)	12 (0.25)	1		1		1		1	
Asp/Glu	22 (0.71)	54 (0.78)	26 (0.81)	80 (0.80)	34 (0.71)	0.86 (0.31-2.38)	0.49	1.36 (0.56-3.29)	0.32	1.53 (0.514.62)	0.32	1.64 (0.66-4.09)	0.21
Glu/Glu	0	1 (0.01)	0	1 (0.01)	2 (0.04)	–		–		–	–	–	
Asp	40 (0.65)	85 (0.59)	38 (0.59)	123 (0.57)	58 (0.60)	1		1		1		1	
Glu	22 (0.35)	56 (0.41)	26 (0.41)	82 (0.43)	38 (0.40)	0.83 (0.43-1.63)	0.36	1 (0.59-1.71)	0.54	1.04 (0.55-1.99)	0.51	1.21 (0.67-0.31)	0.31

Table VI. Genotype distribution, allele frequencies and odds ratios of the 148 Asp/Glu *APE1* gene polymorphism in POAG according to retinal neuron fiber layer (RNFL) for each eye counted

Genotype/ Allele	RNFL 0.21-0.187	RNFL 0.187-0.13	RNFL < 0.130	RNFL < 0.187	RNFL 0.31-0.21	OR (95% CI)*	P-value	OR (95% CI)**	P-value	OR (95% CI)***	P-value	OR (95% CI)****	P-value
	Number (n = 35) (Frequency)	Number (n = 48) (Frequency)	Number (n = 24) (Frequency)	Number (n = 72) (Frequency)	Number (n = 67) (Frequency)								
Asp/Asp	7 (0.28)	11 (0.23)	8 (0.33)	19 (0.26)	14 (0.23)	1		1		1			
Asp/Glu	18 (0.72)	37 (0.77)	16 (0.67)	53 (0.74)	44 (0.73)	0.82 (0.28-2.36)	0.45	1.07 (0.43-2.64)	0.54	0.63 (0.22-1.80)	0.28	1.08 (0.39-3.01)	0.54
Glu/Glu	0	0	0	0	2 (0.03)	–		–		–			
Asp	32 (0.64)	59 (0.61)	32 (0.67)	91 (0.63)	72 (0.60)	1		1		1		1	
Glu	18 (0.36)	37 (0.39)	16 (0.33)	53 (0.34)	48 (0.40)	0.84 (0.43-1.67)	0.38	0.94 (0.54-1.63)	0.47	0.75 (0.37-1.51)	0.27	1.03 (0.53-20.02)	0.53

marek suggested that progressive neuronal death that is characteristic for glaucomatous optic nerve change may be associated with oxidative stress [18]. Our previous study supported the hypothesis that oxidative stress may play an important role in POAG development. We noted increased levels of oxidative DNA damage among glaucomatous patients compared to controls [19].

Human cells have developed mechanisms that protect them against endogenous and exogenous factors. The function of DNA repair enzymes is removal of DNA lesions, thereby protecting against accumulation of DNA damage. Some data have suggested that presence of DNA repair gene polymorphisms may have an important influence on genome stability [7]. Many reports have postulated that polymorphisms in DNA repair genes may be associated with decreased activity of DNA repair pathways that may lead to development of some diseases such as cancer or neurodegenerative disorders, e.g. Alzheimer disease.

Base exaction repair is the main pathway that protects cells against accumulation of DNA lesions that are caused by endogenous and exogenous agents. Therefore recent data have suggested that increased levels of oxidative DNA lesions in TM cells among glaucomatous patients may be associated with BER deficiency [20].

This hypothesis may suggest a crucial role of BER impairment in the pathogenesis of POAG. Therefore, the aim of this study was to evaluate the association of *APE1* gene polymorphism encoding the crucial protein of the BER pathway with the risk of POAG development.

Our previous studies indicated a relationship between DNA repair genes such as the 399 Arg/Gln *XRCC1* and 762 Val/Ala *ADPRT* gene polymorphisms with the risk of POAG development in the Polish population [21, 22]. The aim of the present study was to evaluate the association of the 148 Asp/Glu *APE1* gene polymorphism with the risk and progression of POAG.

Recent reports have suggested that presence of the 148 Asp/Glu *APE1* gene polymorphism is associated with decreased activity of this enzyme, which may lead to development of various diseases. In spite of extensive studies analyzing the influence of this polymorphism on the development of many diseases, this is the first report focusing on the relationship between *APE1* gene polymorphism and the risk of POAG development in the Polish population.

This study did not reveal an association between the 148 Asp/Glu *APE1* gene polymorphism and the risk of POAG development. The 148 Asp/Glu *APE1* gene polymorphism has been widely studied in relation to cancer disease. Wang *et al.* did not find a significant association between the 148 Asp/Glu *APE1* gene and bladder cancer [23], but Agaçhan *et al.* reported a connection between the 148 Asp/Glu *APE1* gene polymorphism and the risk of lung cancer development among smoking patients [14].

Heidelberg Retina Tomography was used to assess clinical parameters among POAG patients. In the present study, we analyzed the following clinical parameters that are evaluated during glaucoma diagnosis: RA, RNFL, c/d and VF. We analyzed the distribution of genotype and allele frequency in a group of patients with POAG in correlation with three stages of primary open angle glaucoma progression. Despite numerous studies evaluating the molecular background of POAG, there have not been previous studies which combine genetic polymorphism of base excision repair genes with glaucomatous parameters.

The present study indicated that the 148 Asp/Glu genotype of *APE1* may play a protective role in POAG progression in relation to the VF parameter.

The results of this study suggested that functional DNA polymorphism of the repair genes encoding crucial proteins for the base excision repair pathway may be used as a predictive risk factor of POAG. However, further studies are needed to evaluate the biological influence of analyzed polymorphisms on the risk of POAG.

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