**Paraoxonase 1 (*PON1*) promoter (*−107T/C*) and coding region (*192Q/R* and *55L/M*) genetic variations in pseudoexfoliation syndrome and pseudoexfoliative glaucoma risk**

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**Abstract**

**Purpose:** Pseudoexfoliation syndrome (PEX) is characterized by the accumulation of microscopic extracellular material in the anterior chamber of the eye and can lead to the development of pseudoexfoliative glaucoma (PEG) in some patients. The pathogenesis of PEX is not fully understood, and there are no objective biomarkers for its early diagnosis. Recent research has indicated that oxidative stress and inflammation might play a role in the pathophysiology of the production of pseudoexfoliation material. Therefore, in the present study, we aimed to analyze the possible association between three genetic variants of paraoxonase 1 (*PON1*), a well-recognized anti-oxidant and anti-inflammatory enzyme, and PEX/PEG.

**Methods:** The study population consisted of patients with PEX (n=150), patients with PEG (n=150) and control subjects (n=150). *PON1* *−107T/C*, *192Q/R* and *55L/M* genotypes were determined using PCR followed by restriction fragment length polymorphism analysis. The correlation between these genetic alterations and clinical visual characteristics was also investigated.

**Results:** The minor allele frequencies and genotype distributions of *PON1* did not differ significantly between the PEG, PEX, and control groups. Moreover, *PON1* genotypes did not significantly influence visual clinical parameters in stratification analysis. On the other hand, in correlation analysis, pattern standard deviation was significantly correlated with the *−107T/C* genotypes in PEX group. In addition, intraocular pressure was correlated with the *55L/M* genotypes and mean deviation was correlated with the *−107T/C* genotypes in the control group. Furthermore, intraocular pressure was significantly inversely correlated with sex (*r* = −0.116, P = 0.011) in the overall study group. Logistic regression analysis showed that having a *PON1* *−107TC* or *CC* genotype is significantly associated with PEX (OR=1.909, P=0.020).

**Conclusions:** This study, for the first time, analyzed the relationship between *PON1* genetic variants, clinical visual parameters, and PEX/PEG. The results indicated a possible role for the *PON1* promoter variant in PEX.

**Keywords:** IOP; mean deviation; pattern standard deviation; polymorphism; visual field score

**Abbreviations**

DNA: Deoxyribonucleic acid

IOP: Intraocular pressure

MD: Mean deviation

PCR: Polymerase chain reaction

PEX: Pseudoexfoliation syndrome

PEG: Pseudoexfoliative glaucoma

PON1: Paraoxonase 1

PSD: Pattern standard deviation

RFLP: Restriction fragment length polymorphism

VFS: Visual field score

**Introduction**

Pseudoexfoliation syndrome (PEX) is an aging-related systemic disorder characterized by the accumulation of microscopic granular extracellular material composed of amyloid-like proteins surrounded by glycosaminoglycans, in the anterior segment of the eye [1]. Pseudoexfoliation material can be observed in the iris, the ciliary body, and the anterior lens capsule. The circulation of aqueous humor is blocked when this material occludes the trabecular meshwork, increasing the intra ocular pressure (IOP), which in turn causes optic nerve damage. This condition is referred to as glaucoma**,** a group of eye diseases resulting in damage to the optic nerve and vision loss. It is estimated that approximately 40–50% of patients with PEX eventually develop pseudoexfoliative glaucoma (PEG) [2-4]. The onset and progression of PEX is insidious; patients are often diagnosed incidentally via slit lamp examination or when they present with visual symptoms of glaucoma such as peripheral visual field constriction. Unfortunately, no biomarkers have been identified that can be used for the early diagnosis of PEX and to predict which PEX patients will ultimately develop PEG. This is partly because the pathophysiology of PEX is not completely understood.

PEX is a disorder related to abnormal extracellular matrix synthesis. In recent years, a growing body of evidence has implicated that oxidative stress and inflammation might play important roles in the pathology [5-14]. Inflammation, which can be a manifestation of increased oxidative stress, can activate the fibrotic process, which can in turn lead to the formation of characteristic fibrotic deposits in the eye [15]. Hence, some reports have shown increased levels of proinflammatory cytokines in the aqueous humor samples of PEX and PEG patients [14,15].

Human paraoxonase 1 (PON1) (EC.3.1.8.1) is a well-recognized anti-oxidant and anti-inflammatory enzyme, associated with serum high density lipoprotein. It is also found in the aqueous humor and in tears [16,17]. Moreover, several lines of evidence indicate that PON1 reduces inflammation. For example, *PON1* knockout has pro-inflammatory and pro-atherogenic effects; and the overexpression of human *PON1* is anti-inflammatory and anti-atherogenic [18]. PON1 has also been observed to reduce macrophage inflammatory responses [19]. However, its activity, stability and expression levels are affected by the presence in the *PON1* gene of single-nucleotide polymorphisms, which are defined as variants found at a frequency of 1% or higher in a population. The coding region polymorphisms *192Q/R* (glutamine (Q) to arginine (R) substitution at codon 192) and *55L/M* (leucine (L) to methionine (M) substitution at codon 55) determine the PON1 activity, while the promoter region variants *−107T/C* and *−162A/G* influence the PON1 expression levels [20-22]. The *–107T/C* variation is known as the strongest predictor of the observed variability in *PON1* expression levels [22].

Thus, PON1 concentration or activity levels may play a role in the pathogenesis of PEX/PEG, which several studies measuring serum PON1 activity have indicated [10,12]. However, PON1 activity and expression levels are also affected by different physiological states, lifestyle and dietary factors, such as smoking, alcohol consumption, certain pharmaceutical drugs, dietary intake of bioactive compounds such as quercetin, resveratrol, curcumin, betanin, isothiocyanates, olive oil and pomegranate juice [23-28]. As genetic alterations are not affected by such factors, they can serve as better candidates for reliable biomarkers; however, *PON1* variations have not been previously studied in PEX/PEG patients.

The worldwide prevalence of PEX is 10–20% in individuals over 60 years old [29]. Considering that average life expectancy has been increasing globally, an informed prediction can be made that PEX and PEG will be much more prevalent in the future. Therefore, in an effort to identify objective biomarkers for the early detection of PEX and PEG, this study aimed to evaluate the association of the *PON1* promoter region variant *-107T/C* (*rs705379*) and coding region alterations *192Q/R* (*rs662*) and *55L/M* (*rs85456*0) with PEX and PEG risk. The correlation between these genetic alterations and some clinical visual characteristics was also investigated.

**Materials and Methods**

**Subjects**

The study population consisted of consecutive, unrelated adult patients with PEX (n = 150) and PEG (n = 150), and unrelated symptom-free control subjects (n = 150) examined at the Department of Ophthalmology, Gülhane Training and Research Hospital, Ankara, Turkey. All the subjects were Caucasian and from the same geographic region (Central Anatolia, Turkey). The study was approved by the ethics committee of the hospital and written informed consent was obtained from all the subjects. The study was carried out according to the principles of the Declaration of Helsinki.

The diagnosis of PEX and PEG was performed as previously explained [12,30]. Briefly, PEX diagnosis was made via slit lamp examination following mydriasis and included the presence of typical pseudoexfoliation material on the anterior lens capsule and/or the pupillary border. Patients with PEG followed up on by the Glaucoma Service at the Hospital were also recruited into the study. PEG was diagnosed when the anterior segment findings of PEX accompanied an IOP of > 21 mmHg without treatment or of < 21 mmHg with treatment, typical optic nerve head changes, and visual field defects. Consecutive subjects with an IOP of ≤ 21 mmHg, a normal optic disk appearance, and no pseudoexfoliation material on the anterior lens capsule and pupil margin, and no visual field defects were included as controls. Both the healthy subjects and the patients received a comprehensive ophthalmological examination including best-corrected Snellen visual acuity testing, slit lamp examination, Goldmann applanation tonometry, gonioscopic evaluation, dilated fundus examination using a 90-diopter lens, and visual field evaluation using the 30-2 SITA-Standard algorithm (Humphrey Instruments, San Leandro, CA, USA).

The demographic characteristics of the study participants are given in Table 1. The mean ages in the PEG, PEX and control groups were 73.7± 8.3, 70.4 ± 7.1 and 68.9 ± 9.8, respectively, and the percentages of male subjects were 57.3%, 50.7% and 52%, respectively. Information about systemic hypertension, diabetes, and smoking status is also included in Table 1. Hypertension was defined in subjects with systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg and/or use of antihypertensive drugs. Diabetes was defined as fasting glucose levels ≥ 6.99 mmol/L and/or use of pharmacological treatment. Smoking status was assigned “yes” if the individual was currently smoking or quit less than 3 months previously. No significant difference was found between the study groups in terms of the prevalence of hypertension, diabetes or smoking.

Visual field score (VFS), mean deviation (MD), and pattern standard deviation (PSD) values are also given in Table 1. The visual field was staged using the Advanced Glaucoma Intervention Study scoring system [31], which takes into consideration the number and depth of neighboring depressed test locations on the total deviation plot in the nasal area, upper hemifield, and lower hemifield, dividing the visual field into 4 concentric-like regions, with the outermost being the most sensitive to a depression. Each visual field is given a score between 0 and 20, where 0 indicates that no defective points were measured, and 20 indicates that at least 2 depressed locations in the nasal area and 9 depressed locations in each hemifield were measured. The healthiness of a visual field is categorized based on this score: (i) a score of 0 is a normal field, categorized as stage 1; (ii) scores 1–5 are fields with mild damage, categorized as stage 2; (iii) scores 6–11 are fields with moderate damage, categorized as stage 3; (iv) scores 12–17 are fields with severe damage, categorized as stage 4; (v) scores 18–20 are end-stage fields, categorized as stage 5. All the fields of the study participants could be unambiguously classified.

The exclusion criteria were having other eye disorders such as uveitis and age-related macular degeneration, having kidney disease, having any central nervous system disease that might interfere with a visual field test, and using non-steroidal anti-inflammatory drugs, supplemental vitamin C and/or vitamin E, or diuretics. Peripheral blood samples were taken from all the study participants through venipuncture and stored at −80 °C until use.

**Determination of genetic variations**

Genomic DNA was isolated from the whole blood samples using the method described by Lahiri and Schnabel [32]. Standard PCR, followed by restriction enzyme digestions was employed to determine the −107T/C (*rs705379*), *192Q/R* (*rs662*) and *55L/M* (*rs854560*) genotypes of all subjects, as described previously [33,34]. The PCR mixtures contained specific primers as given in Campo et al. [35].

The PCR reaction of a total volume of 50 μL contained 400 ng template genomic DNA, 200 mmol/L of each dNTPs, 400 nmol/L of each primer, 2.0 mmol/L MgCl2, and 1.25 units of Taq polymerase. The PCR conditions were an initial melting temperature of 94 °C for 3 min, followed by 35 cycles of melting (95 °C, 30 s), annealing (67 °C for *−107T/C*, 60.5 °C for *192Q/R* and 59 °C for *55L/M*, 20 s), and extension (72 °C, 50 s), with an additional final extension step (72 °C, 10 min).

The expected PCR product length for the *−107T/C* variation was 240 bp. All PCR products with the expected length were subjected to digestion with 10-unit *Bsr*BI at 37 °C for 45 min, which resulted in 28 and 212 bp fragments for the *C* allele and a non-digested 240 bp fragment for the *T* allele. For the *192Q/R* variation, PCR products with the expected length of 238 bp were digested with 2-unit *Alw*I at 55 °C for 17 h, resulting in 66 and 172 bp fragments for the *192R* allele and a non-digested 238 bp fragment for the *192Q* allele. The PCR products for the *55L/M* variationwith the expected length of 172 bp were digested with 5-unit *Nla*III at 37 °C for 17 h. The digestion resulted in 66 and 106 bp fragments for the *55M* allele and a non-digested 172 bp fragment for the *55L* allele. Digestion products were resolved by 2.5% agarose gel electrophoresis and visualized by ethidium bromide staining. The allele frequencies were obtained by direct gene counting.

**Statistical analysis**

The continuous variables and the interval variable, namely VFS, are expressed as mean values ± SD, median, and the first and third quartiles. The normality of the sample distribution was investigated with the Kolmogorov–Smirnov test, finding that none of the samples followed a normal distribution. Therefore, differences between the three groups were determined by the Kruskal-Wallis test, and Conover’s formula [36] was used as a post-hoc test to demonstrate which of the two groups differed significantly.When there are two groups (such as the genotypes in Tables 5, 6, and 7), they were compared using the Mann–Whitney U test. The categorical variables are expressed as frequencies and percentages and they were compared using the chi-squared test or Fisher’s exact test. The Bonferroni correction was used to correct for the statistical significance level for multiple testing; for example, a *P* value of 0.05 was reduced to 0.0083 when 6 comparisons were employed (0.05 / 6). The strength of the association of the genotypes and alleles with PEX or PEG was estimated by calculating the odds ratio (OR) values. Two-tailed probability values with 95% confidence intervals (CIs) were estimated for each OR. Logistic regression analysis with the backward stepwise (likelihood ratio) method was used to test the ability of the study parameters to predict PEX and/or PEG status. The Hosmer–Lemeshow goodness-of-fit test was used for the calibration of the logistic regression. SPSS version 16.0 (Chicago, Illinois, USA) was used for these statistical analyses. P values of < 0.05 were considered statistically significant, unless indicated otherwise. The “Genetic Association Study (GAS) Power Calculator” was used for sample size calculation [37]. A power value > 50% was considered adequate. With the lowest allele frequency being 0.18, disease prevalence 10%, and significance level 0.05, the calculated power at the start of the study was 62% with 150 subjects in each study group. The observed lowest power at the end of the study was 71%, with 0.25 as the lowest observed allele frequency.

**Results**

In this study we determined the *PON1* *−107T/C* (*rs705379*), *192Q/R* (*rs662*) and *55L/M* (*rs854560*) genotypes of PEX patients, PEG patients, and healthy controls. The results are presented in Tables 2, 3, and 4. The *−107C* allele frequency was found to be 0.397 in the PEX patients, 0.470 in the PEG patients and 0.437 in the controls (Table 2). The distribution of the *C* allele was not significantly different between the three study groups. Although the genotype distribution in the dominant model (*CC* + *TC* vs. *TT*) resulted in a P value of 0.030 between the PEX patients and the controls as well as between the PEG patients and the PEX patients, this result showed no significant association after multiple testing with a significance cut-off value of 0.0083. The *192Q/R* genotype and allele frequencies did not differ significantly between the groups (Table 3). The *R* allele frequencies were 0.250, 0.290 and 0.303 in the PEG, PEX, and control groups, respectively. Similarly, the frequencies of the *55M* allele were not different between the three study groups (Table 4). The genotype distribution was also not significantly different between the study groups after multiple testing correction is applied.

We also analyzed the distribution of the triple combined genotypes of the *PON1* gene in the study groups. It was observed that the *QQLLCC* genotype was more expressed in PEX patients than in the controls (OR = 3.222, P = 0.035). Likewise, *QQLMTC* genotype was more represented in the PEG patients than the PEX group (OR = 2.037, P = 0.041). The prevalence of the *QRLLTC* genotype was lower in the PEX patients (OR = 0.469, P = 0.029) and PEG patients (OR = 0.396, P = 0.010) compared with the controls. However, after multiple testing correction, only the distribution of *QRLLTC* genotype between PEG patients and controls reached statistical significance.

Stratification analysis was carried out to reveal any differences in visual clinical parameters according to the presence of the minor *PON1* alleles (Tables 5, 6, and 7). Even though PSD was higher in PEX patients with at least one *−107C* allele compared with PEX patients with the wild type genotype (*−107TT*) (P = 0.038), and having at least one *55M* allele decreased the IOP of the controls (P = 0.041), none of these P values reached statistical significance after correction for multiple testing by Bonferroni. *PON1 192Q/R* genotypes had no significant effect on visual clinical parameters. In Table 8, we have shown the comparison between the frequencies of minor *PON1* alleles across the 5 VFS groups, no significantly over- or underrepresented allele was observed.

Correlation coefficients were also calculated to reveal the strength of the association between the parameters in this study. In the overall study population, IOP was found to be significantly inversely correlated with sex (*r* = −0.116, P = 0.011), in other words IOP was significantly directly correlated with being female. The same significant correlation was also observed in the PEG group (*r* = −0.189, P = 0.019). In the overall study population, IOP was also correlated with VFS (*r* =0.179, P = 0.000), MD (*r* = −0.149, P = 0.001) and PSD (*r* = 0.134, P = 0.003). In the PEG group, VFS was significantly correlated with MD (*r* = −0.946, P = 0.000) and PSD (*r* = −0.829, P = 0.000), as expected. In the PEX group, PSD was significantly correlated with the PON1 *−107T/C* genotypes (*r* = 0.176, P = 0.031). In the control group, IOP was correlated with the *PON1 55L/M* genotypes (*r* = −0.249, P = 0.002) and MD was correlated with the *PON1 −107T/C* genotypes (*r* = 0.199, P = 0.014).

Logistic regression analysis was performed with the *PON1 192Q/R*, *55L/M* and *−107T/C* genotypes, and the age, sex, hypertension, diabetes, cardiovascular disease, smoking, IOP, VFS, MD and PSD parameters entered on step 1. In the bivariate regression analysis using the backward LR method, only a PEG–control, PEX–control or PEG–PEX risk analysis was performed at each time. The *PON1 −107TC* + *CC* genotype was found to be significantly associated with the PEX group compared with the control (OR = 1.909, 95% CI = 1.107–3.293, P=0.020). No parameter was found to be a significant predictor through the PEG–control and PEG–PEX comparisons. The model correctly predicted 60% of the cases, and the Hosmer–Lemeshow goodness-of-fit test demonstrated that the calibration of the model was satisfactory (χ2 = 9.854, 8 df, P = 0.275) for logistic regression.

**Discussion**

Glaucoma is one of the leading causes of blindness in the elderly, and PEG is one of the rare forms of glaucoma. As previously mentioned, PEX and PEG are insidious diseases; the presence of pseudoexfoliation material, even with an increase in IOP, cannot be recognized by patients themselves. Moreover, the prognosis for PEG is worse than that for primary open angle glaucoma (POAG); as the IOP in PEG can rise dramatically within months and is much higher than in POAG. IOP-lowering medication is used as the first step in the management of PEG. Although early diagnosis is therefore very important in PEX/PEG, there are unfortunately no valid objective biomarkers that can be used for this [38].

Moreover, PEG is known to be more resistant to medical therapy than POAG. While the success of laser trabeculoplasty to enhance aqueous drainage is high in PEG patients, its effects might diminish over time and IOP may increase again. The last treatment option would be advanced surgical interventions such as trabeculectomy or glaucoma drainage device implantation[39].

The ultimate treatment solution for PEX and PEG requires that PEX pathogenesis be fully elucidated and its early biomarkers defined. The disturbed local oxidative/antioxidative environment leading to PEX development can be a result of a PON1 enzyme with low activity and/or low expression levels. The main physiological function of PON1 is to degrade oxidized lipids and oxidized cholesteryl esters in lipoproteins. The anti-inflammatory roles of PON1 include coordinating the inflammatory response by inactivating pro-oxidant and pro-inflammatory mediators and inhibitingtheproductionof cytokinemonocyte chemoattractant protein*-*1 [40]. Hence, PON1 has been shown to be involved in the pathogenesis of diseases such as diabetes, coronary artery disease (CAD), cerebrovascular disease, and ischemic stroke, which share the common pathophysiology of oxidative stress and inflammation [33,41-43]. In our previous studies, we also determined that some genotypes of *PON1* are significantly related with atherothrombotic ischemic stroke [33]. The pathophysiology of PEX shares common features with that of cardiovascular and cerebrovascular diseases, such as vascular endothelial dysfunction, elastosis in the vessel wall, increased vascular resistance, and decreased blood flow velocity, hyperhomocysteinemia, and disorders of the extracellular matrix [44]. Thus, PON1 is the candidate protein with the most potential to have an important role in the pathogenesis of PEX/PEG as well as other types of glaucoma.

Liton et al. [45] analyzed the genome-wide expression profile of human trabecular meshwork cultured cells from nonglaucomatous and POAG tissue, observing statistically significant upregulation of several genes associated with inflammation and acute-phase response, including E-selectin, as well as the downregulation of the antioxidants paraoxonase 3 and ceruloplasmin. Joe and Tomarev [46] found that antioxidant proteins paraoxonase 2 and glutathione peroxidase 3 are down-regulated in the eye angle tissue of transgenic mice expressing a myocilin mutant. Mutations in the myocilin gene are associated with juvenile and adult-onset primary open-angle glaucoma.

Some previous research has investigated PON1 enzyme activity in PEX, PEG, and other types of glaucoma [10,12,13,47,48]. Yağcı et al. [10] reported lower serum paraoxonase activity in PEX patients. Dursun et al. [13] found that the serum and aqueous humor paraoxonase and arylesterase activity of PEX and PEG patients were significantly decreased compared with the control group. Moreover, these parameters were found to be significantly different between PEX and PEG groups. However, the paraoxonase and arylesterase activities of the aqueous humor did not differ significantly between the PEX and PEG patients [13]. Decreased PON1 activity, as well as increased MDA and 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels, implying increased oxidative stress, were observed in patients with primary open-angle glaucoma [47]. In our previous study, we observed that the basal serum PON1 activity of PEX patients was significantly higher than that of the controls; on the other hand, there was no difference between the PEG patients and the controls in terms of basal PON1 activity. Salt-induced PON1 activity and arylesterase activity did not differ significantly between the patients and controls either. Three phenotypes were then determined by considering the proportion of stimulated PON1 activity to arylesterase activity: AA (low activity), AB (moderate activity), and BB (high activity). The BB phenotype was more common in the PEX patients (25%) than in the controls (3.1%) [12]. The BB phenotype has a low antioxidant protection capacity, but a high (salt-induced) paraoxon hydrolysis rate [49]. Thus, our findings indicated a possible role for the anti-oxidant and anti-inflammatory PON1 enzyme in the pathogenesis of PEX [12]. A recent study in the Turkish population also analyzed PON1 phenotypes in PEG as well as normal tension glaucoma (NTG). The prevalence of the RR phenotype (corresponding to the BB phenotype in our previous work) was reported to be 6.5%, 3.1%, and 7.5% in the PEG, NTG, and control groups, respectively. However, this study did not identify any statistically significant variation in the PON1 phenotypes of the PEG, NTG, and control groups [48].

There is considerable variation in the activity and expression levels of PON1 even in healthy populations [50-53], which is determined by the coding region (*192Q/R*, *55L/M*) and the promoter region (*−107T/C*) variations of the *PON1* gene as well as life-style and dietary factors [23-28, 54]. Nevertheless, the largest effect on PON1 activity levels, which can vary by over 40-fold between individuals, comes from *PON1* genetic variations [28]. Therefore, in the present study we investigated the possible association between three important *PON1* variants (*192Q/R*, *55L/M* and *−107T/C*) and PEX/PEG risk. The results did not indicate a significant role of the minor alleles of these varaints alone in PEX/PEG. However, the *55L/M* and *−107T/C* genotype distributions and some triple combined haplotypes were significantly related with PEX/PEG status. Logistic regression analysis revealed that having at least one *C* allele in the *−107* position of the *PON1* gene is significantly associated with PEX. A *T* allele at position *–107* disrupts the recognition sequence for stimulating protein-1, and *–107TT* genotype is associated with the lowest serum PON1 levels [22]. The high expressor *−107C* allele and *55L* alleles of the *PON1* gene are in strong linkage disequilibrium [55], and PON1 enzyme with leucine as the 55th amino acid (the *L* allele) has the lowest lipid peroxide protection activity [49]. Therefore, even though individuals with the *PON1 −107C* allele have high expression levels of PON1, the enzyme conveys low protection against oxidation.

Knowledge about patients’ *PON1* genetic profile can also be of interest to glaucoma patients and ophthalmologists because some medications used in glaucoma treatment are metabolized by the PON1 enzyme. For example, the major metabolic pathways of pilocarpine, a medication used for the treatment of angle closure glaucoma to decrease IOP, includes hydrolysis by the PON1 enzyme. Moreover, it has been shown that the *PON1 192Q/R* variation affects pilocarpine hydrolase activity [56].

No other genetic association studies in the literature have analyzed the role of *PON1* variants in PEG and PEX risk. However, in a Chinese population the *PON1 192Q/R* genetic variation was reported as significantly associated with POAG [57]. On the other hand, in a study analyzing the associations of *PON1 55L/M* and *192Q/R*, as well as *PON2 311S/C* and *PAF-AH/V279F* with POAG and normal-tension glaucoma in a Japanese population, the genotype and allele frequencies of these alterations did not differ significantly between any patient group and controls. Interestingly, the IOP at diagnosis was significantly higher in glaucoma patients carrying PON1*192R* than in patients not carrying it (P = 0.006) [58].

We also analyzed the relationship between PON1 genetic variations and visual clinical characteristics. Even though we did not find any association between the *192Q/R* variation and visual clinical characteristics, PEX patients with at least one *−107C* allele had higher PSD scores. Moreover, PSD was correlated with the *−107T/C* genotypes of the PEX patients and MD was correlated with the −*107T/C* genotypes of the controls. Furthermore, having at least one *55M* allele was associated with lower IOP, and IOP was negatively correlated with the *55L/M* genotypes of the controls. This finding may be due to the association of the *55M* allele of *PON1* with the greatest protective capacity against LDL oxidation, and the association of *55L* with the lowest [48]. On the other hand, we did not observe any allele to be overrepresented according to visual field severity stage; in other words, VFS was not associated with the *PON1* variants. The inconsistency of our findings with those of Inagaki et al. [58] and Zhou and Liu [57] might be due to differences in the pathogenesis of PEX/PEG and open angle glaucoma, as well as differences in the ethnicities and life-style (e.g., smoking, diet, exercise) of the populations studied.

PEX is best described as a systemic disorder because pseudoexfoliation deposits have also been found in the skin, lung, heart, liver, gall bladder, kidneys and meninges [59]. The presence of PEX is significantly associated with a high risk of hypertension, myocardial infarction, CAD, and stroke [60-63]. Moreover, PEX patients have been observed to have myocardial ischemia at a subclinical stage, verified by tissue Doppler echocardiography, in a Turkish population [64]. In addition, PEG was also found to be significantly associated with the presence of cardiovascular disorders [65]. On the other hand, some studies have reported no significant relationship between PEX and any systemic diseases such as hypertension, cardiovascular disease, and diabetes [66], as well as cerebrovascular disease [67-71]. Similarly, Emiroglu et al. did not find any association between PEX and CAD, aortic aneurysm, or peripheral artery disease [72]. In the present study, the prevalence of systemic hypertension, diabetes, and the percentage of smokers did not differ significantly between the PEG, PEX, and control groups.

A limitation of this study was the lack of access to serum samples of all the subjects, for the evaluation of their PON1 enzyme activity levels. Further studies analyzing PON1 status and genetic variations at the same time might provide more information about their relation with PEX/PEG. There are still no valid and objective early biomarkers for these disorders. Therefore, carefully designed multidisciplinary studies are still needed to find objective parameters that can be used for the early diagnosis of PEX and the discrimination of PEX patients prone to developing PEG so that precautions can be taken before the damage to the optic nerve advances.

In conclusion, this study, for the first time, evaluated PON1 genetic variations in relation to their association with PEX and PEG, and the results indicate that the *PON1* promoter variation might have has some involvement in the pathogenesis of PEX. Given the large inter-ethnic variability in PON1 expression levels which result mainly from different distribution of genetic variations, further studies in other populations might help clear the role of PON1 in these disorders.

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**Compliance with Ethical Standards:**

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Informed consent**

Informed consent was obtained from all individual participants included in the study.

**Ethical approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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**Table 1.** Demographic and visual clinical characteristics of PEG and PEX patients and control subjects.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **PEG (n=150)** | **PEX (n=150)** | **Control (n=150)** | **P** |
| Age | 73.7 ± 8.3  74 (67.8 – 80.0) | 70.4 ± 7.1  69.0 (66.0 – 75.3) | 68.9 ± 9.8  69.0 (62.0 – 76.3) | 0.000a |
| Sex  Male/female  Male/female % | 86/64  57.3/42.7 | 76/74  50.7/49.3 | 78/72  52/48 | 0.353b  0.817c  0.247d |
| Systemic hypertension, *n* (%) | 76 (50.7) | 77 (51.3) | 77 (51.3) | 1.000b,c,d |
| Diabetes, *n* (%) | 32 (21.3) | 31 (20.7) | 32 (21.3) | 1.000b  0.887c  0.887d |
| Cardiovascular disease, *n* (%) | 40 (26.7) | 41 (27.3) | 47 (31.3) | 0.373b  0.447c  1.000d |
| Smokers, *n* (%) | 22 (14.7) | 19 (12.7) | 18 (12.0) | 0.497b  0.861c  0.614d |
| IOP (mmHg) | 21.6 ± 5.0  21.0 (18.0 – 24.0) | 19.3 ± 5.3  18.0 (16.0 – 22.3) | 19.8 ± 5.9  19.0 (16.0 – 24.0) | 0.000a |
| Visual Field Score (VFS) | 2.6 ± 0.8  2.0 (2.0 – 3.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 0.000a |
| Mean deviation (MD) | -6.7 ± 5.7  -4.3 (-7.7 – -2.7) | -1.0 ± 0.6  -0.9 (-1.5 – -0.5) | -0.9 ± 0.6  -0.7 (-1.3 – -0.4) | 0.000a |
| Pattern standard deviation (PSD) | 4.9 ± 3.1  3.7 (2.7 – 6.3) | 1.4 ± 0.2  1.4 (1.2 – 1.6) | 1.5 ± 0.2  1.5 (1.3 – 1.6) | 0.000a |

Data which were expressed as mean + SD in the first row and median (quartiles) in the second row were compared using the Kruskal-Wallis test; a P value is for comparison of three groups (PEG vs. PEX vs. Control);

Data which were expressed as frequencies and percentages were compared using the chi-squared test; b PEG vs. control, c PEX vs. control, d PEG vs. PEX.

**Table 2.** *PON1* *−107T/C* (*rs705379*) genotype and allele frequencies of PEG patients, PEX patients and controls

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **PEG**  **(*n*=150)** | **PEX**  **(*n*=150)** | **Control**  **(*n*=150)** | **OR (95% CI)** | ***P*** |
| **Genotypes, *n* (%)** |  |  |  |  |  |
| ***TT*** (*n*=153) | 45 (30.0) | 63 (42.0) | 45 (30.0) | 1.506a (0.856 - 2.650)  1.293b (0.727 - 2.300)  1.165c (0.678 - 2.001)  1.000d (0.610 - 1.639)  0.592e (0.367 - 0.953)  1.690f (1.049 - 2.721) | 0.154a  0.380b  0.581c  1.000d  0.030e  0.030f |
| ***TC*** (*n*=203) | 69 (46.0) | 55 (36.) | 79 (52.) |
| ***CC*** (*n*=94) | 36 (24.0) | 32 (21.) | 26 (17.) |
| **Allele frequency** |  |  |  |  |  |
| ***T*** | 0.530 | 0.603 | 0.563 | 1.144g (0.829 - 1.578)  0.848 h (0.613 - 1.174)  1.349i (0.976 - 1.865) | 0.412g  0.320h  0.070i |
| ***C*** | 0.470 | 0.397 | 0.437 |
| All the P values were calculated using the chi-squared test. Bonferroni corrected significance cut-off value was 0.0083 for genotypes, and 0.017 for allele frequency.  a PEG vs. Control, *CC* vs. *TC*+*TT*  b PEX vs. Control, *CC* vs. *TC*+*TT*  c PEG vs. PEX, *CC* vs. *TC*+*TT*  d PEG vs. Control, *CC*+*TC* vs. *TT*  e PEX vs. Control, *CC*+*TC* vs. *TT*  f PEG vs. PEX, *CC*+*TC* vs. *TT*  g PEG vs. Control, *C* vs. *T*  h PEX vs. Control, *C* vs. *T*  i  PEG vs. PEX, *C* vs. *T* | | | | | |

**Table 3.** *PON1 192Q/R* (*rs662*) genotype and allele frequencies of PEG patients, PEX patients and controls

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **PEG**  **(*n*=150)** | **PEX**  **(*n*=150)** | **Control**  **(*n*=150)** | **OR (95% CI)** | ***P*** | |
| **Genotypes, *n* (%)** |  |  |  |  |  | |
| ***QQ*** (*n*=230) | 84 (56.0) | 77 (51.) | 69 (46.0) | 0.894a (0.352 - 2.266)  1.441b (0.619 - 3.355)  0.620c (0.260 - 1.480)  0.669d (0.425 - 1.055)  0.808e (0.513 - 1.271)  0.829f (0.526 - 1.305) | 0.813a  0.395b  0.278c  0.083d  0.355e  0.418f | |
| ***QR*** (*n*=187) | 57 (38.0) | 59 (39.) | 71 (47.) |
| ***RR*** (*n*=33) | 9 (6.0) | 14 (9.) | 10 (6.) |
| **Allele frequency** |  |  |  |  |  | |
| ***Q*** | 0.750 | 0.710 | 0.697 | 0.766g (0.535 - 1.096)  0.938h (0.661 - 1.332)  0.816i (0.569 - 1.171) | 0.144 g  0.721h  0.270i | |
| ***R*** | 0.250 | 0.290 | 0.303 |
| All the P values were calculated using the chi-squared test. Bonferroni corrected significance cut-off value was 0.0083 for genotypes, and 0.017 for allele frequency.  a PEG vs. Control, *RR* vs. *QR*+*QQ*  b PEX vs. Control, *RR* vs. *QR*+*QQ*  c PEG vs. PEX, *RR* vs. *QR*+*QQ*  d PEG vs. Control, *RR*+*QR* vs. *QQ*  e PEX vs. Control, *RR*+*QR* vs. *QQ*  f PEG vs. PEX, *RR*+*QR* vs. *QQ*  g PEG vs. Control, *R* vs. *Q*  h PEX vs. Control, *R* vs. *Q*  i  PEG vs. PEX, *R* vs. *Q* | | | | | |

**Table 4.** *PON1* *55L/M* (*rs854560*) genotype and allele frequencies of PEG patients, PEX patients and controls

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **PEG**  **(*n*=150)** | **PEX**  **(*n*=150)** | **Control**  **(*n*=150)** | **OR (95% CI)** | ***P*** | |
| **Genotypes, *n* (%)** |  |  |  |  |  | |
| ***LL*** (*n*=201) | 57 (38.0) | 76 (50.) | 68 (45.) | 1.000a (0.49 - 2.042)  1.565b (0.806 - 3.036)  0.639c (0.329 - 1.240)  1.353d (0.854 - 2.144)  0.807e (0.513 - 1.271)  1.676f (1.058 - 2.653) | 1.000a  0.183b  0.183c  0.198d  0.355e  0.027f | |
| ***LM*** (*n*=191) | 76 (50.) | 49 (32.) | 65 (43.) |
| ***MM*** (*n*=58) | 17 (11.) | 25 (16.) | 17 (11.) |
| **Allele frequency** |  |  |  |  |  | |
| ***L*** | 0.633 | 0.670 | 0.670 | 1.175g (0.840 - 1.645)  1.000h (0.712 - 1.405)  1.175i (0.840 - 1.645) | 0.346g  1.000h  0.346i | |
| ***M*** | 0.367 | 0.330 | 0.330 |
| All the P values were calculated using the chi-squared test. Bonferroni corrected significance cut-off value was 0.0083 for genotypes, and 0.017 for allele frequency.  a PEG vs. Control, *MM* vs. *LM*+*LL*  b PEX vs. Control, *MM* vs. *LM*+*LL*  c PEG vs. PEX, *MM* vs. *LM*+*LL*  d PEG vs. Control, *MM*+*LM* vs. *LL*  e PEX vs. Control, *MM*+*LM* vs. *LL*  f PEG vs. PEX, *MM*+*LM* vs. *LL*  g PEG vs. Control, *M* vs. *L*  h PEX vs. Control, *M* vs. *L*  i  PEG vs. PEX, *M* vs. *L* | | | | | |

**Table 5**. Stratification of visual clinical characteristics of PEG, PEX and control groups with respect to *PON1* *−107T/C* genotypes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Clinical characteristic** | ***−107T/C* Genotype** | **PEG** | **PEX** | **Control** | **P** |
| **IOP (mmHg)** | *TT* | 21.2 ± 4.9  2.0 (18.0 – 25.0) | 19.6 ± 4.8  18.0 (16.0 – 23.0) | 19.1 ± 6.3  18.0 (14.0 – 22.0) | 0.051a  0.016b  0.335c  0.100d |
| *TC* + *CC* | 21.8 ± 5.0  21.0 (18.0 – 24.0) | 19.1 ± 5.6  18.0 (15.0 – 22.0) | 20.1 ± 5.8  19.0 (16.0 – 24.0) | 0.001a  0.011b  0.168c  0.000d |
| P\* | 0.654 | 0.335 | 0.172 |  |
|  |  |  |  |  |  |
| **VFS** | *TT* | 2.5 ± 0.8  2.0 (2.0 – 3.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 0.000a  0.000b  1.000c  0.000d |
| *TC* + *CC* | 2.7 ± 0.8  2.0 (2.0 – 3.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 0.000a  0.000b  1.000c  0.000d |
| P\* | 0.275 | 1.000 | 1.000 |  |
|  |  |  |  |  |  |
| **MD** | *TT* | -6.0 ± 5.9  -3.6 (-7.5 – -2.3) | -1.0 ± 0.6  -1,1 (-1.5 – -0.4) | -1.0 ± 0.6  -0.8 (-1.5 – -0.6) | 0.000a  0.000b  0.963c  0.000d |
| *TC* + *CC* | -7.0 ± 5.6  -4.3 (-8.0 – -3.3) | -1.0 ± 0.5  -0.8 (-1.4 – -0.6) | -0.8 ± 0.6  -0.7 (-1.3 – -0.3) | 0.000a  0.000b  0.006c  0.000d |
| P\* | 0.109 | 0.915 | 0.066 |  |
|  |  |  |  |  |  |
| **PSD** | *TT* | 4.6 ± 3.0  3.5 (2.3 – 6.2) | 1.4 ± 0.2  1.3 (1.2 – 1.6) | 1.5 ± 0.2  1.5 (1.2 – 1.6) | 0.000a  0.000b  0.123c  0.000d |
|
| *TC* + *CC* | 5.1 ± 3.1  3.8 (2.8 – 6.5) | 1.5 ± 0.2  1.5 (1.3 – 1.7) | 1.5 ± 0.2  1.4 (1.3 – 1.7) | 0.000a  0.000b  0.591c  0.000d |
| P\* | 0.273 | 0.038 | 0.908 |  |

Data given as mean ± SD in the first row, and as median and quartiles (first quartile-third quartile) in the second row.

a Comparison of three groups (PEG vs. PEX vs. Control) by Kruskal-Wallis test, b PEG vs. Control; c PEX vs. Control; d PEG vs. PEX by Conover’s formula.

\**TC*+*CC* vs. *TT* by Mann-Whitney U test and Bonferroni corrected significance cut-off value was 0.0125.

**Table 6**. Stratification of visual clinical characteristics of PEG, PEX and control groups with respect to *PON1* *192Q/R* genotypes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Clinical characteristic** | ***192Q/R* Genotype** | **PEG** | **PEX** | **Control** | **P** |
| **IOP (mmHg)** | *QQ* | 21.4 ± 4.8  21.0 (18.0 – 23.8) | 19.5 ± 5.6  18.0 (16.0 – 22.5) | 18.4 ± 5.8  18.0 (14.0 – 20.5) | 0.000a  0.000b  0.133c  0.008d |
| *QR*+ *RR* | 21.7 ± 5.1  20.0 (18.0 – 25.3) | 19.2 ± 5.0  18.0 (16.0 – 22.5) | 19.4 ± 5.8  18.0 (16.0 – 22.0) | 0.007a  0.006b  0.933c  0.005d |
| P\* | 0.974 | 0.841 | 0.169 |  |
|  |  |  |  |  |  |
| **VFS** | *QQ* | 2.7 ± 0.8  2.0 (2.0 – 3.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 0.000a  0.000b  1.000c  0.000d |
| *QR*+ *RR* | 2.6 ± 0.8  2.0 (2.0 – 3.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 1.0 ± 0.0  1.0 (1.0 – 1.0) | 0.000a  0.000b  1.000c  0.000d |
| P\* | 0.375 | 1.000 | 1.000 |  |
|  |  |  |  |  |  |
| **MD** | *QQ* | -6.9 ± 5.5  -4.5 (-8.1 – -3.1) | -1.0 ± 0.5  -1.1 (-1.5 – -0.6) | -0.9 ± 0.6  -0.7 (-1.3 – -0.4) | 0.000a  0.000b  0.051c  0.000d |
| *QR*+ *RR* | -6.3 ± 6.0  -3.7 (-7.3 – -2.4) | -1.0 ± 0.6  -0.8 (-1.6 – -0.4) | -0.9 ± 0.6  -0.8 (-1.4 – -0,4) | 0.000a  0.000b  0.393c  0.000d |
| P\* | 0.148 | 0.644 | 0.547 |  |
|  |  |  |  |  |  |
| **PSD** | *QQ* | 4.8 ± 3.0  3.7 (2.8 – 6.2) | 1.5 ± 0.2  1.5 (1.3 – 1.7) | 1.5 ± 0.2  1.5 (1.3 – 1.7) | 0.000a  0.000b  0.768c  0.000d |
| *QR*+ *RR* | 5.0 ± 3.2  4.2 (2.5 – 6.5) | 1.4 ± 0.2  1.4 (1.2 – 1.6) | 1.6 ± 0.2  1.5 (1.3 – 1.6) | 0.000a  0.000b  0.126c  0.000d |
| P\* | 0.678 | 0.193 | 0.739 |  |

Data given as mean ± SD in the first row, and as median and quartiles (first quartile-third quartile) in the second row.

a Comparison of three groups (PEG vs. PEX vs. Control) by Kruskal-Wallis test, b PEG vs. Control; c PEX vs. Control; d PEG vs. PEX by Conover’s formula.

\**QR*+*RR* vs. *QQ* by Mann-Whitney U test and Bonferroni corrected significance cut-off value was 0.0125.

**Table 7**. Stratification of visual clinical characteristics of PEG. PEX and control groups with respect to *PON1 55L/M* genotypes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Clinical characteristic** | ***55L/M* Genotype** | **PEG** | **PEX** | **Control** | **P** |
| **IOP (mmHg)** | *LL* | 21.8 ± 5.2  21.0 (18.0 –24.0) | 19.7 ± 5.3  19.0 (16.0 –23.0) | 19.7 ±6.2  19.0 (15.5 –23.5) | 0.014a  0.008b  0.797c  0.012d |
| *LM* + *MM* | 21.4 ± 4.7  21.0 (18.0 –24.0) | 18.6 ± 5.3  18.0 (14.5 –22.0) | 17.7 ± 4.9  17.0 (14.0 –20.0) | 0.000a  0.000b  0.330c  0.000d |
|
| P\* | 0.871 | 0.151 | 0.041 |  |
|  |  |  |  |  |  |
| **VFS** | *LL* | 2.6 ± 0.8  2.0 (2.0 – 3.0) | 1.0 ± 0.0  1.0 (1.0 –1.0) | 1.0 ± 0.0  1.0 (1.0 –1.0) | 0.000a  0.000b  1.000c  0.000d |
| *LM* + *MM* | 2.7 ± 0.8  3.0 (2.0 – 3.0) | 1.0 ± 0.0  1.0 (1.0 –1.0) | 1.0 ± 0.0  1.0 (1.0 –1.0) | 0.000a  0.000b  1.000c  0.000d |
|
| P\* | 0.267 | 1.000 | 1.000 |  |
|  |  |  |  |  |  |
| **MD** | *LL* | -6.3 ± 5.4  -3.9 (-7.5 – -2.4) | -1.0 ± 0.6  -0.9 (-1.5 – -0.6) | -0.9 ± 0.6  -0.8 (-1.4 – -0.4) | 0.000a  0.000b  0.278c  0.000d |
| *LM* + *MM* | -7.0 ± 6.0  -6.3 (-7.8 – -2.9) | -1.0 ± 0.6  -1.1 (-1.4 – -0.4) | -0.8 ± 0.5  -0.7 (-1.3 – -0.4) | 0.000a  0.000b  0.110c  0.000d |
|
| P\* | 0.186 | 0.838 | 0.408 |  |
|  |  |  |  |  |  |
| **PSD** | *LL* | 4.8 ± 3.1  3.7 (2.8 – 6.2) | 1.5 ± 0.2  1.4 (1.3 – 1.6) | 1.5 ± 0.2  1.5 (1.3 – 1.7) | 0.000a  0.000b  0.172c  0.000d |
| *LM* + *MM* | 5.0 ± 3.0  4.4 (2.7 –6.4) | 1.4 ± 0.2  1.4 (1.2 – 1.6) | 1.4 ± 0.3  1.4 (1.2 –1.7) | 0.000a  0.000b  0.586c  0.000d |
|
| P\* | 0.561 | 0.191 | 0.079 |  |

Data given as mean ± SD in the first row and as median and quartiles (first quartile-third quartile) in the second row.

a Comparison of three groups (PEG vs. PEX vs. Control) by Kruskal-Wallis test, b PEG vs. Control; c PEX vs. Control; d PEG vs. PEX by Conover’s formula.

\**LM*+*MM* vs. *MM* by Mann-Whitney U test and Bonferroni corrected significance cut-off value was 0.0125.

**Table 8**. Distribution of *PON1 -107T/C*, *192Q/R* and *55L/M* minor allele frequencies in different visual field severity stages (VFS)

|  |  |  |  |
| --- | --- | --- | --- |
| VFS | Minor allele frequency | | |
| *PON1 -107C* | *PON1 192R* | *PON1 55M* |
| 1 | 0.417 | 0.297 | 0.330 |
| 2 | 0.433 | 0.271 | 0.348 |
| 3 | 0.522 | 0.200 | 0.402 |
| 4 | 0.500 | 0.278 | 0.306 |
| 5 | 0.500 | 0.250 | 0.625 |

The highest and lowest frequencies were compared using the chi-squared test. None of the frequencies differed significantly across the VFS groups