Association of IL-10 gene promoter polymorphisms with susceptibility to pseudoexfoliation syndrome, pseudoexfoliative and primary open-angle glaucoma

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Abstract
Background: The involvement of cytokines in pathogenesis of pseudoexfoliation syndrome and glaucoma has been demonstrated in several studies. The aim of the present study was to explore the association between three promoter polymorphisms -592C/A (rs1800872), -819C/T (rs1800871) and -1082A/G (rs1800896) of interleukin 10 (IL-10) gene promoter with susceptibility to pseudoexfoliation syndrome (PEX), pseudoexfoliative glaucoma (PEXG), and primary open-angle glaucoma (POAG).

Results: In all three SNPs studied, there was a significant difference in the genotype distribution between patients and control subjects. Results revealed that the AA genotype of IL-10 -592C/A SNP is associated with PEX. However, TT genotype of -819C/T and AA genotype of -1082A/G SNP are significantly associated with susceptibility to either PEX or PEXG and POAG disorders. Furthermore, the ACC haplotype containing the IL-10 -1082A allele was associated with PEX, PEXG and POAG.

Conclusions: Our results demonstrated that IL-10 gene promoter polymorphisms are associated with susceptibility to PEX, PEXG and POAG in Iranian population. Considering the fact that IL-10 polymorphisms are associated with various IL-10 expressions, further research is needed to explain its involvement in these disorders and the formation of extracellular fibrillar amyloid deposits in PEX and PEXG.

Background
Pseudoexfoliation (PEX) syndrome, as an age-related disorder of the extracellular matrix is characterized by pathologic accumulation of abnormal fibrillar material in various intra- and extraocular tissues [1]. PEX syndrome is the most common cause of secondary glaucoma, named pseudoexfoliative glaucoma (PEXG) which is considered by higher intraocular pressures (IOP), more serious clinical course, more rapid progression, and worse prognosis compared to primary open-angle glaucoma (POAG) [2].

Although the exact etiology and pathogenesis of PEX, PEXG and POAG disorders are still not known, the strong pattern of familial aggregation [3] as well as genome-wide [4] and case-control [5–7] association studies indicate significant genetic contribution to pathology of these disorders. Furthermore, the association of microRNA-related polymorphisms with PEX, PEXG and POAG disorders
have been recently investigated [8]. Therefore, identification of the genes causing or modifying PEX/PEXG/POAG phenotype remains a challenge for researchers working on pathology and pathophysiology of these three eye disorders. Such genetic data may not only provide a better understanding of the molecular and pathogenesis mechanisms underlying PEX, PEXG and POAG disorders, but also enable the possible development of new drugs or treatments.

Previous studies have shown the expression relationship of cytokines with pseudoexfoliation syndrome and glaucoma pathology [9–11]. Interleukin–10 (IL–10) is a potent anti-inflammatory cytokine which plays a central role in anti-inflammation [12]. Three common single nucleotide polymorphisms (SNPs) –592C/A (rs1800872), –819C/T (rs1800871) and –1082A/G (rs1800896) have been previously reported in the promoter region of IL–10 gene. These SNPs control the transcription of IL-10 mRNA and IL–10 protein expression in vitro [13]. To date, several studies have exhibited associations between –592C/A, –819C/T and –1082A/G promoter SNPs with susceptibility to aging [14], risk of cancer [15–17], schizophrenia [18], Alzheimer’s disease [19–23], acute myocardial infarction (AMI) [24] and inflammatory bowel disease (IBD) [25]. However, no association studies have been conducted in order to investigate the possible relationships between these promoter polymorphisms and susceptibility to PEX, PEXG and POAG disorders.

The aim of the present study was to explore the possible association of three IL–10 gene promoter SNPs –592C/A (rs1800872), –819C/T (rs1800871) and –1082A/G (rs1800896), and their related haplotypes with susceptibility to PEX, PEXG and POAG eye disorders in well-characterized patient groups originating from Iran. To best of our knowledge, this study is the first comprehensive report on these polymorphisms in PEX, PEXG and POAG patients from Iranian population and other populations worldwide.

Results

Genotype and allele frequencies of IL–10 gene promoter polymorphisms

The genotype and allele frequencies of IL–10 gene promoter SNPs –592C/A, –819C/T and –1082A/G in control subjects and PEX, PEXG and POAG affected patients are shown in Table 1. With respect to
genotype frequencies (AA vs. AC and CC), at position -592C/A, significant difference was observed for
the frequency of AA genotype in PEX patients (but not in PEXG and POAG patients) compared to
controls (14 % vs. 3.2 %). At position -819C/T (TT vs. TC and CC), frequencies of TT genotype (14%,
8.5% and 10.5% for PEX, PEXG and POAG patients, respectively vs. 1.6% in controls) demonstrated
significant differences between patients and healthy controls. Similar results were obtained for -
1082A/G polymorphism, so that comparison of AA genotype frequency in PEX, PEXG and POAG
patients (19.3 %, 20.3 % and 21.3 %, respectively) exhibited a significant difference compared to
controls (1.6 %) (Table 1). Totally, among the studied genotypes, TT and AA genotypes of -819C/T
and -1082A/G SNPs, respectively, were much more frequent in PEX, PEXG and POAG patients in
comparison with healthy controls. However, at position -592C/A, higher frequency of AA genotype
was observed in just PEX affected patients compared to controls.

**Haplotype analysis of IL–10 gene promoter polymorphisms**

Based on the obtained results, five different haplotypes including GCC (reference haplotype), ACC,
GTA, ATA and GCA were investigated in studied population. Constituents of the haplotypes were
written in the order of -1082A/G, -819C/T and -592C/A of the IL–10 gene promoter. The frequencies of
these haplotypes for PEX, PEXG and POAG affected patients and control subjects are summarized in
Table 2. According to this table, the frequency of ACC haplotype in PEX (14 %), PEXG (18.6 %) and
POAG (19.3 %) patients are much higher than healthy controls (3.2 %). However, no significant
differences were observed between the other studied haplotypes in both groups.

**Association of studied polymorphisms/haplotypes with susceptibility to PEX, PEXG and POAG eye disorders**

Associations between three studied promoter polymorphisms of IL–10 gene with susceptibility to PEX,
PEXG and POAG eye disorders were evaluated. With regard to -592C/A polymorphism, the AA
genotype significantly increased the susceptibility to PEX disorder ($P = 0.04$, OR = 4.97, 95 % CI =
4.45–21.08) compared to the wild-type genotypes. However, no association was found between this
genotype and susceptibility to PEXG and POAG disorders (Table 1). In regards to -819C/T promoter
position, significant association was observed between TT genotype with susceptibility to PEX ($P = 0.004$, $OR = 10.12$, 95% CI = 13.29–71.61), PEXG ($P = 0.03$, $OR = 5.74$, 95% CI = 7.98–43.34) and POAG ($P = 0.01$, $OR = 7.29$, 95% CI = 9.89–53.53). Similarly, the AA genotype of -1082A/G promoter SNP was significantly associated with susceptibility to PEX ($P = 0.02$, $OR = 7.29$, 95% CI = 6.37–29.69), PEXG ($P = 0.002$, $OR = 7.79$, 95% CI = 6.76–31.39) and POAG ($P = 0.005$, $OR = 8.13$, 95% CI = 7.06–32.82) (Table 1).

At the haplotype level, the ACC haplotype was significantly associated with susceptibility to PEX ($P = 0.02$, $OR = 5.76$, 95% CI = 5.17–24.49), PEXG ($P = 0.006$, $OR = 7.54$, 95% CI = 6.62–30.76) and POAG ($P = 0.003$, $OR = 8.11$, 95% CI = 7.13–33.15). However, no statistically significant association was found between ATG, ATA and ACG haplotypes with PEX, PEXG and POAG (Table 2).

Discussion

Several studies have previously explored the role of different genes or loci in PEX, PEXG, and POAG eye disorders [4, 5, 7, 8, 26]. These findings have indicated that the genetic mechanisms involved in pathogenesis of these disorders are complex. Therefore, the existence of additional susceptibility loci for PEX, PEXG, and POAG remains to be identified.

It has been shown that pro-inflammatory cytokines are involved in the pathology and pathophysiology of pseudoexfoliation syndrome/glaucoma [11, 27]. Interleukin–10 (IL–10) is known to play key roles in immune-regulating and anti-inflammatory responses. The present study was conducted in order to investigate the possible association of three promoter SNPs -592C/A, -819C/T and -1082A/G of IL–10 gene as well as their related haplotypes with susceptibility to PEX, PEXG, and POAG in Iranian population. AA genotype of -592C/A SNP significantly increased the susceptibility to PEX disorder compared to controls. However, the AA genotype of -1082A/G SNP, showed a strong association with susceptibility to either PEX (OR = 7.29) or PEXG (OR = 7.79) and POAG (OR = 8.13). In regards to -819C/T SNP, much higher frequency of TT genotype in studied patients compared to control group clearly suggested a significant association of this genotype with susceptibility to PEX, PEXG and POAG. Several researches have found similar associations between -592AA, -819TT and -1082AA genotypes with susceptibility to different diseases. Based on experimental evidences, it has been
revealed that subjects with rheumatoid arthritis show higher frequency of -592AA [28, 29]. Also, patients suffering from asthma demonstrated -592AA and -1082AA genotypes more frequently [30], while -592AA and -819TT genotypes were more observed in prostate and colon cancers [31,32]. A recent study has indicated that -819TT and AA prevalence is significantly higher in AML cases compared to the healthy controls [24]. Moreover, it has been found that the frequency of IL-10 -819T/T is apparently increased in higher age groups and it is suggested that IL-10 -592A/C and -819T/C can be an appropriate candidate as an aging-related gene [14]. Based on the findings of several researches, it seems that Alzheimer’s disease and glaucoma have some features in common since they are both age-related neurodegenerative diseases. Results of the present study revealed higher prevalence of AA genotype of -1082A/G SNP in studied eye disorders. Similarly, a significant increase of the -1082A allele has been reported in Alzheimer’s disease cases compared to controls [19]. Also, meta-analysis has recently revealed an association between IL-10 –1082A/G and the risk of developing the Alzheimer’s disease in a Brazilian cohort, in a way that A allele carriers (AA+AG) demonstrated a higher risk of the disease in comparison with the homozygote GG [23]. Moreover, in present work the association of IL-10 promoter haplotypes with susceptibility to PEX, PEXG, and POAG was evaluated which demonstrated an association of the ACC haplotype containing the IL-10 –1082A allele with PEX, PEXG and POAG. This finding revealed a very little linkage disequilibrium between IL-10 –1082 position with -592C/A and -819C/T SNPs, suggesting that the effect is largely attributable to IL-10 –1082A/G polymorphism. However, despite the absence of the association of GTA, ATA and GCA haplotypes with the studied eye disorders, the lack of ATA haplotype as well as very low frequency of GTA and GCA haplotypes in control group compared to patients clearly validated the reliability of the association found between AA, TT and AA genotypes of -592C/A, -819C/T and -1082A/G polymorphisms, respectively, with susceptibility to PEX, PEXG and POAG in the studied population. Other studies have reported similar associations between IL-10 –592C/A, –819C/T and –1082A/G haplotypes and susceptibility to diseases. It has been shown that GCC/ACC haplotype is more frequent in Alzheimer’s disease cases compared to controls [22]. Moreover, the haplotype -1082A/-819T is shown to be associated with a higher risk of developing the Alzheimer’s disease [20]. On the
other hand, the IL-10 promoter SNPs may affect IL-10 mRNA and protein expression [13, 33]. As an instance, it has been confirmed by reverse transcriptase-PCR that -819TT/-592AA haplotype was a determinant of high IL-10 transcription and mRNA transcription in lipopolysaccharide-stimulated peripheral blood mononuclear cells [34]. New findings have demonstrated that serum level of the cytokine IL-10 is increased in patients with Alzheimer’s disease compared to vascular dementia and Down syndrome and healthy controls [35]. From molecular point of view, over-expression of IL-10 exacerbates the Alzheimer’s disease in mouse model by unexpectedly giving rise to deposition of amyloid-β (Aβ) plaques in brain [36]. In a recent research work, the IL-10 deficiency induced by knocking out the IL-10 gene in Alzheimer’s-afflicted mice model is shown to promote the clearance of Aβ plaques from the brain and improves memory restoration [37]. Surprisingly, PEX and PEXG are characterized by ocular accumulation of fibrils containing amyloid-related proteins [38]. As demonstrated by extensive evidences, extracellular fibrillar amyloid deposits are accumulated in retinal ganglion cells, the walls of iris arterioles, lens capsule and occasionally cornea of PEX and PEXG patients [39–41]. Based on these findings, it might be suggested to assess whether the IL-10 polymorphisms can be influential on fibrillar amyloid deposition in PEX and PEXG glaucoma.

Conclusions
In conclusion, our results revealed that while the AA genotype of IL-10 –592C/A SNP is just associated with PEX, the AA and TT genotypes of IL-10 promoter –1082A/G and –819C/T polymorphisms, respectively, are associated with susceptibility to PEX, PEXG and POAG in Iranian population. ACC haplotype containing the IL-10 –1082A allele was associated with PEX, PEXG and POAG, suggesting that IL-101082A allele plays an important role in susceptibility to PEX, PEXG and POAG eye disorders. Although, based on our findings it might be suggested that PEX, PEXG and POAG subjects having AA genotype of –592C/A, TT genotype of –819C/T and AA genotype of –1082A/G SNPs should be under control for possible Alzheimer’s disease, further studies on a greater number of patients and their long-term follow-up are required to confirm these results. Since both the Alzheimer’s disease and glaucoma are age-related, an increased understanding of the role of IL-10 in these three eye disorders may open the door to future treatments.
Methods

Subjects and diagnostic criteria

A total of 346 unrelated patients including 114 PEX, 118 PEXG and 114 POAG cases who had undergone detailed standardized ophthalmic examinations at Department of Ophthalmology, Glaucoma Service, Farabi Eye Hospital (Tehran, Iran), as well as 126 healthy controls were recruited for study participation. Patients and healthy controls were all of Iranian origin. Subjects with PEX were defined as those with clinical evidences of pseudoexfoliation on the anterior capsule and pupillary margin in mydriasis with an IOP of less than 21 mm Hg as well as no clinical evidence of glaucomatous optic neuropathy. All PEXG patients were defined as those with clinical evidences of PEX, elevated IOP, and glaucomatous optic neuropathy with compatible visual field loss. The diagnostic criteria for POAG were applied including exclusion of congenital glaucoma, exfoliation syndrome, or other secondary causes; gonioscopically open anterior chamber angle (Shaffer grade III or IV); characteristic optic disc changes; characteristic visual field changes according to Anderson’s criteria [42], and IOP greater than 22 mm Hg in both eyes without medications. With respect to control subjects, they all had IOP below 20 mm Hg, and no glaucomatous disc damage, no PEX material deposits on anterior lens capsule and/or pupillary margin, no criteria indicating early or suspect PEX and no family history of PEX and glaucoma.

DNA extraction and genotyping

Genomic DNAs were extracted from peripheral blood leukocytes of 114 PEX, 118 PEXG and 114 POAG affected patients and 126 healthy controls using the standard phenol-chloroform procedure, with slight modifications [43]. Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR) was performed for genotyping of -592C/A, -819C/T and -1082A/G SNPs using primer pairs (Table S1) as described by Abanmi and colleagues [44] with slight modifications. Human growth factor hormone primers (Table S1) were included in each PCR reaction as internal control. Briefly, genomic DNA was amplified with the use of Taq DNA polymerase in two different PCR reactions for each polymorphism; each reaction employed a generic antisense primer and one of the two allele specific sense primers. In order to assess the success of PCR amplification in both reactions, 429 bp of
Human growth factor hormone gene (accession number M13438) was amplified as an internal control.

PCR conditions are summarized in Table S2.

**Statistical analysis**

Allele, genotype and haplotype frequencies were compared between patients and control groups using chi-squared test (χ²) or Fisher’s exact test where appropriate. In order to evaluate the association between the specific alleles, genotypes and IL-10 promoter haplotypes with susceptibility to PEX, PEXG and POAG disorders in patients compared to controls, chi-square and odds ratios (ORs) were estimated within 95% confidence intervals. A p-values of less than 0.05 were considered statistically significant. All statistical analysis was performed using SPSS Software, version 22 (SPSS Inc., Chicago, Illinois, USA).

**Abbreviations**

AMI = acute myocardial infarction; ARMS-PCR = amplification refractory mutation system-polymerase chain reaction; CI = confidence interval; IBD = inflammatory bowel disease; IL-10 = Interleukin-10; IOP = intraocular pressures; OR = odds ratio; PEX = pseudoexfoliation; PEXG = pseudoexfoliative glaucoma; POAG = primary open-angle glaucoma; SNPs = single nucleotide polymorphisms

**Declarations**

**Ethics approval and consent to participate**

All subjects gave written informed consent and the study was approved by the Ethical Committees of Shahid Beheshti University of Medical Sciences, IR.SMBU.NRITLD.REC.1395.254.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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Not applicable.

Authors’ contributions

GF diagnosed the eye disorders. PF performed the analysis of PCR-RFLP, and was a major contributor in writing the manuscript. The main idea of the research was the work of PF and GF. FP analyzed and interpreted the patient data, and was a contributor in writing the manuscript. SS Collected the samples and performed DNA extraction. JG analyzed the samples. All authors read and approved the final manuscript.

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Tables

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### Table 1 Distribution of alleles and genotypes of IL-10 SNPs

| Alleles | Genotypes | p-Value |
|---------|------------|---------|
| -592 (rs1800872) | | |
| PEX, n (%) | 114 | 130 (57.02) | 98 (42.98) | 0.39 |
| PEXG, n (%) | 118 | 128 (54.24) | 108 (45.76) | 0.68 |
| POAG, n (%) | 114 | 126 (55.26) | 102 (44.74) | 0.57 |
| Control, n (%) | 126 | 130 (51.59) | 122 (48.41) | Ref group |

| Alleles | Genotypes | p-Value |
|---------|------------|---------|
| -819 (rs1800871) | | |
| PEX, n (%) | 114 | 130 (57.02) | 98 (42.98) | 0.39 |
| PEXG, n (%) | 118 | 128 (54.24) | 108 (45.76) | 0.68 |
| POAG, n (%) | 114 | 126 (55.26) | 102 (44.74) | 0.57 |
| Control, n (%) | 126 | 126 (50) | 126 (50) | Ref group |

| Alleles | Genotypes | p-Value |
|---------|------------|---------|
| -1082 (rs1800896) | | |
| PEX, n (%) | 114 | 132 (57.89) | 96 (42.11) | 0.22 |
| PEXG, n (%) | 118 | 130 (55.08) | 106 (44.92) | 0.43 |
| POAG, n (%) | 114 | 130 (57.02) | 98 (42.98) | 0.28 |
| Control, n (%) | 126 | 126 (50) | 126 (50) | Ref group |

### Table 2 Haplotype structures and frequencies in the IL-10 gene promoter

| Subjects | n | GCC | ACC | GTA | ATA |
|----------|---|-----|-----|-----|-----|
| PEX, n (%) | 114 | 82 (71.9) | 16 (14) | 10 (8.8) | 6 (5.3) |
| Control, n (%) | 126 | 118 (93.6) | 4 (3.2) | 2 (1.6) | 0 (0) |
| p-value | | Ref. group | 0.02 | 0.08 | 0.07 |
| OR (95 % CI) | | - | 5.76 (5.17-24.49) | NA | NA |
| PEXG, n (%) | 118 | 86 (72.9) | 22 (18.6) | 8 (6.8) | 2 (1.7) |
| Control, n (%) | 126 | 118 (93.7) | 4 (3.2) | 2 (1.6) | 0 (0) |
| p-value | | Ref. group | 0.006 | 0.16 | 0.42 |
| OR (95 % CI) | | - | 7.54 (6.62-30.76) | NA | NA |
| POAG, n (%) | 114 | 80 (70.2) | 22 (19.3) | 10 (8.8) | 2 (1.8) |
| Control, n (%) | 126 | 118 (93.7) | 4 (3.2) | 2 (1.6) | 0 (0) |
| p-value | | Ref. group | 0.003 | 0.08 | 0.41 |
| OR (95 % CI) | | - | 8.11 (7.13-33.15) | NA | NA |

* Numbers of haplotypes are shown with their frequencies in parentheses. Constituents of the haplotypes are written in the order of -1082 G/A, -819 C/T and – 592 C/A SNPs of IL-10.