Molecular Vision 2006; 12:1380-5 <http://www.molvis.org/molvis/v12/a155/>
Received 24 August 2006 | Accepted 7 November 2006 | Published 15 November 2006

Polymorphism in the IL-1α (-889) locus associated with elevated risk of primary open angle glaucoma

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Purpose: Recent laboratory evidence indicates that the inflammatory cytokine, interleukin-1 (IL-1), has either protective or adverse effects on primary open angle glaucoma (POAG). Inheritance of the IL-1α (-889) polymorphism (the T allele), previously shown to increase IL-1 production, has been associated with an elevated risk of Alzheimer's disease. The neuronal injuries associated with Alzheimer's disease have a number of similarities with the optic nerve changes often seen with POAG. In this report we have explored the possible association between the IL-1α (-889) polymorphism and the development of POAG.

Methods: Chinese patients with POAG (156) were recruited and compared with 167 healthy chinese controls. Genomic DNA was amplified by polymerase chain reaction, followed by enzymatic restriction fragment length polymorphism technique (PCR-RFLP). Patients and controls were genotyped for the C/T polymorphism at position -889 of the IL-1α gene promoter region.

Results: The frequency of the IL-1α (-889) T allele (21% versus 13%, respectively; p=0.007) and the carriers of the IL-1α (-889) T allele (37% versus 25%; p=0.019, OR 1.76, 95%CI 1.1-2.83) were greater in POAG patients compared with controls. There is a higher risk of POAG associated with homozygosity for the IL-1α (-889) T allele (TT genotype) compared with the control population (CC genotype; 5% versus 1%, respectively, p=0.04; OR 5.1, 95% CI 1.19-21.66).

Conclusions: The IL-1α (-889) T allele polymorphism, previously shown to increase IL-1 gene expression, may be a risk factor in the development of POAG.

Glaucoma is characterized by cupping of the optic nerve head and irreversible loss of retinal ganglion cells. Glaucoma affects over 60 million people worldwide and constitutes the second largest cause of bilateral blindness in the world [1]. Primary open angle glaucoma (POAG) is a multifactorial neurodegenerative disease. The etiology of POAG is poorly understood, but both genetic and environmental factors are thought to contribute to the pathophysiology of the disease.

POAG is genetically heterogeneous, with at least eight loci found to be associated with the disease. Mutations in genes such as *MYOC*, *OPTN*, and *WDR36* have been implicated in POAG. [2-4]. Heterozygous *CYP1B1* mutations are more frequent in POAG subjects than in normal controls [5,6]. Genetic data shows that the incidence of POAG in first-degree relatives of affected individuals is 7-10 times higher than the general population [7]. Family studies have mapped disease-causing mutations to a number of different loci [2,8-10]. Susceptibility to POAG in most cases, however, is likely to be inherited as a complex trait involving multiple genes, modified by other factors such as environment, nutritional status, or aging [11,12]. POAG usually presents later in life, and diagnosis is often delayed until visual field loss has already occurred. However, genetic factors may also cause early disease onset [13]. Early diagnosis of this disease can be facilitated by a genetic approach that identified those at risk of developing the disease.

There is evidence to support the hypothesis that the immune system plays a potential pathogenic role in glaucomatous optic nerve degeneration [14,15]. Balancing the benefit of protective immunity and the risk of inducing an autoimmune neurodegenerative disease is critical as the effect of such immuneregulation may be either neuroprotective or neurodestructive [16]. For example, increased autoantibodies were found in the serum of glaucoma patients. These autoantibodies include those with specificities to heat shock proteins (hsp) such as hsp60 and hsp27, and alpha-crystallins [17,18]. Interleukin-1 (IL-1) plays an important role in mediating ischemic and excitotoxic damage in the retina [19]. The association between the degree of immune responses and the development of glaucomatous optic nerve degeneration may be fluid, and in certain cases, may result in retinal ganglion cell death through an aberrant immune signaling process.

A C/T polymorphism at position -889 of the IL-1α gene promoter region has been reported to be associated with Alzheimer's disease, with the IL-1α (-889) T allele polymorphism found to increase the risk for developing Alzheimer's disease [20-22]. In the IL-1α gene, the IL-1α (-889)T allele

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has also been shown to increase the IL-1α protein level with respect to the IL-1α (-889)C allele [23]. There is evidence that the IL-1α protein may act to promote the development of β-amyloid deposits [24-27]. Similar evidence also indicates that there are β-amyloid build-up in retinal ganglion cells in rats with experimental glaucoma [28,29]. Tamura et al. have shown a high frequency of POAG in patients with Alzheimer's disease [30]. In this regard, glaucoma may be viewed as a chronic neurodegenerative disease similar to Alzheimer's disease, and a slow build up of β-amyloid in ganglion cell may eventually trigger cell death and optic nerve axon loss.

Given the potential similarities in cellular events leading to neurodegeneration between Alzheimer's disease and glaucoma, we hypothesized that the IL-1α (-889) polymorphism may be a genetic factor predisposing affected individuals to glaucoma due to its effect on IL-1 protein expression. Thus we investigated the distribution of the IL-1α (-889) polymorphism in patients with POAG and compared them with a healthy control population.

METHODS

Study subjects: Subjects were recruited from the outpatient clinic in the Department of Ophthalmology at the Veterans General Hospital, Taichung, Taiwan from January 2004 to January 2006. POAG patients were approached as they visited the clinic for appointments, and were enrolled after consenting to participate in the study. Normal control subjects were recruited when they visited the outpatient clinic for other reasons.

All participants received comprehensive ophthalmologic examinations including visual acuity testing with refraction, intraocular pressure (IOP) measurement, Humphrey 30-2, slit lamp examination, and dilated slit lamp stereo biomicroscopy. Comprehensive ophthalmologic history and longitudinal follow-up data were also obtained for each individual. The definition for POAG included characteristic arcuate, Bjerrum, Seidel, paracentral scotoma as well as nasal step on Humphrey 30-2 with reference to Anderson's criteria for minimal abnormality in glaucoma [31], and corresponding cupping of optic nerve heads as well as nerve fiber layer defects on stereobiomicroscopy. Open drainage angles on gonioscopy; and the absence of a secondary cause for glaucomatous optic neuropathy, such as previous trauma, a period of steroid administration, or uveitis were required. The POAG cases had an elevated IOP of >21 mmHg on diurnal testing. Cases with a history of inflammation, ocular hypertension, congenital glaucoma, or normal tension glaucoma were excluded.

Unrelated control subjects were recruited from those attending the clinic for conditions such as senile cataract, floaters, refractive errors, or itchy eye. All normal control subjects had no systemic disease and no family history of glaucoma. They were excluded from the glaucoma grasp using the same criteria of diagnosis as the POAG patients after relieving the same ophthalmic examination procedure. The study was carried out with the approval of the Human Study Committee of the Veterans General Hospital. Written informed consent was obtained from all study subjects prior to enrollment.

DNA preparation and genotyping: Blood samples were collected from each subject (5 ml) and genomic DNA was isolated using the Qiagen QiaAmp Blood mini kit (Qiagen, Valencia, CA). Interleukin-1α C(-889)T genotyping of genomic DNA was determined with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique on blood samples obtained for routine clinical work according to standard procedures [32]. RCR fragments of the IL-1α promoter region (-889) were amplified using the following primers: 5'-GCA TGC CAT CAC ACC TAG TT-3' and 5'-TTA CAT ATG AGC CTT CCA TG-3' as upstream and downstream primers, respectively. These primers amplified the region of IL-1α from -1062 to -869 (194 base pairs [bp]) [33]. The PCR products were digested with *Nco* I (New England Biolabs, Inc, Beverly, MA) overnight at 37 °C and were run on ethidium bromide-stained 6% polyacrylamide gels for 45 min at 200 V and detected under ultraviolet (UV) light. The IL-1α (-889) C allele showed two fragments of 178 bp and 16 bp, and the IL-1α (-889) T allele showed an intact fragment of 194 bp. To ensure accuracy, each test was performed three times for each sample.

Statistical analysis: Genotype and allele frequencies between the control and POAG groups were compared using the chi-square test. Fisher's exact test was used if any expected frequency was lower than 5. Age and gender were compared between the control and POAG groups using the Mann-Whitney U test and chi-square test, respectively. Odds ratios were computed to assess the strength of association between the presence of each genotype and the clinical diagnosis of POAG. A p-value of less than 0.05 was defined to be of statistical significance. All statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, IL).

RESULTS

Subject characteristics: In our study, 156 Chinese patients with POAG and 167 normal Chinese controls were enrolled. The mean age was 72 years for the POAG patients (range 35-

Table 1.

	POAG (%) n= 156	Control (%) n=167	Odds ratio (95% CI)	p-value
Genotype				
C/C	98 (63%)	125 (75%)	1	NA
C/T	50 (32%)	40 (24%)	1.63 (0.99, 2.00)	0.051
T/T	8 (5%)	2 (1%)	5.1 (1.19, 21.66)	0.04
Allele				
C	246 (79%)	290 (87%)		
T	66 (21%)	44 (13%)	1.77 (1.17, 2.68)	0.007

Genotype and allele frequencies of IL-1α (-889). Distribution of genotypes and allelic frequencies in primary open angle glaucoma (POAG) and controls. In POAG patients, the genotype IL-1α (-889) T/T was more frequent than in controls (5% versus 1%; p=0.04), whereas the C/T genotype was a trend overrepresented in the POAG group (32% versus 24%; p=0.08). The frequency of the IL-1α (-889) T allele was significantly increased in POAG group (21% versus 13%, p= 0.007).

87) and 70 years for the controls (range 30-85). There was no difference between the control and POAG groups in age (p>0.05). There was no difference between the POAG (75 males and 81 females) and control (80 males and 87 females) groups in terms of gender (p>0.05).Patients were followed up for between 1-9 years (with a mean of 5 years). Eighteen patients had received trabeculectomy and four of the 18 patients had received trabeculectomy twice from different sites. Of the POAG patients, 140 were prescribed antiglaucoma eyedrops. All medical treatment included primarily topical beta-blockers and prostaglandin. Each patient used an average of 1.4 types of antiglaucoma drugs. Sixteen patients did not need medication to control IOP after trabeculectomy.

IL-1α (-889) T association with elevated risk of primary open angle glaucoma: The distribution of IL-1α (-889) genotypes and alleles is shown in Table 1. In POAG patients, the genotype IL-1α (-889) T/T was more frequent than in controls (5% versus 1%; p=0.04). In addition, the C/T genotype was also slightly overrepresented in the POAG group compared with controls (32% versus 24%; p=0.08). The frequency of the IL-1α (-889) T allele was significantly increased in POAG group (21% versus13%, p= 0.007). In comparison with controls there were significantly more carriers of the IL-1α (-889) T allele among patients with POAG (37% versus 25%; p=0.019), with the odds ratio of 1.76 (95% CI: 1.2-2.8; Table 2). The distribution of genotypes in the population of patients controls was consistent with Hardy-Weinberg equilibrium, with no significant detectable differences between the expected and the observed numbers.

DISCUSSION

Glaucoma is a complex clinical trait, and its inheritance has been shown to follow both Mendelian and non-Mendelian models [34]. In addition to identified genes with an autosomal dominant pattern of inheritance (myocillin, optineurin) [2,3], there may be many gene variations that may elevate the risk of the retinal degeneration characteristic of glaucoma (OPA1, apolipoprotein E) [35,36]. Many more important gene variants have recently been associated with glaucoma risk (CYP1B1, DWR36, E-cadherin [E-CDH]) [4,6,37]. Given the prevalence of POAG and that this disease is amenable to treatment when detected early, a genetic predisposition screening could potentially reduce the overall morbidity of the disease. In addition, genetic association studies aimed at defining susceptibility to POAG may provide important insights into the pathogenesis of POAG.

Table 2.

IL-1α(-889)	POAG(%) n=156	Control(%) n=167	Odds ratio (95% CI)	p-value
TT+CT	58 (37)	42 (25)	1.76(1.10, 2.83)	0.019
CC	98 (63)	125 (75)		

IL-1α (-889) T allele carriage frequency. There were significantly more carriers of the IL-1α (-889) T allele among patients with POAG than among controls (37% versus 25%; p=0.019). The odds ratio was 1.76 (95% CI: 1.2-2.8).

The development of glaucoma involves tissues in both the trabecular meshwork and the retina of the eye. IL-1 has been broadly implicated in protective responses and glaucoma disease pathogenesis in both tissue locations [38-41]. This study investigated the association between POAG and the IL-1α (-889) polymorphism that has already been implicated in diseases involving diverse organ systems. Here we report an association between the IL-1α (-889) polymorphism and the susceptibility to POAG, with a significant overrepresentation of the IL-1α (-889) T allele carriers among POAG patients. Patients with IL-1α (-889) T/T genotype have an increased relative risk of developing POAG compared to healthy controls.

In this study we showed that IL-1α (-889) polymorphism, one of the genetic factors leading to aberrant immune responses, is tightly associated with retinal ganglion degeneration in POAG and thus is a possible predisposing factor to the development of POAG in Chinese population. Further studies with POAG cohort of different ethnic background are required to further define this association. The possibility that linkage disequilibrium between IL-1α polymorphisms and other genes on chromosome 2 cause the increasing POAG risk cannot be excluded.

Published evidence suggests an autoimmune component to the pathophysiology seen at the optic nerve head of POAG, which could include cytokines involved in the immune response such as IL-1 [42-44]. The mechanisms by which IL-1 contributes to retinal ganglion cell degeneration remain unknown. In the optic nerve ligation model (which may mimic some aspects of glaucoma), IL-1 is induced locally and promotes optic nerve damage, at least in part, by increasing synthesis of matrix metalloproteinase-9 (MMP-9) [45,46]. IL-1 can also induce nitric oxide synthesis, another mediator of optic nerve head damage in experimental models [47,48]. The IL-1α (-889) T allele could potentially alter the risk of POAG by increasing the levels of IL-1 protein produced in response to stress [23]. An increased production of IL-1 in response to stressful stimuli could act on either the outflow pathways or retinal ganglion cells. Such an increase in IL-1 production may confer greater cytodestructive properties toward the trabecular meshwork cells of the outflow pathways and the retinal ganglion cells. Additionally, inheritance of the IL-1α (-889) T allele has been associated with an elevated risk of developing Alzheimer's disease [20-22]. There is evidence that the IL-1α protein may act to promote the development of β-amyloid deposits in Alzheimer's patients [24-27], and McKinnon and colleagues have demonstrated evidence of buildup of β-amyloid in retinal ganglion cells in the rat glaucoma model [28,29]. The death of retinal ganglion cells in glaucoma involving chronic β-amyloid neurotoxicity may mimic Alzheimer's disease at the molecular level. These data point to a potential overlap between the degenerative pathways underlying POAG and Alzheimer's disease.

In our study, we noted that the IL-1α (-889) T allele polymorphism may be a risk factor in the development of POAG. Besides the IL-1α gene, previous studies have noted other cytokine genes (IL-1β, TNF-α) and growth factor gene (insu-

lin-like growth factor-II) polymorphisms are associated with an elevated risk of POAG [49-52]. Lin et al. found that the IL-1β (+3953) T allele was significantly more common in POAG patients than in control [49]. The IL-1β (+3953) C/T polymorphisms, in exon 5 of the IL-1β gene, do not alter the encoded amino acid sequence. The previous work showed the homozygosity for the IL-1β (+3953T) allele has been associated with a fourfold increase in the production of IL-1β when compared to homozygosity for IL-1β (+3953C) allele [53]. Shinji et al. [54] found IL-1β plays an important role in mediating ischemic and excitotoxic damage in the retina in glaucoma. Pro-inflammatory cytokines such as IL-1, as well as other indicators of microglial activation, have been suggested as drivers of neuropathological changes in several neurodegenerative conditions. Taken together, these results suggest that IL-1α and IL-1β are common inflammatory components associated with POAG, and genetic variants in the IL-1α and IL-1β genes may play a role in susceptibility to POAG. Genes coding for the two isoforms of IL-1 (IL-1α and IL-1β) and for the IL-1 receptor antagonist (IL-1RA) are located within the IL-1 gene cluster at chromosomal locus 2q13. The possibility that linkage disequilibrium between IL-1α, IL-1β gene polymorphisms and other genes on chromosome 2 cause an increased POAG risk should be further investigated. The exact roles of IL-1α and IL-1β genes may need to be determined by proteomics in the future.

Medical treatment included primarily topical beta-blockers and prostaglandin in our study. The production of IL-1 depends on a variety of clinical factors. Published evidence reported that antiglaucoma eyedrops with preservatives may induce expression of cytokines (IL-1α, IL-1β, and IL-6) [55-57]. Goto et al. [55] reported that both timolol maleate and latanoprost can stimulate expression of IL-1α in human lens epithelial cells. Benzalkonium chloride, the most frequently used preservative in antiglaucoma eyedrops, is the damages lens epithelial cells and strongly stimulates the expression of IL-1α in these cells. Antiglaucoma eyedrops can lower IOP, but increase the level of IL-1α protein. Increased IL-1α protein may play a role in retinal ganglion cell death. These findings may explain why POAG progresses, despite IOP well controlled with the use of antiglaucoma eyedrops. Thus, the use of preservative-free antiglaucoma eyedrops should be preferable for hypotensive therapy due to lesser expression of IL-1α.

Controversy exists regarding whether or not there is an absolute increased level of IL-1α protein in the vitreous or plasma that coincides with an increased level in the retinal ganglion tissue of patients with POAG. The genotyping data from this work now allows us to identify potential subpopulations within POAG patients, namely carriers of the IL-1α (-889) T allele, who we predict may have an elevated level of circulating cytokines in the vitreous fluid. Such data will also further strengthen the current hypothesis that neuro-inflammation is a contributing component in the pathogenesis of POAG.

In conclusion, we found an increased risk for individuals carrying (-889) T allele in a Chinese population of POAG patients. Detection of this predisposing gene polymorphism in POAG may lead to early intervention and new strategies for prevention of POAG. Importantly, proper control of inflammation may become an additional therapeutic adjuvant in the treatment of POAG.

ACKNOWLEDGEMENTS

This work was supported by grants (TCVGH-T-947802) from the Taichung Veteran General hospital and Tunghai university Taichung, Taiwan, Republic of China, to Dr. Chun-Yuan Wang. We express our sincere thanks to Dr. M. Elizabeth Fini at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, for helpful comments during the preparation of this manuscript, and Dr. A.Y. Huang at Laboratory of Immunology, National Institutes of Health, Bethesda, for his contribution in correcting the English language of this paper.

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The print version of this article was created on 15 Nov 2006. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.