Association between HSPA5 Promoter Polymorphisms and a Reduced Risk of Normal Tension Glaucoma

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Abstract

Introduction: In normal tension glaucoma (NTG), factors other than elevated intraocular pressure (IOP) are likely to play a role in the pathogenesis of optic neuropathy. The potential similarities between Alzheimer’s disease (AD) and NTG in cellular apoptosis leading to neurodegeneration have been shown in recent studies. Heat Shock Protein family A member 5 (HSPA5) promoter polymorphisms have been reported to be associated with a risk of AD. The purpose of our study was to investigate the role of HSPA5 promoter polymorphisms in NTG patients.

Methods: A total of 222 patients with NTG, along with 236 normal controls were enrolled in this study. Genomic DNA was amplified through a polymerase chain reaction (PCR) and identified for the polymorphic HSPA5 (−415 and −370) by Xmn1 and BstY1 restriction digestion, respectively. PCR fragments with potential polymorphic HSPA5 (−180) were subjected to sequence-analyses by a Hex-labeled primer. Genotypes for both NTG patients and control groups were compared for statistically significant differences. Results: Polymorphisms (−415) G/A and (−180) del/G were completely linked in our population. The genotype and allele frequency distribution at the −415 G/A and −180 del/G sites showed a significant difference between the NTG cases and controls. The genotype frequency of HSPA5 (−415) AA/(−180) GG and the allele frequency of HSPA5 (−415) A/(−180) G were significantly lower (\( p = 0.04 \) and \( p = 0.01 \), respectively) in the NTG patients when compared with those in the control group. There was no significant difference in genotype or allele frequency distribution of the HSPA5 (−370) C/T between the NTG and control groups. There was a reduced risk of NTG associated with the carriers for the HSPA5 (−415) A/(−180) G allele compared with that in the control population (\( p = 0.01 \)). Conclusion: HSPA5 (−415) A and (−180) G allele polymorphisms may be protective factors in the development of NTG.

Introduction

Glaucoma is a degenerative optic neuropathy characterized by loss of retinal ganglion cells, cupping of the optic nerve head and visual field (VF) defects often related to elevated intraocular pressure (IOP). The disease...
affects approximately 76 million people worldwide and is the second most common cause of blindness [1]. Factors other than IOP are likely to have a role in the pathogenesis of glaucomatous optic neuropathy, particularly in individuals with normal tension glaucoma (NTG). NTG is a subtype of primary open angle glaucoma (POAG) and accounts for approximately 20–50% of all POAG [2]. Patients with NTG show IOP levels that are within the statistically normal diagnosis range and are usually present late in life when a VF defect has already occurred [3, 4]. Both genetic and environmental factors are thought to contribute to the pathophysiology of the disease. To assist in the early diagnosis of NTG, a genetic approach to identifying those risks involved in developing this disease is very attractive.

Despite the pathogenesis of glaucoma and Alzheimer’s disease (AD) in decreasing retinal nerve fiber layer (RNFL) is different, there are certain similarities in the pathways for neurological dysfunction between glaucoma and AD: both have an excess concentration of β-amyloid and a loss of thickness in the nerve fiber layer [5–7]. Our previous study found that the patients with NTG have a greater risk of developing AD [8]. Bayer et al. [9] and Tamura et al. [10] have shown a high frequency of NTG occurring in patients with AD. Vickers et al. [11] have presented evidence that the neuronal pathology of AD contributes to an aberrant regenerative response in nerve cells triggered by the gradual compression and physical damage to axons within the β-amyloid plaques that form in the brain [12]. In this regard, glaucoma may be viewed as a chronic neurodegenerative disease similar to AD [13, 14], and a slow buildup of β-amyloid in the ganglion cells may eventually trigger cell death and optic nerve axon loss. There is evidence that the HSPA5 may bind to the amyloid precursor protein and decrease β-amyloid deposits [15].

The HSPA5, also known as glucose-regulated protein (GRP78) 78 kDa or immunoglobulin heavy chain-binding protein (BiP), plays a key role in neuroprotection, preventing neuronal damage from apoptosis by assisting protein folding in the endoplasmic reticulum (ER) [16]. Previously, ER stress was reported to induce retinal ganglion cell death and functional impairment of trabecular meshwork cells in glaucoma models [17, 18]. The unfolded protein response system is activated by ER stress and generates chaperones to accelerate protein folding in ER lumen. Aside from being a chaperone, HSPA5 can initiate positive feedback to increase the transcriptional efficiency of chaperones through the unfolded protein response system [19].

Polymorphisms of the HSPA5 gene promoter region, including −415 G/A, −370 C/T, and −180 del/G, have been reported to be associated with AD. Additionally, the HSPA5 −415 A/−180 G allele has been found to play a protective role surrounding the risk of developing AD. Given the potential similarities in cellular events leading to neurodegeneration between AD and glaucoma, we have hypothesized that the HSPA5 promotor polymorphism may be a genetic factor predisposing affected individuals to glaucoma due to its effect on HSPA5 protein expression. Thus, we investigated the distribution of the HSPA5 promotor −415 G/A, −370 C/T, and −180 del/G polymorphisms in patients with NTG and compared them with a healthy control population.

Materials and Methods

Study Subjects

Subjects were enrolled at the outpatient clinic in the Department of Ophthalmology at Veterans General Hospital, Taichung, Taiwan, from 2017 to 2021. NTG patients were approached in the clinic, while they were seeking treatment. Normal control subjects were also recruited as they visited the outpatient clinic for various reasons. All the experimental subjects were enlisted after consenting to participate in the study. This study was implemented with the approval of the Human Study Committee of Veterans General Hospital, approval number: CF11117.

Comprehensive ophthalmologic examinations were performed for all subjects, including visual acuity testing with refraction, IOP measurement, Humphrey 30-2 VF test, slit-lamp examination, dilated fundoscopy, and OCT scanning. The definition of NTG included characteristic arcuate, Bjerrum, Seidel and/or paracentral scotoma and/or nasal step on Humphrey 30-2 with reference to Anderson’s criteria for minimal abnormality in glaucoma [20]; corresponding cupping of optic nerve heads and/or nerve fiber layer defects; open anterior chamber angles on gonioscopy; and absence of systemic disorder or a secondary cause for glaucomatous optic neuropathy such as a previously raised IOP after trauma, a period of steroid administration, or uveitis were required. Patients also did not have evidence of high myopia or congenital ocular abnormality and had no other cause than glaucoma for disc changes and VF loss. Patients with NTG were diagnosed with untreated IOP measurements 21 mm Hg or lower on the diurnal test and at follow-up. The Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) test was used for analysis of clinical parameters, including RNFL thickness, disc size, cup/disc (C/D) ratio, and rim area. Unrelated control subjects were recruited from those attending the clinic for condition of senile cataract, floater, refractive errors, or itchy eye. All normal control subjects had no systemic disease and no family history of glaucoma.

DNA Preparation and Genotype Identification

Blood samples (5 mL) were collected from each individual, with the genomic DNA isolated by a DNA extraction kit (Roche) according to the manufacturer’s manual. The biallelic SNPs of −415 G/A and −370 C/T were determined using polymerase chain
reaction (PCR). We used PCR to amplify the genomic DNA with a pair of primers as follows: 5′-TCAGAGACTGGATGGAGATGG-3′ (forward primer), 5′-TGGCTGCTATTCTGGTTTCTAACG (reverse primer), GAAANNNNTTC (Xmn1, −415 G/A), and RGATCY (BstY1, −370 C/T). The initial denaturation step was set at 94°C for 2 min, followed by 35 cycles at 92°C for 30 s, 56°C for 40 s, and 72°C for 30 s. The PCR product was then incubated at 37°C or 60°C for 90 min with BstY1 or Xmn1 (NEB), respectively. The digested DNA product was run on ethidium bromide-stained 2% agarose gel. The DNA product incubated with BstY1 either remained intact at 206 bps (C allele) or cut into two fragments of 174 and 32 bps (T allele). The digested product by the Xmn1 was preserved as a fragment at 304 bps (G allele) or separated into two fragments of 212 and 92 bp (A allele).

Hexachloro-fluorescein (HEX) sequencing was used to screen for genotype −180 del/G and genomic DNA was amplified by the following primers: 5′-HEX-CGGGGTCAGAAGTCGCAGGAGAGAT-3′ (forward primer) and RP2 5′-CGTTGGAGGCCTTCTGAAGCCTGTTCTACAC (reverse primer). The preliminary denatured temperature was set at 94°C for 2 min, followed by 35 cycles at 92°C for 20 s, 50°C for 30 s, and 72°C for 30 s. The amplified products were sequenced using electrophoresis in a linear polyacrylamide gel on an automated sequencer.

**Statistical Analysis**

The χ2 test and Fisher’s exact test were used to compare genotypes and allele frequencies between the control and NTG groups. Age and gender were compared between the control and NTG groups using the Mann-Whitney U test and χ2 test, respectively. Odds ratios were calculated to evaluate the strength of the association between the presence of each genotype and the clinical diagnosis of NTG. A p value of less than 0.05 was defined as statistically significant. All statistical analyses were performed by SPSS 27.0 (SPSS Inc., Chicago, IL, USA). Measures of pairwise linkage disequilibrium (LD) between SNPs, including Lewontin’s standardized disequilibrium coefficients (D′) and the squared pairwise correlations (Δ2), and eigenvalues (λs) were computed using the LDMAX software-part of the GOLD Command Line Tools package. Haplotype frequencies were determined using Haploview version 4.2.

| Mean age, years | NTG (n = 222) | Control (n = 236) | p value |
|----------------|---------------|------------------|---------|
| Male, %        | 55            | 54               | 0.89    |
| Mean IOP, mm Hg| 17±3.5        | 16±3.2           | 0.55    |
| VF mean deviation | −10.1±2.8  | −1.2±1.0         | <0.001  |
| VF PSD         | 7.5±2.4       | 1.6±1.0         | <0.001  |
| Optic disc size, mm2 | 2.11±0.58  | 2.01±0.44        | 0.79    |
| Rim area, mm2  | 1.26±0.38     | 1.48±0.30        | 0.02    |
| Vertical cup/disc ratio | 0.74±0.15 | 0.41±0.19         | <0.001  |
| RNFL thickness, μm | 68±13.5      | 95±16.6          | <0.001  |

IOP, intraocular pressure; SD, standard deviation; VF, visual field; RNFL, retinal nerve fiber layer; PSD, pattern standard deviation.

**Table 2. Pairwise LD measures for HSPA5 promotor Gene**

|          | −415 G/A   | −370 C/T   | −180 del/G |
|----------|------------|------------|------------|
| D’       | 1.42       | 1.00       | 1.00       |
| Δ2       | 1.00       | 0.37       | 0.4        |

Lewontin’s standardized disequilibrium coefficients (D’) are given above the diagonal and the squared pairwise correlations (Δ2) are given below the diagonal; the eigenvalues (λs) associated with the LD correlation matrix are given along the diagonal (bold and italic).

**Results**

The study group consisted of both 222 NTG patients (55% men, mean age 69 years at inclusion) and 236 normal controls (54% men, mean age 68 years at inclusion). There was no difference between the control and POAG groups in age and gender (p > 0.05). The mean IOP of the NTG patients and control subjects were both within the normal range (17 ± 3.5 and 16 ± 3.2, respectively). The mean vertical cup-disc ratio was 0.74 ± 0.15 in the NTG group and 0.41 ± 0.19 in the control group. Mean RNFL thickness was 68 ± 13.5 μm in the NTG group and 95 ± 16.6 μm in the control group. Demographic information is summarized in Table 1. No deviations from the Hardy-Weinberg equilibrium could be seen in either the NTG patients or the controls studies.

In this study, 115 of newly diagnosed NTG patients and 107 of NTG patients who have already been treated were enrolled. Patients were followed up for between 1 and 7 years (with a mean of 3 years). Eight patients had
received trabeculectomy. Of the NTG patients, 217 were prescribed with antiglaucoma eyedrops. All medical treatments included primarily topical beta-blockers, alpha-2 agonist, and prostaglandin analogue. Each patient used an average of 1.4 types of antiglaucoma drugs. Five patients did not need medication to control IOP after trabeculectomy.

The SNPspD method was employed for correction of multiple SNP testings. The pairwise linkage disequilibrium data are displayed in Table 2. As described by Cheverud [21], a high correlation among variables leads to high λs. In this case, the first λ (1.42) is less than 2 (the number of variables in the correlation matrix), suggesting that not all variables are completely correlated. The magnitude of pairwise LD was quantified by the metrics $D'$ and $\Delta^2$. The $D'$ coefficient of (−415) G/A and (−180) del/G was equal to 1 ($D' = 1.0$), strongly suggesting that there had been no recombination in the region, while a very strong LD was observed between the (−415) G/A and (−180) del/G sites ($\Delta^2 = 1.0$). SNPs (−415) G/A and (−180) del/G were completely linked in our study groups.

Table 3. Genotype, allele, and haplotype frequencies of HSPA5 (−415), (−370), and (−180)

| Genotype/allele       | Glaucoma (N = 222), n (%) | Control (N = 236), n (%) | Odds ratio (95% CI) | p value |
|-----------------------|---------------------------|--------------------------|---------------------|---------|
| **HSPA5(−415)/(−180)**|                           |                          |                     |         |
| G/G (del/del)         | 126 (56.8)                 | 108 (45.8)               | 1                   |         |
| G/A (del/G)           | 80 (36)                    | 101 (42.8)               | 0.6 (0.46–1.0)      | 0.05    |
| A/A (G/G)             | 16 (7.2)                   | 27 (11.4)                | 0.5 (0.26–0.99)     | 0.04    |
| G (del)               | 332 (74.8)                 | 317 (67.2)               | 1                   |         |
| A (G)                 | 112 (25.2)                 | 155 (32.8)               | 0.69 (0.51–0.91)    | 0.01    |
| **HSPA5(−370)**       |                           |                          |                     |         |
| C/C                   | 49 (22.1)                  | 58 (24.6)                | 1                   | NA      |
| C/T                   | 111 (50)                   | 118 (50)                 | 1.1 (0.7–1.7)       | 0.64    |
| T/T                   | 62 (27.9)                  | 60 (25.4)                | 1.2 (0.7–2.0)       | 0.44    |
| C                     | 209 (47.1)                 | 234 (49.6)               | 1                   |         |
| T                     | 235 (52.9)                 | 238 (50.4)               | 1.1 (0.85–1.43)     | 0.44    |
| **Haplotype**         |                           |                          |                     |         |
| (−415/−370/−180)      |                           |                          |                     |         |
| G-T-del               | 235 (53)                   | 238 (50)                 | 1                   |         |
| G-C-del               | 97 (22)                    | 79 (17)                  | 1.2 (0.88–1.76)     | 0.22    |
| A-C-G                 | 112 (25)                   | 155 (33)                 | 0.73 (0.54–0.99)    | 0.04    |

For −415 G/A and −180 del/G, all individuals had identical polymorphic genotypes. The genotype frequencies and allele frequencies of HSPA5 (−415)/(−180) were significantly different between the NTG patients and control subjects ($p = 0.04$ and 0.01, respectively). The genotype frequencies and allele frequencies of HSPA5 (−370) C/T were not significantly different.

Table 4. HSPA5 (−415) A/(−180) G allele carriage frequency

|                     | Glaucoma, n (%) | Control, n (%) | Odds ratio (95% CI) | p value |
|---------------------|-----------------|----------------|---------------------|---------|
| **HSPA5(−415)/(−180)**|                 |                |                     |         |
| AA + GA (GG + G/del)| 94 (42.3)       | 128 (54.2)     | 0.61 (0.42–0.89)    | **0.01**|
| GG (del/del)        | 128 (57.7)      | 108 (45.8)     | 1                   |         |
respectively). The GF of HSPA5 (−415) AA/(−180) GG was lower in the NTG group than the control group (7.2% vs. 11.4%, \( p = 0.04 \)), with less frequent (−415 A)/(−180 G) allele found among the NTG group than the control subjects (25.2% vs. 32.8%, \( p = 0.01 \), respectively). On the contrary, the results of HSPA5 (−370) C/T were not significantly different in either GF or AF. The haplotype distribution of the HSPA5 gene was significantly different, with less −415/−370/−180 A-C-G haplotype among the NTG group than that in the controls (25% vs. 33%, \( p = 0.04 \), respectively).

The HSPA5 (−415)/(−180) allele carriage frequency is further analyzed in Table 4. There are significantly less HSPA5 (−415) A/(−180) G allele carriers in the NTG group than in the control group (42.3% vs. 54.2%, \( p = 0.04 \), respectively).

**Discussion**

The contribution of genetic polymorphisms to NTG has not been studied extensively, and it is likely that multiple genes may be associated with the disease. Mutations in four genes, myocilin, optineurin, WDR36, and TBK1, have been implicated in NTG [22–27]. Mutation in the optineurin gene was initially reported in 16.7% of families experiencing hereditary POAG, with most of them having NTG [28]. Powell et al. [29] and Aung et al. [28] both reported that NTG demonstrates an association with polymorphisms of the OPA1 gene on chromosome 3, which is responsible for dominant optic atrophy in the Caucasian population [30]. Additionally, many more important gene variants have recently been associated with glaucoma risk, including apolipoprotein E (APOE) [11, 31], the endothelin receptor type A gene (EDNRA) [32, 33], IL-1 alpha [34], methylenetetrahydrofolate reductase (MTHFR) [35, 36], \( \beta \)-adrenergic receptors [37], and IL-6 [38]. However, these genes cannot interpret the overall inheritance susceptibility of NTG pathogenesis. Any other associations involved in the development of NTG should be further investigated.

This is the first study to investigate the polymorphisms of HSPA5 in Taiwanese NTG patients. Our interest in studying the role of HSPA5 polymorphism in NTG is due to the following reasons: First, recent evidence has shown that there is a close link between chronic neurodegenerative disease and HSPA5 expression. The death of retinal ganglion cells in glaucoma patients involving the accumulation of misfolded protein in ER mimics AD at the molecular level [39]. Glaucoma is inferred to be induced by ER stress [17, 40]. The HSPA5 gene plays a key role in neuronal protection via encoding chaperone proteins [41]. The reduction in ER stress was reported as a strategy in order to help alleviate optic neuropathy [42]. Second, the HSPA5 gene in humans is located on the long arm of chromosome 9 (9q33.3). Polymorphism in the HSPA5 gene clusters has been shown to occur in patients with bipolar disorder [43] and AD [44]. Some of these polymorphisms have been shown to alter the amount of HSPA5 produced. These allelic variants are also known to alter function. The HSPA5 transcriptional activity of the (−415) A/(−180) G alleles was significantly lower than that of the (−415) G/(−180) del alleles, whereas the induced HSPA5 expression after ER stress was evident in the cells with the (−415) A/(−180) G allele.

Since the genetic association analysis of HSPA5 promoter SNPs with NTG has never been reported, using a case-control study we found that the linked HSPA5 (−415) AA and (−180) GG genotypes and carriers of HSPA5 (−415) A/(−180) G allele offer a decreased risk of NTG. Our study indicates that HSPA5 (−415) A and (−180) G polymorphism may be protective factors for NTG.

LD reflects the nonrandom associations of alleles at the 3 promoter loci of the HSPA5 gene. HSPA5 (−415) G/A and (−190) del/G were completely linked (\( r^2 = 1.00 \)) in our study group. This LD pattern was similar to those previously reported in other studies, including those involving Chinese Han and Japanese populations [43, 44].

We found that HSPA5 promoter (−415) G/A and (−180) del/G polymorphisms may be associated with the development of NTG. Further studies involving NTG cohorts of different ethnic backgrounds are still needed however in order to confirm this association. The exact role of HSPA5 genes may need to be determined through proteomics in the future. Mechanisms underlying the association of HSPA5 polymorphism to NTG may suggest that any new therapeutic strategies target HSPA5 production and activity for treatment of NTG.

In our study, we have noted that HSPA5 (−415) A and (−180) G allele polymorphism may be protective factors surrounding the development of NTG. Along with the HSPA5 gene, previous studies have noted other HSP gene (HSP70-1) polymorphisms have been associated with an elevated risk of POAG [45–47]. Gene polymorphisms of HSP70 have been reported in glaucoma patients from Japan, Pakistan, and Poland. Tosaka et al. [48] found that the distribution of −110 A/C polymorphisms of HSP70-1 differed significantly between a normal population, and POAG and NTG patients in a Japanese population. The
190 G/C polymorphism of HSP70 has been found to be associated with primary angle closure glaucoma in a Pakistani population [49]. HSP70-1 190 G/C polymorphism has also been correlated with the progression of POAG in a Polish population [50].

Controversy still remains regarding whether or not there is an absolute increased level of HSPA5 protein in the vitreous body or plasma which coincides with an increased level in retinal ganglion tissue among patients with NTG. The genotyping data obtained in the present study may now enable researchers to identify potential subpopulations within NTG patients, who we predict are likely to have increased HSPA5 in their vitreous fluid. These data also further strengthen the current hypothesis that neuro-inflammation is a contributing component in the pathogenesis of NTG.

In conclusion, our results indicate that the HSPA5 (−415) A and (−180) G allele polymorphisms may be protective factors in the development of POAG. The data indicate that therapeutic strategies designed to induce HSPA5 protein production or activity may be a valuable treatment for NTG.

Statement of Ethics

This study protocol was reviewed and approved by the Human Study Committee of Veterans General Hospital, approval number: CF11117. All the experimental subjects have given their written informed consent to participate in the study.

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