Original Article

The genetic contribution of *HLA-E*01:03* and *HLA-E*01:03-G*01:01* to Posner-Schlossman syndrome in southern Chinese

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Background: The polymorphisms of classical *HLA-Ia* and *HLA-II* loci have been associated with Posner-Schlossman syndrome (PSS) in the southern Chinese population. However, the associations of non-classical *HLA-Ib* (e.g., *HLA-E* and *HLA-G*) loci with PSS have not been reported for in the southern Chinese population. This study aimed to evaluate the associations of the *HLA-E* and *HLA-G* loci with PSS in a southern Chinese Han population group.

Methods: Ninety-seven unrelated patients with PSS and 90 ethnically matched control subjects were recruited from the Shenzhen Eye Hospital in China. The full-length sequences of *HLA-E* and *HLA-G* genes were amplified by long-range high-fidelity PCR, and the third exon of the *HLA-E* gene and the coding region of the *HLA-G* gene were sequenced.

Results: The allele frequency of *HLA-E*01:03* in patients with PSS was significantly higher than that in the control group (P=0.017, corrected P=0.034, OR =1.66). The genotype frequencies of *HLA-E*01:01/01:03* and *HLA-E*01:03/01:03* in the PSS group were significantly higher than that in the control group (P=0.027, OR =2.62; P=0.011, OR =3.05; respectively). There were no significant differences in the frequency of *HLA-G* alleles and genotypes between the two groups (all P>0.05). The haplotype frequency of *HLA-E*01:03-G*01:01* in the PSS group was significantly higher than that in the control group (P=0.019, OR =1.63), although this association did not survive the Bonferroni correction (corrected P=0.13).

Conclusions: This study proved for the first time that *HLA-E*01:03* and *HLA-E*01:03-G*01:01* might be risk factors for PSS.

Keywords: Posner-Schlossman syndrome (PSS); *HLA-E; HLA-G*; genetic association; Chinese

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Introduction

Posner-Schlossman syndrome (PSS), also known as a glaucomatocyclitic crisis, was first reported by Posner and Schlossman in 1948 (1). PSS is a secondary glaucoma, which occurs in young adults. PSS is a self-limiting and recurrent eye disorder, and 24.3% of patients have more than 2 episodes per year, up to 12 episodes in some cases (2). The main clinical manifestations of PSS are the elevated intraocular pressure (IOP) in one eye with keratic precipitates

(KPs). Normally, symptoms in most patients can be relieved by using IOP-reducing and anti-inflammatory drugs, but many studies have shown that PSS is not a completely benign disease (3). Long-term recurrent PSS can lead to optic nerve damage and a reduced number of corneal endothelial cells. Permanent visual impairment can develop in severe cases. Anti-glaucoma surgery is needed in some patients with PSS because of inadequate disease control (3,4).

The human leukocyte antigen (*HLA*) gene is located in the short arm of chromosome 6 (6p21.31), with a total length of about 3.6 Mb. It is rich in polymorphism and takes part in immune response and the regulation of immune function (5). *HLA* gene polymorphisms are associated with a variety of eye diseases, such as uveitis, glaucoma, Graves' ophthalmopathy, and the transplant rejection after corneal transplantation (6-10). The polymorphisms of the classical *HLA-Ia* and *HLA-II* genes have been associated with PSS (11-13). The study of Hirose *et al.* [1985] first reported that the HLA-Bw54 and HLA-Bw54-Cw1 haplotype had a significantly higher frequency in Japanese patients with PSS than in normal controls (11). In two recent studies of the southern Chinese population, Zhao *et al.* found that *HLA-C*14:02*, *HLA-A*11:01-C*14:02* and *HLA-B*51:01-C*14:02* were associated with increased risk of PSS, while *HLA-B*13:01*, *HLA-DPA1*02:01*, *HLA-DPB1*14:01*, *HLA-DPB1*17:01*, *HLA-B*13:01-C*03:04* and *HLA-DPB1*14:01-DPA1*02:01* might be protective factors for PSS (12,13).

Non-classical *HLA-Ib (HLA-E* and *HLA-G*) molecules play an essential inhibitory role in innate and adaptive immunity (14,15). The receptors can recognize *HLA-E* molecules on natural killer (NK) cells and some cytotoxic lymphocytes (CTL) (CD94/NKG2 receptor) to regulate cytotoxic activity (15). *HLA-G* molecules can directly inhibit the function of immune cells (NK cells, CTLs, B cells, and dendritic cells) (14,15). *HLA-E* and *HLA-G* gene polymorphisms are closely related to viral infection, rejection after organ transplantation, tumor surveillance, and autoimmune system abnormalities (16-25). However, the correlation between *HLA-E* and *HLA-G* gene polymorphisms and the pathogenesis of PSS is still unclear. In this study, we evaluated the association between *HLA-E* and *HLA-G* gene polymorphisms and PSS in a southern Chinese Han population.

Methods

Patients and controls

Between December 2015 and December 2018, a total of 97 unrelated PSS patients were recruited from patients attending the Shenzhen Eye Hospital Clinic. The diagnosis of PSS was based on the following criteria (1-4,12,13): (I) single-eye onset in young adults, mild discomfort in the eye, and no significant decrease or slight decrease in visual acuity; (II) elevated IOP with recurrent episodes and mutton-fat KPs; (III) open iridocorneal angle under high IOP without peripheral anterior synechia; (IV) no visual field loss and optic nerve damage in patients with shorter course of disease; and (V) no history of other eye diseases except for refractive error. Ninety unrelated subjects were recruited at the Shenzhen Blood Center from healthy volunteer blood donors with normal IOP and optic discs. Patients and controls were all southern Han Chinese and matched on age, sex, and ethnicity. The study protocol was approved by the Ethics Committee of Shenzhen Eye Hospital and was in accordance with the tenets of the Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all study participants.

DNA extraction

DNA was extracted from peripheral blood samples of all participants using the MagCore nucleic acid extraction kit according to the instructions of the manufacturer (Promega Corporation, Madison, WI, USA).

Polymerase chain reaction (PCR) amplification

The full-length sequences of *HLA-E* and *-G* were amplified by long-range high-fidelity PCR. PCR amplification was performed in a 20 μL reaction system, including 0.5 μL pfuUltraTM Fusion HS DNA polymerase, 2 μL of 10× pfuUltraTM Rxn Buffer, 1 μL of dNTP (2.5 mmol/L) mixture, 0.5 μL of each PCR primer (10 μmol/L, *Table 1*), 14.5 μL ddH_2O, and 1 μL genomic DNA.

The PCR products were purified using a magnetic bead reagent before the sequencing reaction to remove non-specific products generated during PCR amplification. Eighteen μL Mag-Bind EZ Pure magnetic beads were added to each well and mixed thoroughly. After standing for 10 min, the plate was placed on a magnetic stand. After adsorbing on the magnetic beads for 10 min, the supernatant was discarded. 200 μL of 70% ethanol was used to wash twice for 1 min. After standing at room temperature for 20 min for the ethanol completely evaporated, 30 μL of ddH_2O was added to each well to

Table 1 PCR primers for amplification of *HLA-E* and *HLA-G* genes

PCR primer	Nucleotide position	Primer sequence (5'→3')	Amplicon size (bp)
HLA-E-PCR-F	–75	CAGCGTCGCCACGACTCCCGAC	3,600
HLA-E-PCR-R	3502	CCTAAGTGCTGGGATTACAGG	
HLA-G-PCR-F	–294	AGAACGCTTGGCACAAGAGTA	3,100
HLA-G-PCR-R	2776	CCTCAACAACCCACACACATC	

F, forward; R, reverse.

Table 2 Sequencing primers for *HLA-E* and *HLA-G* genes

Sequencing primer	Nucleotide position	Primer sequence (5'→3')	Target exon
HLA-E-SEQ-3F	549	AGATTCACCCCAAGGCTG	3
HLA-E-SEQ-3R	1061	TCCCTGTTTCTTCTAC	
HLA-G-SEQ-1F	282	ACAAGAGTAGCGGGGTCAG	1
HLA-G-SEQ-1R	250	GATGAAGCGGGGCTCCCCGCG	
HLA-G-SEQ-2F	201	CTCCCACTCCATGAGGTAT	2
HLA-G-SEQ-2R	780	CGAGGTAATCCTTGCCATCGT	
HLA-G-SEQ-3F	706	ACCCTCCAGTGGATGATTG	3
HLA-G-SEQ-3R	1276	GAGGCAGAGAACAAGCCTG	
HLA-G-SEQ-4F	1252	CTTGGCACCAGGACTTTTC	4
HLA-G-SEQ-4R	1771	TGCTCCTCTCCAGAAGGCAC	
HLA-G-SEQ-5F	1778	CTGGAGAGGAGCAGAGATA	5
HLA-G-SEQ-5R	2281	CCATCACTACAATCATCAAG	
HLA-G-SEQ-6F	2291	GTAGTGATGGGGACCTGAT	6
HLA-G-SEQ-6R	2776	CTCAACAACCCACACACAT	

F, forward; R, reverse.

collect the purified products.

Selection of polymorphisms and genotyping

Because the *HLA-E*01:01* allele and the *HLA-E*01:03* allele are different at the rs1264457 site of the third exon, exon 3 of the *HLA-E* gene was selected for sequencing (26,27). Since there are 43 single nucleotide polymorphism sites in the *HLA-G* gene according to the IMGT/HLA database (http://www.ebi.ac.uk/ipd/imgt/hla/, Release 3.36.0, 2019 April), the coding region of the *HLA-G* gene was sequenced. The sequencing primers were listed in *Table 2*.

The sequencing reaction products (10 μL) were purified by adding 2.5 μL NaOAc/EDTA and 50 μL of 80% ethanol to each well, mixed well, and centrifuged at 3,000 g for 30 min. Two hundreds μL of 80% ethanol was used to wash again, centrifuged at 3,000 g for 5 min. After standing at room temperature for 20 min for the ethanol completely evaporated, a 15 μL formamide solution was added to dissolve the products and denatured at 95 ℃ for 2 min. Electrophoresis of the purified sequencing reaction products was done in an ABI 3730 sequencer (Applied Biosystem, Foster City, CA, USA).

The sequencing reaction products were electrophoresed in an ABI 3730 sequencer (Applied Biosystem, Foster City, CA, USA). The sequence data was imported into the Assign 3.5 genotype calling. *HLA* genotypes were assigned at the four-digit level. *HLA* haplotypes were analyzed using the Arlequin 3.5.1 software.

Statistical analysis

Statistical analysis was performed using SPSS (version 20.0, SPSS Inc., Chicago, IL, USA). Age and IOP were compared between patients with PSS and controls using independent-samples *t*-test. Hardy-Weinberg equilibrium (HWE) was evaluated using the chi-squared test. The difference in sex, allele frequency, genotype frequency, and haplotype frequency between cases and controls were evaluated using the chi-squared test or Fisher's exact test. The maximum expectation algorithm determined haplotype frequency in the Arlequin 3.5.1 software. Multiple testing was corrected using the Bonferroni method. P<0.05 was considered statistically significant. Odds ratio (OR) and 95% confidence interval (CI) were calculated whenever applicable.

Results

Demographic and clinical features of participants

There were 46 (47.4%) males and 51 (52.6%) females in the PSS group, with an average age of 41.5±12.9 years. In the control group, there were 45 (50.0%) males and 45 (50.0%) females, with an average age of 40.4±12.0 years. No significant difference in sex and age was found between cases and controls (P=0.73 and 0.55, respectively, *Table 3*). The mean IOP was 44.5±7.9 mmHg in patients with PSS while 15.3±3.5 mmHg in controls. The IOP in cases was significantly higher than that in controls (P<0.001, *Table 3*).

Table 3 The demographic and clinical features of the PSS cases and controls

Feature	PSS (n=97)	Controls (n=90)	P
Sex (M/F)	46/51	45/45	0.73[a]
Age (year, mean ± SD)	41.5±12.9	40.4±12.0	0.55[b]
IOP (mmHg, mean ± SD)	44.5±7.9	15.3±3.5	<0.001[b]
KPs (Y/N)	Y	N	

[a], Chi-squared test; [b], independent-samples *t*-test. PSS, Posner-Schlossman syndrome; M, male, F, female; IOP, intraocular pressure; KPs, keratic precipitates; Y, yes; N, no.

HLA-E allele and genotype frequencies

Two alleles (*E*01:01* and *E*01:03*) and three genotypes (*E*01:01/01:01*, *E*01:01/01:03* and *E*01:03/01:03*) at the *HLA-E* locus were detected in both PSS and control groups (*Table 4*). The genotype distributions of *HLA-E* in both groups were following HWE (P>0.11; data not shown). The allele frequency of *HLA-E*01:03* in patients with PSS was significantly higher than that in the control group (P=0.017, OR =1.66, 95% CI: 1.09–2.53, *Table 4*), which survived the Bonferroni correction (corrected P=0.034). The genotype frequencies of *HLA-E*01:01/01:03* and *HLA-E*01:03/01:03* in the PSS group were significantly higher than that in the control group (P=0.027, OR =2.62, 95% CI: 1.10–6.22; P=0.011, OR =3.05, 95% CI: 1.27–7.35, respectively, *Table 4*).

HLA-G allele and genotype frequencies

Four alleles at the *HLA-G* locus were detected in the PSS group (*G*01:01*, *G*01:04*, *G*01:05N* and *G*01:06*) and control group (*G*01:01*, *G*01:03*, *G*01:04* and *G*01:06*) respectively (*Table 5*). Five genotypes (*G*01:01/01:01*, *G*01:01/01:04*, *G*01:04/01:04*, *G*01:01/01:05N* and *G*01:01/01:06*) were detected in the PSS group, while 6

Table 4 *HLA-E* allele and genotype frequencies of the PSS cases and controls

Variable	Count (%)	Count (%)	P	OR (95% CI)
Allele	PSS (2n=194)	Controls (2n=180)		
*E*01:01*	64 (33.0)	81 (45.0)		1.00 (ref.)
*E*01:03*	130 (67.0)	99 (55.0)	0.017	1.66 (1.09–2.53)
Genotype	PSS (n=97)	Controls (n=90)		
*E*01:01/01:01*	10 (10.3)	22 (24.4)		1.00 (ref.)
*E*01:01/01:03*	44 (45.4)	37 (41.1)	0.027	2.62 (1.10–6.22)
*E*01:03/01:03*	43 (44.3)	31 (34.4)	0.011	3.05 (1.27–7.35)

P was assessed using a Chi-squared test. PSS, Posner-Schlossman syndrome; OR, odds ratio; CI, confidence interval; ref., reference.

Table 5 *HLA-G* allele and genotype frequencies of the PSS cases and controls

Variable	Count (%)	Count (%)	P	OR (95% CI)
Allele	PSS (2n=194)	Controls (2n=180)		
*G*01:01*	142 (73.2)	121 (67.2)		1.00 (ref.)
*G*01:04*	50 (25.8)	56 (31.1)	0.24	0.76 (0.48–1.20)
*G*01:03*	0 (0.0)	2 (1.0)	0.21	2.17 (1.91–2.48)
*G*01:05N*	1 (0.5)	0 (0.0)	1.00	1.85 (1.66–2.07)
*G*01:06*	1 (0.5)	1 (0.6)	1.00	1.70 (0.15–19.03)
Genotype	PSS (n=97)	Controls (n=90)		
*G*01:01/01:01*	52 (53.6)	45 (50.0)		1.00 (ref.)
*G*01:01/01:04*	36 (37.1)	30 (33.3)	0.91	1.04 (0.55–1.95)
*G*01:04/01:04*	7 (7.2)	12 (13.3)	0.18	0.50 (0.18–1.39)
*G*01:01/01:03*	0 (0.0)	1 (1.1)	0.47	0.29 (0.01–7.27)
*G*01:01/01:05N*	1 (1.0)	0 (0.0)	1.00	2.60 (0.10–65.41)
*G*01:01/01:06*	1 (1.0)	0 (0.0)	1.00	2.60 (0.10–65.41)
*G*01:03/01:04*	0 (0.0)	1 (1.1)	0.47	0.29 (0.01–7.27)
*G*01:04/01:06*	0 (0.0)	1 (1.1)	0.47	0.29 (0.01–7.27)

P was assessed using Chi-squared test or Fisher's exact test. PSS, Posner-Schlossman syndrome; OR, odds ratio; CI, confidence interval; ref., reference.

genotypes (*G*01:01/01:01*, *G*01:01/01:04*, *G*01:04/01:04*, *G*01:01/01:03*, *G*01:03/01:04* and *G*01:04/01:06*) were detected in the control group (*Table 5*). The top three *HLA-G* genotypes were *G*01:01/01:01*, *G*01:01/01:04*, *and G*01:04/ 01:04*. The genotype distributions of *HLA-G* polymorphisms in both PSS and control groups were in accordance with HWE (P>0.11; data not shown). There was no significant difference in the frequency of *HLA-G* alleles and genotypes between the two groups (P>0.05, *Table 5*).

HLA-E-G haplotype frequencies

In PSS and control groups, seven haplotypes were detected (*Table 6*). The top 3 *HLA-E-G* haplotypes were *E*01:03-G*01:01*, *E*01:01-G*01:04*, and *E*01:01-G*01:01*. The haplotype frequency of *HLA-E*01:03-G*01:01* in the PSS group was significantly higher than that in the control group (P=0.019, OR =1.63, 95% CI: 1.08–2.46, *Table 6*), although this association did not survive the Bonferroni correction (corrected P=0.13). No significant difference in the other haplotypes was found between the two groups (all P>0.05, *Table 6*).

Discussion

HLA-E and *HLA-G* gene polymorphisms affect their expression levels and immune function (26-28). The *HLA-E* and *HLA-G* alleles exhibit limited polymorphisms, with only ten 4-digit *HLA-E* alleles and twenty-two 4-digit *HLA-G* alleles (IMGT/HLA, http://www.ebi.ac.uk/ipd/imgt/hla/, Release 3.36.0, 2019 April). In this study, the distributions of *HLA-E* and *HLA-G* alleles in the control group are similar to those in the normal Chinese Han population (*Table 4*) (21,24,29).

The frequency of the *HLA-E*01:03* allele in the PSS group was significantly higher than that in the control group (*Table 4*), suggesting that the *HLA-E*01:03* allele is a susceptibility gene for PSS. The *HLA-E*01:03* allele has been associated with cytomegalovirus (CMV) infection in patients after kidney transplantation, chronic hepatitis B, rheumatoid arthritis, pemphigus vulgaris, nasopharyngeal carcinoma and ovarian cancer, while the *HLA-E*01:01* allele is a protective gene for diseases such as hepatitis C virus infection, Behcet's disease and Hodgkin's lymphoma (16-23,25). The difference between the *HLA-E*01:01* allele-encoded protein ($HLA\text{-}E^{R}$) and the *HLA-E*01:03* allele-

Table 6 *HLA-E-G* haplotype frequencies of the PSS cases and controls

Haplotype	PSS (2n=194), count (%)	Controls (2n=180), count (%)	P	OR (95% CI)
*E*01:01-G*01:01*	31 (16.0)	38 (21.1)	0.20	0.71 (0.42–1.20)
*E*01:01-G*01:04*	32 (16.5)	40 (22.2)	0.16	0.69 (0.41–1.16)
*E*01:03-G*01:01*	112 (57.7)	82 (45.6)	0.019	1.63 (1.08–2.46)
*E*01:03-G*01:04*	17 (8.8)	17 (9.4)	0.82	0.92 (0.46–1.86)
*E*01:01-G*01:03*	0 (0.0)	2 (1.1)	0.23	0.18 (0.01–3.85)
*E*01:01-G*01:06*	1 (0.5)	1 (0.6)	1.00	0.93 (0.06–14.94)
*E*01:03-G*01:05N*	1 (0.5)	0 (0.0)	1.00	2.80 (0.11–69.14)

P was assessed using Chi-squared test or Fisher's exact test. PSS, Posner-Schlossman syndrome; OR, odds ratio; CI, confidence interval; ref., reference.

encoded protein (HLA-E^G) is caused by the nucleotide change from adenine to guanine (A→G) at the rs1264457 site (16,27). Compared with HLA-E^R, HLA-E^G is characterized by the higher expression on the surface of NK cells, higher affinity for binding to receptors, and higher stability of binding to signal peptides (26,27). Besides, several studies have shown that CMV infection may be the main pathogenic factor of PSS (3), which might inhibit the immune surveillance function through HLA-E molecules. For example, the CMV UL40 protein has a similar structure to the HLA-E signal peptide, which can up-regulate the expression of HLA-E molecules on the cell surface and enhance the binding of HLA-E molecules to inhibitory receptors (CD94/NKG2A), inhibiting the immune function of NK cells or some CTLs (30).

Polymorphisms in the coding region of the *HLA-G* gene can affect the coding of nucleotides. For example, the *HLA-G*01:13N* allele changes the first base of codon 54 (α1 domain) from cytosine to thymine (C→T), ending the coding early, resulting in the inability to synthesize the HLA-G protein (28). The *HLA-G*01:05N* allele deletes the last nucleotide of codon 129 or in the first nucleotide of codon 130 (exon 3), causing a stop codon in advance at the codon 189, which encodes an incomplete HLA-G protein, affecting its function (28). The *HLA-G*01:04* and *HLA-G*01:05N* alleles are susceptibility genes for habitual abortion (23). The *HLA-G*01:05N* allele is also a protective gene for HIV infection, while the *HLA-G*01:01:08* allele is a susceptibility gene for HIV infection (21). In this study, we did not find a significant difference in the *HLA-G* allele and genotype frequency between patients with PSS and controls (*Table 5*), indicating that the *HLA-G* gene polymorphisms might not be related to PSS in the southern Chinese Han population.

The *HLA-E* and *HLA-G* loci are adjacent loci at 660 kb. Studies have reported that *HLA-E* and *HLA-G* polymorphisms are simultaneously related to a variety of diseases. For instance, both the *HLA-E*01:03* allele and the *HLA-G 14bp* INS/DEL polymorphism are associated with CMV infection (31,32). Both *HLA-E*01:03* and *HLA-G*01:05N* alleles are protective factors for HIV-1 infection (33). The *HLA-E*01:01* allele and the *HLA-G*01:01:01* allele are both protective factors for Behcet's disease (34). We found that the haplotype frequency of *HLA-E*01:03-G*01:01* was higher in the PSS group than in the control group (*Table 6*), despite this association did not survive the Bonferroni correction. We hypothesized that the *HLA-G*01:01* encoded protein as a signal peptide can enhance the stability of the *HLA-E*01:03* encoded HLA-E^G peptide complex and inhibited the function of NK cells or some CTLs so that the *HLA-E*01:03-G*01:01* haplotype may be more likely to promote the pathogenesis of PSS. Further research must reveal the underlying mechanisms. We reported for first time that polymorphisms of non-classical *HLA-Ib* genes (i.e., *HLA-E* and *HLA-G*) were associated with PSS in the southern Chinese Han population. We found that the *HLA-E*01:03* allele was a susceptibility gene for PSS, and the *HLA-E*01:03-G*01:01* haplotype might be a risk factor for PSS. Further investigation into the expression of HLA-E and HLA-G molecules at the transcriptional and protein levels is required to must evaluate their role in the pathogenesis of PSS.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were following the ethical standards of the local Ethics Committee of Shenzhen Eye Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all study participants.

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