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Association of *Interleukin 6* gene polymorphisms with genetic susceptibilities to spastic tetraplegia in males: A case-control study

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ABSTRACT

Background: Cerebral palsy (CP) is a group of non-progressive motor impairment and permanent disorders causing limitation of activity and abnormal posture. It may be caused by infection (such as chorioamnionitis), asphyxia or multiple genetic factors. The *Interleukin 6* gene (*IL6*) was suggested to be involved in the susceptibilities to CP risk as a kind of proinflammatory cytokine.
Objective: To explore the genetic association between the polymorphisms of the *IL6* gene and CP in the Chinese population.
Methods: A total of 542 CP patients and 483 healthy control children were recruited in this study to detect five single nucleotide polymorphisms (rs1800796, rs2069837, rs2066992, rs2069840, and rs10242595) in the *IL6* locus. Genotyping of SNPs was performed by the MassArray platform-based genotyping approach. The SHEsis program was applied to analyze the genotyping data.
Results: Of the five selected SNPs, no significant allelic and genotypic association was found between CP patients and controls. However, subgroup analysis found significant differences in allele frequencies between spastic tetraplegia in males compared with controls at rs1800796 (OR = 1.39, $P = 0.033$, $P = 0.099$ after SNPSpD correction) and rs2069837 (OR = 1.58, $P = 0.012$, $P = 0.035$ after SNPSpD correction). The frequencies of the C allele of rs1800796 and the A allele of rs2069837 were greater in males with spastic tetraplegia than in the controls. The two SNPs haplotype rs1800796 (G) – rs2069837 (G) were also associated with a decreased risk of spastic tetraplegia in males (OR = 0.619, $P = 0.009$, $P = 0.027$ after Bonferroni correction).
Conclusion: Genetic variation of the *IL6* gene may influence susceptibility to spastic tetraplegia in males and its role in cerebral palsy deserves further evaluation in a large-scale and well-designed study.
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1. Introduction

Cerebral palsy (CP) is defined as a group of permanent disorders of movement and posture, which is often accompanied with disturbances of sensation, perception, cognition, communication, as well as epilepsy, and secondary musculoskeletal problems [1]. Its prevalence is about 2.0/1000 in different investigated populations [2,3]. Despite being commonly attributed to a range of environmental factors, particularly birth asphyxia, genetic factors may contribute to CP risk as suggested by familial aggregation of CP in groups with high consanguinity and by the observation of increased familial risk for CP in a national Swedish database. The estimated contribution of genetic causes to congenital idiopathic CP was more than 40% [4]. A growing body of evidence suggests that cerebral palsy is probably caused by multiple genetic factors, similar to other neurodevelopmental disorders such as autism and intellectual disability [5–23].

The *Interleukin 6* gene (*IL6*) is a pleiotropic cytokine with various activities that regulate the inflammatory and acute phase reaction responses, hematopoiesis, ischemic injury, and brain development. It was previously noted to be associated with CP risk in several studies [11,15]. The polymorphism rs1800795 (G-174C), involved in the regulation of *IL6* expression [24–26], was associated with hemiplegia (OR, 1.38; 95% CI, 1.05–1.83) and quadriplegic CP (OR, 10.42; 95% CI, 1.34–80.82) within the infants born 32–36 weeks gestational

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age in Australia [12]. Furthermore, it was also linked with clinical chorioamnionitis and preterm birth, with a three-fold increased risk for the development of cystic periventricular leukomalacia (PVL, a leading cause of cerebral palsy in preterm infants) in the preterm infants (OR, 3.1; 95% CI, 1.1–8.7) [16,17]. Therefore, *IL6* appears to be closely related to susceptibility to CP.

Even though strong evidence for association was reported and confirmed in Caucasians [15–17], the studies focused only on one polymorphism (rs1800795) of *IL6*. We conducted a replicate genetic study on polymorphisms from different regions of the *IL6* gene in another population to further evaluate the importance of *IL6* in the etiology of CP.

2. Methods

2.1. Study population

This is a Chinese Han population-based case-control study. All subjects are genetically unrelated children from centers for CP rehabilitation in the Third Affiliated Hospital of Zhengzhou University, Zhengzhou Children's Hospital and the First Affiliated Hospital of the Henan Traditional Chinese Medical College. CP was defined as a chronic disability of brain origin, characterized by aberrant control of movement or posture, appearing early in life, and not the result of progressive disease. A total number of 383 male and 159 female patients with CP were recruited (age = 18.3 ± 15.4 months). Among them, 152 boys (39.7% of male patients) and 48 girls (30.2% of female patients) were diagnosed with spastic tetraplegia. Controls were consisted of 318 male and 165 female healthy children from the same area with a mean age of 18.4 ± 18.9 months. The control subjects were frequency-matched to the patients based on age, gender and place of residence. CP patients were diagnosed by two child neurologists either by clinical examination or by using medical records. Children with hypotonia, ataxia, myopathy, genetic syndrome or chromosomal anomaly were excluded. Informed consent was obtained for all tested individuals. The research protocol was reviewed and approved by the Zhengzhou University Ethics Committee.

2.2. Polymorphism selection

The SNP rs1800795 was excluded from further tests for association with CP because it was present at very low frequency in our samples. Five SNPs, rs1800796, rs2069837, rs2066992, rs2069840, and rs10242595 were selected from the International HapMap Project (HapMap Data PhaseIII/Rel#2, Feb09, on NCBI B36 assembly, dbSNP b126) spanning 8 kb in the *IL6* locus (7p21, NT_007819.17). All of rs2069837, rs2066992 in the second intron and rs2069840 in the third intron are tag SNPs. rs1800796 and rs10242595 are located in upstream and downstream of the *IL6* gene, respectively.

2.3. Genotyping

Genomic DNA was extracted from the peripheral blood by using the AxyPrep Blood Genomic DNA Miniprep Kit (Axygen Biotechnology, USA) according to its standard protocol. Probes and primers were designed by the SEQUENOM online tools (https://www.mysequenom.com) and the sequences are available upon request. After the amplification of Polymorphism-spanning fragments by multiplex PCR, genotyping was performed by the Sequenom MassArray SNP genotyping platform (Sequenom, San Diego, CA, USA). Five percent of random samples were used for quality control to verify repeatability and accuracy of the experiment.

2.4. Statistical analysis

Gender and age frequencies between patients and controls were compared by using a 2-sided chi-square test and an independent-sample *t*-test, respectively. Other statistical items such as Hardy–Weinberg equilibrium test, comparison of allele and genotype frequencies, estimation for pairwise linkage disequilibrium (LD), haplotype association analysis, odd ratios (OR) and 95% confidence interval (95% CI) were performed by SHEsis online software platform (http://analysis.bio-x.cn/myAnalysis.php) [27,28]. The multiple testing on each individual SNP was corrected by the SNPSpD program (http://gump.qimr.edu.au/general/daleN/matSpD/), which was based on the linkage disequilibrium information.

3. Theory

Previous studies showed that polymorphism in the *IL6* gene was associated with increased risk for CP [15,21]. The objective of this study is to investigate whether the polymorphisms of the *IL6* gene confer an increased risk for CP in the Chinese population.

4. Results

4.1. Association between SNPs, haplotypes and risk for overall CP

Single-locus association analyses of allelic and genotypic frequencies in each group are presented in Table 1. Genotype frequencies of these polymorphisms in controls showed no significant

Table 1
Allele and genotype distributions of the five selected SNPs in total cases and controls.

Group	Allele frequency		*P*-value	Genotype frequency			*P*-value
rs1800796	C	G		C/C	C/G	G/G	
CP	746 (0.691)	334 (0.309)	0.225	268 (0.496)	210 (0.389)	62 (0.115)	0.213
Control	643 (0.666)	323 (0.334)		215 (0.445)	213 (0.441)	55 (0.114)	
rs2069837	A	G		A/A	A/G	G/G	
CP	870 (0.807)	208 (0.193)	0.174	361 (0.670)	148 (0.275)	30 (0.056)	0.113
Control	753 (0.783)	209 (0.217)		296 (0.615)	161 (0.335)	24 (0.050)	
rs2066992	G	T		G/G	G/T	T/T	
CP	338 (0.312)	746 (0.688)	0.430	62 (0.114)	214 (0.395)	266 (0.491)	0.347
Control	315 (0.328)	645 (0.672)		52 (0.108)	211 (0.440)	217 (0.452)	
rs2069840	C	G		C/C	C/G	G/G	
CP	992 (0.915)	92 (0.085)	0.619	452 (0.834)	88 (0.162)	2 (0.004)	0.878
Control	878 (0.909)	88 (0.091)		397 (0.822)	84 (0.174)	2 (0.004)	
rs10242595	A	G		A/A	A/G	G/G	
CP	964 (0.893)	116 (0.107)	0.671	432 (0.800)	100 (0.185)	8 (0.015)	0.872
Control	853 (0.887)	109 (0.113)		381 (0.792)	91 (0.189)	9 (0.019)	

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