Implication of IL-33 gene polymorphism in Chinese patients with Alzheimer’s disease

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Abstract

Interleukin-33 (IL-33), a newly described member of the IL-1 family, is located on chromosome 9p24, a chromosomal region of interest in Alzheimer’s disease (AD) defined by many genome-wide studies. Three intronic rs1157505, rs11792633, and rs7044343 single nucleotide polymorphisms (SNPs) within IL-33 have recently been reported to be associated with risk of AD in Caucasian populations. In order to assess the involvement of the IL-33 polymorphisms in the risk of developing late onset AD (LOAD), we analyzed the genotype and allele distributions of these 3 polymorphisms in 704 Han Chinese subjects. The minor alleles of the rs11792633 polymorphism within IL-33 was significantly associated with a reduced risk of LOAD (odds ratio [OR] = 0.73, p = 0.005). Furthermore, rs11792633 polymorphism was still strongly associated with LOAD (dominant model: OR = 0.67, p = 0.015; recessive model: OR = 0.57, p = 0.021; additive model: OR = 0.71, p = 0.004) after adjusting for age, gender, and the apolipoprotein E (APOE) ε4 status. Our results support the evidence that genetic variants of IL-33 affect susceptibility to LOAD in Han Chinese.

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1. Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia in the elderly, with a prevalence of over 35 million worldwide (Querfurth and LaFerla, 2010). Considerable evidence gained over the past decade has supported that the risk of AD is substantially influenced by genetic variation in the inflammatory agents, including interleukin (IL)-1, IL-1β, IL-6, IL-18, tumor necrosis factor α (TNF-α) (Di Bona et al., 2008, 2009; Vasto et al., 2008; Yu et al., 2009). Recently, 3 intronic rs1157505, rs11792633, and rs7044343 single nucleotide polymorphisms (SNPs) within IL-33 have been reported to be associated with risk of AD in 3 independent case-control studies and a prospective population-based study from the Caucasian populations (Chapuis et al., 2009). Furthermore, functional studies have shown that these polymorphisms were associated with less cerebral amyloid angiopathy (CAA) in the brain of non-apolipoprotein E (APOE) ε4 AD cases, ultimately leading to a specific decrease in secretion of the amyloid-β40 (Aβ40) peptide. As variants and their frequencies of chromosome IL-33 in various ethnic groups might be different, replication is needed to confirm the potential effects of chromosome IL-33 in other groups. To date, genetic variability of IL-33 has not been examined among Asians. To address this question, we conducted the first genetic association study on IL-33 in an Asian (Chinese) cohort of AD and controls.
2. Methods

2.1. Subjects

Our study comprised of 322 sporadic late onset AD (LOAD) (age at onset ≥65 years) patients (women 179; mean age: 76.53 ± 5.64 years) and 382 healthy controls (women 207; mean age: 75.71 ± 4.82 years) matched for gender and age. All the above subjects were Northern Han Chinese in origin. The patients were recruited from the Department of Neurology of the Qingdao Municipal Hospital, and several other hospitals in Shandong Province. A clinical diagnosis of probable AD was established according to the criteria of National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s disease and Related Disorders Association (NINCDS–ADRDA) (McKhann et al., 1984). No AD patient had a family history of dementia. The control groups were confirmed healthy and neurologically normal by medical history, general examinations, laboratory examinations, and Mini Mental State Examination (MMSE) score ≥28. An informed consent to participate in this study was obtained from each subject or from a guardian, and the protocol of this study was approved by the Ethical Committee of Qingdao Municipal Hospital.

2.2. Genotyping

The polymorphisms at positions rs11792633, rs11792633, and rs7044343 within IL-33 were genotyped by Beijing Genomics Institute (BGI, Shenzhen, China) using MALDI-TOF MS assay (MassArray™, Sequenom, Inc., San Diego, CA, USA). Polymerase chain reaction (PCR) and extension primers were designed using the Sequenom MassARRAY assay-design software (version 3.1; Sequenom Inc, San Diego, CA, USA). Details are available from the authors upon request. Twenty randomly selected DNA samples from each genotype were sequenced to validate the genotyping by MALDI-TOF MS. Results of the MALDI-TOF MS method corresponded with the results of sequencing. APOE genotypes were determined as the method described by Donohoe et al. (1999).

2.3. Statistical analysis

Hardy-Weinberg equilibrium was assessed using the chi-square test. Genotype and allele distributions were compared using the chi-square test. Differences in allele and genotype distribution between cases and controls were analyzed using logistic regression adjusted for age, gender, and APOE \( \varepsilon 4 \) status under various genetic models. The \( p \) value, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Estimation of the statistical power was performed with the STPLAN 4.3 software. Data were analyzed using a commercially available statistical package (SPSS version 11.5, SPSS, Inc., Chicago, IL, USA). The criterion for significant difference is \( p < 0.05 \).

3. Results

Because no rs1157505 polymorphism was detected in any of the 704 subjects, only the wild-type was present in this study. Allelic and genotype frequencies of rs11792633 and rs7044343 SNPs in LOAD patients and controls are reported in Table 1. Distributions of the IL-33 and APOE polymorphisms in both patients and controls did not deviate from those predicted by the Hardy-Weinberg equilibrium except for the rs7044343 polymorphism in control group (\( p = 0.045 \)). For rs11792633, there were significant differences in genotype and allele frequencies between AD and control (genotype \( p = 0.018 \), allele \( p = 0.005 \)). The minor
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