Neuroscience Letters 541 (2013) 111–115

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Polymorphisms in immune/inflammatory cytokine genes are related to Parkinson's disease with cognitive impairment in the Han Chinese population

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HIGHLIGHTS

- We examined IL-10/IL-17A/IFN-γ polymorphisms in PD and PD-cognitive impairment.
- There were no significant links between IL-10/IL-17A/IFN-γ polymorphism and PD.
- IL-17A rs8193036/IL-10 1082G/A may be associated with cognitive impairment in PD.
- Polymorphisms of cytokine genes may be involved in the cognitive impairment of PD.

ARTICLE INFO

Article history:
Received 29 October 2012
Received in revised form 7 January 2013
Accepted 13 February 2013

Keywords:
Polymorphisms
Parkinson's disease
Interferon-γ
Interleukin-10
Interleukin-17A
Cognitive impairment

ABSTRACT

Increasing evidence suggests that immune mediated inflammation contributes to the pathogenesis of Parkinson's disease (PD). However, whether genetic variants of genes coding for inflammatory cytokines influence the risk of cognitive impairment in PD is still unknown. In the present study, we examined whether interleukin-10 (IL-10, 1082G/A), interleukin-17A (IL-17A) rs8193036, rs2275913 and interferon-γ (IFN-γ) polymorphisms were associated with the risk of cognitive impairment in PD. The four gene polymorphisms were analyzed in 302 PD patients and results were compared to those obtained from 294 age- and gender-matched healthy controls (HC) enrolled from the Han Chinese population. PD patients were divided into two subgroups on the basis of mini mental state examination (MMSE) score: PD with cognitive impairment (MMSE scores < 26) and PD without cognitive impairment (MMSE scores ≥ 26). There was no significant difference in the distributions of genotype or allele between PD and control groups in the total population. However, the distribution of the rs8193036 (CC genotype, C allele) in PD individuals with an MMSE score < 26 was significantly increased when compared to PD patients with an MMSE score ≥ 26 (CC genotype: $p = 0.044$; C allele: $p = 0.038$). Also, there were significant differences in genotype and frequencies of the 1082G/A allele between PD cases with an MMSE score < 26 and controls (genotype $p = 0.021$; allele $p = 0.024$). Logistic regression analysis showed that the 1082G/A (AA) genotype decreased (Odds ratio = 0.440, $p = 0.042$), while the rs8193036 (CC) genotype increased the risk of cognitive impairment in PD (OR = 1.838, $p = 0.048$). Based on our study, polymorphisms in immune/inflammatory-related genes such as IL-17A rs8193036 and IL-10 1082G/A might be correlated with the risk of PD with cognitive impairment in the Han Chinese population.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, after Alzheimer's disease (AD). In addition to movement disorders, cognition dysfunction also seriously affects the lives of PD patients. The potential causes of PD remain elusive but studies have revealed that inflammatory processes play a vital role in the pathogenesis [22]. The impairment of inflammatory processes affects the functions of the central nervous system (CNS), among which cognition dysfunction is typical [10,18]. Recent prospective and cross-sectional studies of Alzheimer's and vascular dementia have suggested that certain cytokines are related to cognitive impairment in these patients. For example, homozygosity for the A allele of the interleukin-10 (IL-10) 1082G/A polymorphism promotes a higher risk of AD and cognitive impairment [3], whereas the interferon-γ (IFN-γ; T874A in intron 1) genotype is involved in

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http://dx.doi.org/10.1016/j.neulet.2013.02.024

vascular cognitive impairment via control of IFN-γ production [24]. Of special importance in PD, where widespread cognitive impairment is extremely common [1], is the established relation between cytokines and the pathogenesis of the disease, raising the possibility that inflammatory cytokines may also play a pivotal role in PD with cognitive impairment [19]. To date however, few studies have addressed the association between inflammation-related gene polymorphisms and cognitive impairment in PD, due to the small number of patients with Parkinson's disease with dementia (PDD).

Moreover, inflammation-related genes including IL-10 1082G/A and IFN-γ T874A have been studied in the PD population [5,14,20,21]. Interleukin-17A (IL17A) plays a key role in host defense against infection and development of inflammatory diseases [7,8,12,15]. The two IL-17A single-nucleotide polymorphisms (SNPs) (rs8193036 and rs2275913) were associated with susceptibility to inflammatory diseases such as rheumatoid arthritis (rs2275913, risk GG allele, Norway and New Zealand) [23], paediatric asthma (rs8193036, risk CC genotype, Taiwan) [28] and ulcerative colitis (rs2275913, risk A allele, Japan) [2]. Until now, the genotype and allele distributions of the IL-17A rs8193036 and IL-17A rs2275913 polymorphisms in the PD population or PD with cognitive impairment have not been reported.

Whether IL-10 1082G/A, IL-17A rs8193036, IL-17A rs2275913 and IFN-γ T874A polymorphisms related to cognitive impairment is specific to PD is unknown. This study was undertaken to test the hypothesis that these gene polymorphisms can predict risk of PD with cognitive impairment, representing the most important risk phenotypes in the Han Chinese population.

2. Materials and methods

2.1. Study participants

In this study, 302 cases (166 male and 136 female) with diagnosed idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria were enrolled in Guangdong General Hospital (China) from 2009 to 2011 [9]. All cases of secondary Parkinsonism were excluded from the study. PD patients were divided into two subgroups based on the Mini-Mental State Examination (MMSE) scores: PD with cognitive impairment (MMSE scores < 26) and PD without cognitive impairment (MMSE scores ≥ 26). The former group consisted of 209 cases (age: 64.96 ± 9.96 years; PD symptom onset: 60.94 ± 9.93 years). The later group consisted of 93 cases, 54 females and 39 males (age: 60.72 ± 11.26 years; PD symptom onset: 57.03 ± 11.04 years). 294 age- and gender-matched healthy controls (HC) (152 male, 142 female; age: 65.55 ± 8.0 years), who did not have any known diseases or symptoms were enrolled in our study. All PD cases were defined as sporadic, no family history of Parkinson's disease. As to our screening standard for the control group, healthy and neurologically normal patients were selected by medical history, general examinations and laboratory examinations. Moreover, the Mini Mental State Examination (MMSE) score ≥ 26. Subjects with significant illness were excluded from our study (such as T2DM, autoimmune disease, myocardial infarction, congestive heart failure, asthma and stroke). Written consent was obtained from all subjects. The study was approved by the Ethics Committee of Guangdong General Hospital."

2.2. Clinical assessment

Parkinson's disease was evaluated based on the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) and Hohen & Yahr stage during ON and OFF periods. Cognitive functions were assessed by MMSE test. Cognition was graded by a score ranging from 0 to 30. Cognitive impairment was defined as a score below 26 and no impairment was assigned if the score was above 26 [13]. All patients underwent dopaminergic treatment (levodopa and/or dopamine agonist agent). Information on the family history of PD and Parkinsonism was also collected.

2.3. Single nucleotide polymorphism (SNP) selection and genotyping

SNPs in the IL-10 gene (1082G/A), IL17A gene (rs8193036, rs2275913), and IFN-γ gene (T874A) were selected. All four selected SNPs were included in the Hardy–Weinberg Equilibrium test (HWE, $p > 0.05$). The two IL-17A single-nucleotide polymorphisms (SNPs) (rs8193036 and rs2275913) were in Linkage disequilibrium (LD = 0.774, $r^2 = 0.246$). Genomic DNA was isolated from whole blood using the Nucleospin Blood XL kit (Shanghai Generay Biotech Co., Ltd., China) and stored at −20 °C for analysis. The genotypes were determined by direct sequencing. Genomic DNA was amplified using the following primers: IL-10 1082G/A (sense, 5′-AACACTACTAAGGCTTCTTTGG-3′; antisense, 5′-GTAAGCTTCTGTGGCTGGAGTC-3′; 162 bp, extension primer: TTTTTTTTTTTCTTACC TATCCCTACTTCCCC); IL17A rs8193036 (sense, 5′-GA GTACAGAGAAAAGAA CCGC-3′; antisense, 5′- ACTAGGTTCAAGAGACACGAG-3′; 234 bp, extension primer: CATCACCTTTGTCCAGTCTCTATCCTTTT); IL17A rs2275913 (sense, 5′-CTCTGCTCAGCTTCTAACAAG-3′; antisense, 5′-GGACAAAATGTAGCGCTATCG-3′; 233 bp, extension primer: AGAGATTCTTCTATGACCTCATTGGTTTTTTT); IFN-γ T874A (sense, 5′-CATCTACTGTGCCTTCCTGTAG-3′; and antisense, 5′-CTGTCATAATAATATTCAGACA-3′; 157 bp, extension primer: TTTCAATTGATTTTATTCTTACAACACAAAATCAAATC). The four investigated SNPs were genotyped using the Multiplex SNaPshot System with an ABI 3730XL genetic analyzer (Shanghai Generay Biotech Co., Ltd., China).

2.4. Statistics

Multivariate analysis performed with binary logistic regression analysis (SPSS 13.0 for Windows; SPSS Inc.) was used to assess the genotype and allele (IL-10 1082G/A: AA versus AG/GG; IL-17A rs8193036: CC versus CT/TT; IL-17A rs2275913: AA versus AG/GG; IFN-γ T874A: AA versus AT/TT) distributions in PD patients with and without cognitive dysfunction, adjusted for age, gender, disease duration, and disease severity (UPDRS-β and Hoehn–Yahr (H&Y) scale). The genotype and allele distributions of all the investigated polymorphisms were test deviations from the Hardy–Weinberg equilibrium. Allele and genotype frequencies were compared between groups using χ^2 or two-sided Fisher exact test.

3. Results

There was no statistical difference between the HC group and PD group with regard to gender, age and education level. PD patients had an average age of 62.02 with disease duration of 3.94 ± 4.9 years and a UPDRS-III score in the ON phase of 31.13 ± 13.75. The MMSE scores were normal (≥26) in 30.79% of the PD patients. However, there were statistical differences in the gender, age, age of PD onset, and UPDRS-III between the PD patients with an MMSE score <26 and the PD individual with an MMSE score ≥ 26 (age: $p = 0.003$; gender: $p = 0.002$; age of PD onset: $p = 0.003$; UPDRS-III: $p < 0.001$) (Table 1).