Analysis of the UCHL1 genetic variant in Parkinson’s disease among Chinese


Abstract

The inverse association of the functional ubiquitin carboxy-terminal hydrolase L1 (UCHL1) S18Y variant with Parkinson’s disease (PD) among Caucasian populations has been debated. We conducted a large-scale analysis to investigate the age-of-onset effect of the UCHL1 variant in PD among ethnic Chinese. Individual data sets from 5 centers comprising a total of 4088 study subjects were analyzed. In the univariate analysis, only data from 1 center showed a trend towards a protective effect among young subjects. However, in the combined analysis, no significant association between the UCHL1 variant and PD was detected (A allele frequency 0.531 vs. 0.528, \( p = 0.87, \text{OR} \ 1.01, 95\% \text{ CI} \ 0.92–1.1 \)). Among subjects less than 60 years old, the OR is 0.99 (95\% CI 0.84–1.16, \( p = 0.88 \)). A multivariate logistic regression analysis showed that family history, UCHL1 variant and the interaction of UCHL1 variant and age at onset (\( p = 0.816 \)) were not significantly associated with PD.

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1. Introduction

Both genes and environmental factors play a role in Parkinson’s disease (PD), a progressive neurodegenerative disease characterized by bradykinesia, rigidity, tremor and postural instability. A missense Ile93Met mutation in the UCHL1 gene has previously been found in two German siblings with autosomal dominant PD although linkage to UCHL1 has yet to be identified among PD families. The potential protective effect of a serine to tyrosine polymorphism at codon 18 in exon 3 (S18Y, A to C nucleotide substitution) of UCHL1 has been extensively investigated in PD. Since the vast majority of published studies are in the Caucasian populations and the frequency of the variant is much higher in Asians compared to Caucasians, a multi-center study in the Chinese population would be most helpful to further address the association of the variant
with PD. Here, we have conducted an association study of the UCHL1 S18Y variant in subjects of Chinese ethnicity involving multiple centers in mainland China, Taiwan and Singapore.

2. Methods

All the study subjects were ethnic Chinese recruited from tertiary institutions in 5 centers (designated as Peng, Lu, Robin, Wu and Tan) from mainland China, Taiwan and Singapore. Movement disorders neurologists examined the patients and the diagnosis of PD was made according to widely accepted UK Brain Bank criteria. Control subjects were healthy volunteers (with no evidence of neurodegenerative diseases) matched for age at onset of PD, gender and ethnicity and examined by the authors. Informed consent was taken from all study subjects. The institutional ethics committees from each center had approved the genetic study. Details of genotyping are listed in supplementary material on the web.

3. Results

A total of 4088 study subjects, including 2325 PD and 1763 controls from the 5 centers were included in this analysis (see Table 1, website). Among the 5 centers, part of the data from Tan (Tan et al., 2006) and data from Peng (Zhang et al., 2008) have previously been published. In this combined analysis, there were 55% and 48% men in PD and controls. The mean age, mean age of onset of PD and age of controls was 65.0 ± 12 (range 20–97), 58.0 ± 11 (range 17–94) and 57.0 ± 15 (range 15–100) years. Only 1.5% of the PD patients reported a positive family history. The genotypic distribution of the individual data sets conformed to Hardy–Weinberg equilibrium for both the PD subjects and the controls. There was no significant heterogeneity across the five studies (p = 0.915). In the univariate analysis, only data from 1 center (Tan) showed a trend towards a protective effect among young subjects (Table 2, website). However, in the combined analysis, no significant association between the UCHL1 variant and PD was detected (A allele frequency 0.531 vs. 0.528, p = 0.87, OR 1.01, 95% CI 0.92–1.1). Among subjects less than 60 years old, the OR is 0.99, 95% CI 0.84–1.16, p = 0.88 (Table 2). A multivariate logistic regression analysis was carried out. For controls, age at onset was taken as age at study time. The factors age at onset, UCHL1 (CA/AA, CC), gender, family history, interaction of UCHL1 and age of onset were investigated for entry in the model by stepwise method of variable selection. Family history, UCHL1 and the interaction of UCHL1 and age at onset (p = 0.816) were not significantly associated with PD. Males (OR = 1.467) and higher age of onset (OR = 1.007) were more at risk of PD. For each unit increase in age, the risk of PD increases by 0.7%.

4. Discussion

The frequency of the S18Y variant is much higher among Asians compared to Caucasians (74% vs. 34%) (Maraganore et al., 2004), allowing a greater power of analysis in an association study. Earlier case-control studies in Japan and Singapore have suggested that the variant confer protection among younger subjects. In our multi-center study, we have only involved subjects of similar ethnicity (Chinese) and have a sample size (>4000 subjects) sufficiently powered to detect the effect size difference. We have demonstrated no significant association between PD and controls. There was also no interaction between the age at onset and the S18Y variant in the logistic regression analysis. Could the protective effect of UCHL1 be restricted to certain races? A meta-analysis of published studies involved predominantly Caucasian populations (1970 cases and 2224 controls) revealing a possible protective effect of the variant (Maraganore et al., 2004). Among the Asian studies in this analysis, the association seems to be particularly more robust among Japanese. Subsequently, a case-control study from United Kingdom in Caucasians (3023 subjects) was unable to replicate the finding (using all genetic models of analysis) (Healy et al., 2006). More recently, a third study involving 1757 PD patients and 2016 controls (all Caucasians) from United States also did not observe any association between S18Y genotypes and PD (using recessive or dominant models) (Hutter et al., 2008). The contradictory results in published literature could be a result of methodological differences or presence of modulation by specific epigenetic or environmental factors in some populations. It is also possible that the protective effect of the S18Y variant among early-onset cases is weak and thus not readily reproducible. The continued interest in the S18Y variant is supported by functional evidence for its potential protective effect in PD (Liu et al., 2002). The UCHL1 protein possesses two opposing enzymatic activities that affect alpha-synuclein degradation. The polymorphic S18Y variant of UCHL1 has reduced ligase activity but comparable hydrolase activity as the wild-type enzyme. The dimerization-dependent ubiquityl ligase activity results in ligation of ubiquitin via a K63 linkage to alpha-synuclein, sparing it from proteasomal degradation. It is possible that the ligase/hydrolase activity of S18Y variant may be influenced by yet-to-be identified environmental or epigenetic factors. We are unable to address these issues in our current study. One study has shown that smoking and pesticides exposure did not modulate the protective effect of S18Y in PD (Elbaz et al., 2003), but other potential interacting factors were not examined.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2008.11.008.

References


