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SHORT REPORT

LRRK2 R1628P increases risk of Parkinson's disease: replication evidence

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Abstract We showed that the frequency of a LRRK2 variant (c.4883G > C, R1628P) was higher in Parkinson's disease (PD) compared to controls (8.4 vs. 3.4%, $P = 0.046$, OR 2.5, 95% CI 1.1–5.6). In the multivariate logistic regression (with adjustments made for the effect of age, age of onset, and gender), the heterozygous R1628P genotype was associated with an increased risk of PD compared to controls (OR 3.3, 95% CI 1.4– 7.9, $P = 0.007$). We provided an independent confirmation that the R1628P variant increases the risk of PD among Chinese.

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by tremor, bradykinesia, rigidity and postural instability. Mutations in the leucine-rich repeat kinase 2 (*LRRK2, PARK8*) are the most frequent known cause of familial autosomal dominant PD. A common polymorphic *LRRK2* variant (G2385R) has been associated with PD in both Chinese and Japanese populations (Tan et al. 2007; Di Fonzo et al. 2006; Farrer et al. 2007; Tan and Schapira 2008). More recently, another *LRRK2* variant (c.4883G > C, R1628P) has been found to also increase the risk among Chinese in Taiwan and Singapore (Ross et al. 2008). As replication remains the litmus test of reliability of genetic association studies, we seek to replicate the finding in Singapore by conducting a separate case control study involving an independent cohort of study subjects.

Methods

We recruited ethnic Chinese subjects diagnosed with idiopathic PD by movement disorders neurologists at two major movement disorders centers (Singapore General Hospital and Tan Tock Seng Hospital, National Neuroscience Institute). The PD diagnosis was made in accordance with the UK PD Society Brain Bank Clinical Diagnostic Criteria of PD. The PD subjects were previously screened negative for at least 14 reported *LRRK2* mutations (Tan et al. 2006). Controls of similar age, gender and race controls were recruited. These controls were healthy individuals without neurodegenerative diseases and examined by the authors. None of the study subjects were involved in any previous study on the R1628P variant (Ross et al.

2008). The institutional ethics committees approved the study and all study subjects gave informed consent. Genotyping of the R1628P variant was carried out as previously described (Ross et al. 2008).

Results

A total of 489 subjects comprising of 246 PD and 243 controls similar in age and gender were analyzed. The mean age of PD and controls was 66 ± 12 (32–95) and 62 ± 10 (30–90) years, comprising 56 and 54% men, respectively. The mean age of onset was 59 ± 13 (30–88) years. The genotype frequency of the R1628P in both PD and controls followed the Hardy–Weinberg equilibrium. The frequency of the heterozygous R1628P genotype was higher in PD compared to controls (8.4 vs 3.4%, $P = 0.046$, OR 2.5, 95% CI 1.1–5.6).

In the multivariate logistic regression analysis with the disease group (PD vs. controls) as the dependent variable and genotype as an independent factor with adjustments made for the effect of age, age of onset, and gender, we found that the heterozygous R1628P genotype was associated with an increased risk of PD compared to controls (OR 3.3, 95% CI 1.4–7.9, $P = 0.007$).

Discussion

In an independent case control study, we demonstrated that the R1628P variant increases the risk of PD by about 2.5-fold. The magnitude of this risk detected in this cohort is similar to the twofold increased risk reported in the recent study in Taiwan and Singapore by Owen et al. (Ross et al. 2008). A number of patients in this replication study were recruited from a different geographical region compared to the first cohort reported from our country. Thus validation of the finding further affirms the validity of the original study. A meta-analysis of the two cohorts in Singapore revealed a more robust association because of the increased power (6.5 vs. 2.8%, $P = 0.02$, OR 2.8, 95% CI 1.2–6.7). While it is interesting to note that haplotype analysis suggests that the ancestral founder for R1628P carriers probably occurred more recently (2,500 years ago) than carriers of the G2385R variant (Ross et al. 2008), the current challenge is to determine how R1628P increases the risk of disease. It is possible that other environmental or epigenetic factors may interact with the variant and influence its pathogenicity.

LRRK2 R1628P is located in the COR domain and evolutionarily conserved across species (Lu and Tan 2008). It has been postulated that the substitution of a highly basic polar arginine (R) with a neutral non-polar proline (P) is likely to cause a conformational change in Lrrk2 secondary structure. Functionally, it is unclear how and to what extent this substitution affects the GTP binding capacity and its impact on the kinase activity of the protein. It is possible that the variant could also affect the interaction between the different functional domains of LRRK2 or with other external protein interactors which might ultimately influence the kinase activity. Nevertheless, the identification of the R1628P variant provides an opportunity for in vivo study in animal models and functional imaging study in humans with a view of identifying biological markers which might be important in the development of neuroprotective strategies in PD.

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Conflict of interest statement The authors have no competing interests to declare.

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