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The role of the Ala746Thr variant in the ATP13A2 gene among Chinese patients with Parkinson's disease

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Abstract

The association between idiopathic Parkinson's disease (PD) and the *ATP13A2* (*PARK9*) Ala746Thr variant, associated with Kufor-Rakeb syndrome, is controversial. We investigated this association in 69 patients with early onset PD (EOPD; <50 years of age), 192 patients with late onset PD (LOPD; >50 years of age), and 180 healthy controls in the Chinese population in Hong Kong. The presence of the Ala746Thr variant in the *ATP13A2* locus was examined in all participants. We detected the heterozygous Ala746Thr variant in one healthy control (0.6%), one patient with EOPD (1.4%, $p = 0.50$), and one patient with LOPD (0.5%, $p = 0.96$). We suggest that the *ATP13A2* Ala746Thr variant is not a common risk factor for PD in the Chinese population in Hong Kong.

Keywords

Parkinson's disease; ATP13A2; Chinese; Genetics; PARK9

Conflicts of interest/disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

1. Introduction

Kufor-Rakeb syndrome (KRS) is a disorder characterized by juvenile-onset of atypical parkinsonism, poor response to levodopa, pyramidal signs, supranuclear palsy, and cognitive dysfunction. It is caused by homozygous and compound heterozygous mutations in the *ATP13A2* gene.

Several studies have screened for *ATP13A2* sequence variants in patients with PD. Djarmati et al. screened 112 patients with PD and identified four with *ATP13A2* sequence variants.¹ However, two recent studies suggested that the *ATP13A2* variants were unlikely to be a common risk factor for PD.^{2,3} Furthermore, a missense substitution in *ATP13A2*, 2236G>A (guanine [G] > alanine [A] (Ala746Thr), was detected in three of 182 patients with early onset PD (EOPD) and familial PD Chinese patients in Taiwan and Singapore and in none of the 589 healthy controls ($p = 0.01$).⁴ The clinical features and brain positron emission tomography scans of these patients resembled typical PD.⁴ Another study suggested that the *ATP13A2* Ala746Thr variant was not a major susceptibility factor for PD in the Chinese population.⁵ In light of these differing reports, we aim to study the association between the *ATP13A2* Ala746Thr variant and PD.

2. Material and methods

A total of 261 Chinese patients with PD in Hong Kong were recruited. Healthy controls, unrelated to the patients, were recruited from the hospital staff and community. Informed consent was obtained from each participant. All participants were examined by movement disorders specialists (A.Y.Y.C., V.C.T.M., and N.L.S.T.) and a detailed clinical examination was recorded. The diagnosis of PD was made in accordance with British Brain Bank criteria. Healthy controls did not have evidence of parkinsonism or cognitive impairment on clinical examination. Subjects from consanguineous families were excluded. EOPD was defined as onset ≤ 50 years of age, and a positive family history was defined by the presence of at least one other affected first-degree or second-degree relative who had two or more of the following clinical signs of parkinsonism: tremor, rigidity, bradykinesia, and postural instability.

Genomic DNA was extracted from peripheral blood, and genotyping was performed using previously described methods.⁴ The frequencies of the *ATP13A2* Ala746Thr allele in patients with EOPD and LOPD were compared with controls. The chi-squared analysis was used to compare categorical variables. Two sample independent *t*-tests were used to compare differences in continuous variables, and non-parametric Mann–Whitney *U*-tests were used for non-normally distributed variables.

3. Results

A total of 69 patients with EOPD, 192 patients with LOPD, and 180 healthy controls participated in this study. The clinical features of patients with EOPD and patients with LOPD were similar; however, patients with EOPD had a longer disease duration, less bradykinesia, and more levodopa-induced dyskinesia (all $p < 0.01$).

Two patients with PD were heterozygous for the *ATP13A2* Ala746Thr variant. One patient had EOPD (1.4%, $p = 0.50$) and the other patient had LOPD (0.5%, $p = 0.96$). One control also had this variant (0.6%). The odds ratio (OR) of all patients with PD to controls was 1.38 (95% confidence interval 0.12–15, $p = 0.79$). The frequency of the variant allele did not significantly differ between groups. All three subjects with the variant were men who did not have a family history of PD. On examination, the two patients with the variant had typical clinical signs of PD, including anosmia. In contrast to KRS, signs of corticospinal tract dysfunction or cognitive impairment were absent. The healthy control carrying the variant was 70 years old and did not have a history of anosmia or rapid eye movement behavior disorders.

4. Discussion

We did not find an association between *ATP13A2* Ala746Thr and EOPD or LOPD in our cohort. Similar to a previous study,⁵ we also detected Ala746Thr in one healthy control, supporting the idea that this variant is not a strong risk factor for PD in the Chinese population. In addition, the lack of family history of PD in the two patients carrying this variant further supports this notion.

Our study suggests that *ATP13A2* Ala746Thr is not a major risk factor for PD in the Chinese population. A larger sample is required to determine the relationship between the genetic variant and PD. We estimate that 10,000 patients with PD and 10,000 controls with the same frequency of the variant as we observed (0.68%) would be necessary to exclude a risk effect $OR > 1.42$.

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