ORIGINAL ARTICLE

The G2019S LRRK2 Mutation is Rare in Korean Patients with Parkinson's Disease

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ABSTRACT: ***Background:*** A number of causative mutations such as α-synuclein, parkin, UCHL1, Pink-1, DJ-1 have been identified in Parkinson's disease (PD). They are usually found in the familial cases. One mutation of great interest is the G2019S mutation in the LRRK2 gene, which has been reported in both familial and sporadic PD. Its prevalence has been reported to vary markedly among different races. We examined the prevalence of the G2019S mutation in the Korean PD population for genetic study planning. ***Methods:*** We conducted a genetic analysis of the G2019S mutation by standard PCR and restriction digestion method. 453 PD patients were studied, 34% of whom had an age at onset of <50 years and 3.8% had a positive family history. ***Results:*** None of the 453 study subjects carried the G2019S mutation. ***Conclusions:*** Our result confirms previous reports that the G2019S mutation is rare among PD patients in the Asian population. This result supports the notion that the prevalence of this LRRK2 mutation is population specific, and that there may be a founder effect within western populations.

RÉSUMÉ: La mutation G2019S LRRK2 est rare chez les patients coréens atteints de la maladie de Parkinson. ***Contexte :*** Quelques mutations causales ont été identifiées dans la maladie de Parkinson (MP) telles des mutations des gènes de l'a-synucléine, de la parkine, de l'UCHL1, de la Pink-1 et de la DJ-1. Il s'agit habituellement de cas familiaux. La mutation G2019S du gène LRRK2, qui a été rapportée chez des cas familiaux de MP et chez des cas sporadiques, est très intéressante. Sa prévalence varie beaucoup selon la race. Nous avons examiné la prévalence de la mutation G2019S dans la population coréenne de patients atteints de la maladie de Parkinson afin de planifier une étude génétique. ***Méthodes :*** Nous avons réalisé une analyse génétique de la mutation G2019S par la méthode standard d'amplification en chaîne par polymérase et digestion par enzyme de restriction. 453 patients atteints de MP ont été étudiés. L'âge de début était < 50 ans chez 34% des patients et 3,8% avaient une histoire familiale de MP. ***Résultats :*** Aucun des 453 patients n'était porteur de la mutation G2019S. ***Conclusions :*** Nos résultats confirment des publications antérieures selon lesquelles la mutation G2019S est rare chez les patients atteints de la MP dans la population asiatique. Ce résultat appui la notion que la prévalence de cette mutation du gène LRRK2 est spécifique de la population et qu'il pourrait exister un effet fondateur dans les populations occidentales.

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A number of causative mutations of Parkinson's disease (PD) such as α-synuclein, parkin, UCHL1, Pink-1, DJ-1 have been identified.[1] The discovery of such genetic abnormalities has provided insights into the molecular pathogenesis of PD. These mutations are usually found in the familial cases. Recently, mutations in the LRRK2 gene have been reported to cause autosomal dominant PD (PARK8).[2,3] The locus, PARK8 on chromosome 12q12, was originally identified by linkage analysis in a large Japanese family.[4] The heterozygous mutation, G2019S, appears to be particularly common in Caucasian populations, and has been widely reported to account for about 3-7% of familial PD.[5-9] Of great interest is that the G2019S mutation in LRRK2 may be present in about 0.9-2.7% of sporadic PD cases, and patients tend to share the clinical feature of typical, late-onset PD.[5,10-12]

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The observation that the prevalence of the LRRK2 mutation may vary with race is also of considerable interest. According to previous reports, the frequency of LRRK2 mutations in north African Arabs, Jews, and some Spanish are 6.1-41% in sporadic PD and 18.7-37% in familial PD.[13-15] In Asia, this mutation is rare in PD.[16,17] Among the 16 mutations reported in LRRK2-related PD, G2019S appears to be the most common.[9-11,18,19]

Therefore, we performed a genetic analysis for this mutation in 453 PD patients to determine the prevalence of the G2019S mutation in LRRK2 in Korean population.

Patients and Methods

All patients fulfilled criteria for a clinical diagnosis of PD (1. at least two of the three cardinal signs of tremor, rigidity, and bradykinesia. 2. a positive response to adequate dopaminergic therapy. 3. absence of atypical features or other causes of parkinsonism).

The Institutional Review Board (IRB) of Seoul National University Hospital approved this study. Written informed consent was obtained from all participants.

Four hundred and fifty three PD cases (M: 209, F: 244) were included in the study. Their onset age ranged 22-79 with a mean onset of 54.1 ± 11.4 years. The 154 patients (34%) had onset at ≤ 50 years of age, and 299 patients (66%) had onset at > 50 years of age. Seventeen cases had a positive family history of at least one other affected first degree relative.

DNA was extracted from peripheral blood using standard methodologies. We used a 50 ng DNA template and generated PCR products using the following primer pair (forward: 5'-AAGGGACAAAGTGAGCACAGA-3'; reverse: 5'-TGTTTTCCTTTTGACTCTTCTGA-3' based on NCBI accession number NC_000012.10). The PCR conditions were initial denaturation at 95°C for 10 minutes, and 35 cycles of 95°C for 30 seconds, 60°C for 30 seconds, and 72°C for 1 minute, and a final extension at 72°C for 7 minutes. PCR products (3 uL) were digested with SfcI (New England BioLabs, Beberly, MA, USA) at 37°C.

Wild type products produced fragments of 251 bp and 127 bp and the mutant could produce fragments of 230 bp, 127 bp and 21 bp. Since we did not have a positive control, we used the 677C>T mutant DNAs of the MTHFR gene with similar fragments sizes (175 bp and 23 bp) for the quality control of restriction digestion and electrophoretic separation.

Results

None of the 453 study subjects carried the G2019S mutation.

Discussion

Mutations in LRRK2 appear to be the most common cause of autosomal-dominantly inherited parkinsonism known to date. Unlike other causative mutations of PD, mutations within LRRK2 have been identified in some percentage of sporadic and late-onset PD, which suggests that LRRK2 makes a unique contribution to the development of PD. The heterozygous mutation, G2019S, appears to be particularly common in Caucasian populations. It accounts for 3-7% of familial PD and may be present in about 0.9-2.7% of sporadic PD cases in the western populations.[5-12] Surprisingly, the frequencies of the G2019S mutations in North Africa were 37% (10/27) among patients with a family history, and 41% (20/49) in those without.[13] In Askenazi Jews, the G2019S mutation in LRRK2 was found in 19.7% (11/37) with familial PD and in 13.3% (11/83) with sporadic PD.[14] However, Bialecka et al reported finding no mutation in a Polish population of 174 PD.[20]

A few studies on LRRK2 mutations have been reported in Asian PD patients, and suggest that LRRK2 mutation is rare in this population. Funayama et al and Tan et al[17] reported the absence of the G2019S mutation in 188 Japanese[4] and 675 Chinese respectively. Lu et al[16] reported that none of the 624 ethnic Chinese with sporadic PD carried any of the G2019S, I2020T, I2012T mutations.

Our finding confirms previous reports that the G2019S mutation is rare among patients with sporadic PD in the Asian population supporting that the prevalence of the LRRK2 mutation is population specific and that there may be a founder effect within those populations with high reported prevalence of this mutation. In the present study, we screened for the G2019S mutation only. As the G2019S mutation is the most common[9-11,18,19] among the 16 mutations reported in LRRK2-related PD, routine testing for LRRK2 mutations may not be cost-effective in the Asian population based on our and previous results. However, a wider search other LRRK2 mutations is needed to fully examine the contribution of this gene in our population.

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