The G209A Mutation in the α-Synuclein Gene
Is Not Detected in Familial Cases of Parkinson Disease in Non-Greek and/or Italian Populations

William W. Wang, MD, PhD; Mehrdad Khajavi, BS; Bhavna J. Patel, BS; Jennifer Beach, RN; Joseph Jankovic, MD; Tetsuo Ashizawa, MD

Objective: To determine whether the G-to-A substitution at nucleotide 209 (G209A) mutation in the α-synuclein gene is responsible for familial Parkinson disease (PD) in the US population.

Design: Polymerase chain reaction–based DNA analysis of consecutive patients with PD and family history of PD.

Setting: A university-affiliated movement disorder clinic and a Veterans Affairs clinical research laboratory.

Patients: Forty-four patients with PD and family history of PD and 29 patients with sporadic PD, all with no known Greek and/or Italian background.

Results: None of the DNA samples showed the G209A mutation.

Conclusion: The G209A mutation is rare in US patients with familial PD.

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Parkinson Disease (PD) is one of the most common neurodegenerative disorders, characterized by bradykinesia, cogwheel rigidity, rest tremor, and impaired postural reflexes.1,2 Degeneration of dopaminergic neurons in the central nervous system and the presence of Lewy body cytoplasmic inclusions, particularly in substantia nigra, is the pathological hallmark of PD, but the cause of this selective neuronal degeneration remains unknown.1,2 Although an encephalitis virus (von Economo) and toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have caused clinical and pathological syndromes similar to PD in a small portion of cases, efforts to identify causative environmental factors in PD have been unsuccessful in most patients.1,2 Oxidative stress involving local iron accumulation, reduced glutathione levels, and mitochondrial dysfunction may play a role in the neuronal loss of PD, but it is not known whether these mechanisms are pathogenic events in PD.1

For the past few years, genetic mechanisms have attracted increasing attention in the investigation of pathogenesis of PD. Some studies have demonstrated familial clustering of PD and suggested the existence of heritable predisposition.3,5 The risk for siblings of individuals with PD developing PD may be 2 to 10 times higher than the general population prevalence.5 Genetic loci for several other familial disorders with parkinsonism have been determined,7 but these diseases clinically and pathologically differ from classic Lewy body PD. Genetic linkage analysis of an autosomal-dominant PD family has located markers on chromosome 4 that segregate with PD phenotype of relatively early onset and rapid progression.3 Subsequently, a single nucleotide substitution mutation, G to A at nucleotide 209 (G209A), was identified in the α-synuclein gene in 4q21 to 4q22 in 1 Italian and 3 Greek families with PD.10 This mutation was not detected in patients with sporadic PD,10,11 a healthy population with Italian background,10 or patients with early-onset familial PD in Spain.12 The frequency of this mutation in the US population of patients with familial PD also appears low.11 We report herein the results of our search for this single nucleotide mutation in 88 chromosomes from familial PD cases of no known Italian and/or Greek European background seen in a movement disorder clinic in the United States.
PATIENTS AND METHODS

PATIENTS

Genomic DNA was extracted from peripheral blood samples of 44 patients with familial PD (32 men and 12 women; mean age at onset ± SD, 53.8 ± 16.1 years; age range, 28–76 years) and 29 patients with sporadic PD (14 men and 15 women; mean age at onset ± SD, 49.9 ± 9.1 years; age range, 28–75 years) with no known Italian or Greek background. The ethnic backgrounds of patients with familial PD included northern European, 24; southern European other than Italian or Greek, 6; Hispanic, 4; and unknown/mixed with no known Italian or Greek ancestors, 10. No patient in the study had African, Asian, or Pacific Islander background. The pattern of familial occurrence of PD in the 44 patients was variable; 27 showed parent-child transmission of typical PD phenotype, while 14 of the remaining patients had family history of PD in 1 or more siblings. The remaining 3 patients with familial PD had a family history of PD that did not involve the first-degree relatives. Fourteen of the 44 patients with familial PD had 2 or more additional family members affected by typical PD. One of the 44 patients with familial PD also had a family history of essential tremor. Of the 29 patients with sporadic PD, 13 (7 men and 6 women) had a family history of essential tremor in their first-degree relatives. Among these 13 patients with PD, 8 had a parent, 2 had a child, and 1 had a sibling with essential tremor. For the remaining 2 patients with PD, essential tremor was found in the father and child of 1 patient and in the father and 2 sisters of the other. We also included 16 patients with sporadic PD without family history of essential tremor or other movement disorders. Informed consent was obtained from each patient.

METHODS

For each sample, 500 ng of genomic DNA was used as a template. The 2 primers used were primer 3 and primer 13, with the sequences reported previously. The 2 critical conditions of polymerase chain reaction (PCR), the concentration of magnesium chloride and annealing temperature, were optimized using robustycler gradient 96 (Stratagene, La Jolla, Calif). A magnesium chloride concentration of 4.5 mmol and annealing temperature of 62°C in the PCR consistently gave a clear-cut single band sized at 216 base pairs. The PCR amplification of all genomic DNA samples obtained from the 44 patients with familial PD and 29 patients with sporadic PD yielded the expected 216-base pair product, suggesting that there is no major rearrangement within the amplified region of the α-synuclein gene in these samples. The Tsp45 I digestion did not cut this product in any of these samples (Figure). Complete digestion of the pUC19 DNA under the same conditions indicated that the Tsp45 I was active. Thus, we were unable to detect the G209A mutation in our patients.

COMMENT

The lack of G209A mutation in the α-synuclein gene in our patients suggests that this mutation is not the major mutation responsible for familial PD in a US population without Greek or Italian background. The prevalence of this mutation among patients with familial PD in the Italian and Greek populations is currently unknown; a founder effect of this mutation in these populations has been suggested. Another nucleotide substitution, G to C at nucleotide 88 (G88C) that changes alanine to proline at amino acid 30 (Ala30Pro), was found in a German family with PD. These mutations and the presence of α-synuclein in Lewy bodies suggest that α-synuclein plays an important role in the pathophysiological mechanism of PD. However, these and other mutations in the α-synuclein gene appear to be rare. Recent linkage studies have shown that the 4q21 to 4q23 region can be excluded in most Caucasian familial PD pedigrees, while a susceptibility locus for a normal familial PD phenotype, while 14 of the remaining patients had family history of PD in 1 or more siblings. The remaining 3 patients with familial PD had a family history of PD that did not involve the first-degree relatives. Fourteen of the 44 patients with familial PD had 2 or more additional family members affected by typical PD. One of the 44 patients with familial PD also had a family history of essential tremor. Of the 29 patients with sporadic PD, 13 (7 men and 6 women) had a family history of essential tremor in their first-degree relatives. Among these 13 patients with PD, 8 had a parent, 2 had a child, and 1 had a sibling with essential tremor. For the remaining 2 patients with PD, essential tremor was found in the father and child of 1 patient and in the father and 2 sisters of the other. We also included 16 patients with sporadic PD without family history of essential tremor or other movement disorders. Informed consent was obtained from each patient.

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PD has been mapped to 2p13 in a group of European families. Thus, familial PD is a genetically heterogeneous disorder with ethnic predisposition, and other unidentified chromosomal loci may be involved in familial PD and familial disorders resembling PD.

Based on a frequent association of PD and essential tremor, earlier research indicated that PD and essential tremor may be pathogenetically related. This view has been supported by other studies showing high frequency (approximately 15%-20%) of essential tremor observed in patients with PD compared with 2% to 5% prevalence of essential tremor in the general population. A similar frequent association has also been found in dystonia and familial essential tremor. In our study, we included 13 patients with sporadic PD who had a family history of essential tremor. Additionally, 1 of the 44 patients with familial PD had a sibling with essential tremor, while family history of dystonia was not found in any of our patients. None of these patients showed the G209A mutation, suggesting that this mutation is not the common link to the related pathophysiological mechanism postulated in PD and essential tremor.

We conclude that the G209A mutation is not the major mutation responsible for familial PD in the population of the United States without known Greek or Italian background. The search must be continued for identification of the major genetic mutations responsible for familial PD.

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Reprints: Tetsuo Ashizawa, MD, Department of Neurology, SM1801, Baylor College of Medicine, Houston, TX 77030 (e-mail: tetsuo@bcm.tmc.edu).

REFERENCES


