The role of the $\alpha$-synuclein gene mutation in patients with sporadic Parkinson’s disease in the United Kingdom

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Abstract
Parkinson’s disease is a common neurodegenerative disorder of unknown aetiology. A pathogenic point mutation within the $\alpha$-synuclein gene has recently been identified in one Italian-American kindred and three families of Greek origin with parkinsonism. DNA from 70 patients with Parkinson’s disease was screened for this G209A mutation. No samples were positive for the mutation, suggesting that it is not relevant for most patients with sporadic idiopathic Parkinson’s disease.

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Idiopathic Parkinson’s disease is a common neurodegenerative disease with characteristic neuropathology and lifetime incidence approaching 2%. The neurodegenerative changes, associated with Lewy bodies in the surviving neurons, are centred on the substantia nigra, locus ceruleus, nucleus basalis, cranial nerve motor nuclei, hypothalamus, cerebral cortex, and autonomic nervous system. The pathological processes underlying this neurodegeneration are unknown, but there is increasing evidence for the role of genetic susceptibility in Parkinson’s disease.

Families with autosomal dominant parkinsonism have been described, although the clinical features of many of these are atypical for Parkinson’s disease. Polymeropoulos et al studied a large Italian-American pedigree and linked the Parkinson’s disease-1 locus to chromosome 4q21–23. Further study led to the identification of a point mutation (G209A) within the $\alpha$-synuclein gene on chromosome 4q21–22 in this kindred and three unrelated families of Greek origin with parkinsonism. The mutation leads to an alanine to threonine substitution that is predicted to disrupt an $\alpha$-helix and promote aggregation. The protein itself is thought to be involved in synaptic plasticity, and has been previously identified as a non-\$beta$-amyloid component of Alzheimer’s disease neuritic plaques. Defining the pathogenic mechanisms that are involved in these kindreds will provide valuable insight into how such a mutation can produce selective neuronal degeneration such as is seen in Parkinson’s disease.

Most cases of idiopathic Parkinson’s disease seem to be sporadic, although a recent genetic study in the United Kingdom found that 26% of probands had affected first or second degree relatives by examination. This suggests that genetic factors are more important than previously recognised.

Methods and results
To assess the importance of the G209A mutation in the United Kingdom, cases of Parkinson’s disease and control subjects were analysed. Diagnosis of Parkinson’s disease was made for patients with an akinetic-rigid syndrome with asymmetric onset, a resting tremor, and a positive response to levodopa. Blood samples were taken from the patients after informed consent and stored anonymously. DNA was extracted using standard techniques. We have screened DNA from 70 patients with Parkinson’s disease and 100 control subjects. The mutation creates a novel Tsp45 I restriction site which cuts the normal 216 bp polymerase chain reaction (PCR) product into fragments of 128 and 88 bp and can be used to screen for G209A substitution. The figure shows a Tsp45 I digest of PCR products from patients with Parkinson’s disease (lanes 1–4) and controls (lanes 6 and 7), with fragment sizes indicated. As a positive control for the digest, a PCR product of mitochondrial DNA was used (bp 130–655). Tsp45 I cleaves the 525 bp product (lane 10) into fragments of 300 and 225 bp (lanes 5, 8, and 9).
No samples, whether from the patient group of Parkinson’s disease or the control group, were positive for the G209A mutation.

**Discussion**

The study shows that the G209A mutation was not present in 70 patients with Parkinson’s disease. This suggests that the mutation described does not play a major part in the causation of sporadic Parkinson’s disease in the United Kingdom. Although none of the patients were known to have a positive family history for Parkinson’s disease, it is possible that some had affected relatives, exemplified by the study of Kellet et al. However, there were no identifiable cases of autosomal dominant Parkinson’s disease, and it may be that the G209A mutation is specific to the families described in Italy and Greece. Support for this view comes from a recent linkage study of 13 families with autosomal dominant parkinsonism from other European countries and a cohort of 94 white kindreds in the United States. No definite evidence for linkage of a Parkinson’s disease locus to chromosome 4q21–23 was demonstrated in these families suggesting that mutations of the α-synuclein gene are a rare cause of even dominantly inherited parkinsonism.

The possibility remains, however, that other mutations in the α-synuclein gene are involved in patients with sporadic Parkinson’s disease and these should be sought. We conclude that the G209A α-synuclein mutation is not relevant to most patients with idiopathic sporadic Parkinson’s disease.

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