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Absence of Mutation in the β- and γ-Synuclein Genes in Familial Autosomal Dominant Parkinson's Disease

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Parkinson's disease (PD) is a common progressive neurodegenerative disorder characterized by bradykinesia, muscular rigidity, resting tremor, and impaired postural reflexes.[1] Two missense mutations in the α-synuclein gene have been described in families with autosomal dominant Parkinson's disease: Ala53Thr in one Italian and three Greek families,[2] and Ala30Pro in one family of German origin.[3] These 2 mutations appear to account only for a minority of PD cases.[2,3] Evidence of genetic heterogeneity[4] indicates the necessity to evaluate other candidate genes for PD.

Beta- and γ-synuclein are the two other members of the synuclein family.[5] The α-, β- and γ-synuclein proteins are well conserved across species, and have strong sequence homology between them.[5] In particular, Ala30 of the α-synuclein mutated in a German family[3] is conserved in β- and γ-synuclein.[5] Interestingly, while both human α- and β-synuclein have an alanine at position 53, the human γ-synuclein normally has a threonine analogous to the mutant residue found in some PD patients.[2] The high sequence homology suggests similar functions and properties of the three synucleins. Previous studies have indicated that α-synuclein may be a natively unfolded protein which could facilitate protein-protein interactions.[6] It has also been demonstrated that α-synuclein can promote the formation of amyloid fibrils *in vitro*.[7,8] We have hypothesized that its amyloidogenic properties may promote protein aggregation and deposition.[2] Alpha- and β-synuclein have been shown to be localized in presynaptic nerve terminals in close proximity to synaptic vesicles,[9,10] and recent biochemical data have indicated that they may be able to inhibit phospholipase D2.[11] Gamma-synuclein is a protein which appears to influence neurofilament network integrity, by increasing the susceptibility of NF-H to calcium-dependent proteases,[12] and was originally found to be overexpressed in some advanced infiltrating carcinomas of the breast.[13] The three synucleins are small proteins, with a calculated molecular mass close to 14,000. However, their apparent molecular mass is about 19 to 20 KDa, indicating that they are post-transcriptionally modified. They are also highly expressed in brain and particularly in the substantia nigra,[5] which is the main region of neuronal degeneration in patients with PD.

We searched for mutations in the β- and γ-synuclein genes (SNCB and SNCG) by sequencing the entire coding region in probands of 71 families with Parkinson's disease. This large collection of PD families, with apparent autosomal dominant transmission of the disease, had various ethnic backgrounds: German (21), Greek (7), Serbian (5), Spanish (3), French-Canadian (1), Polish (1), Russian (1), Italian (1), Azorian (1), and the general population from the United States (30). The average number of reported affected individuals per family was 3.2. The age of onset of the probands ranged from 16 to 75; in 31 families the age of onset of the proband was ≤ 45 (mean ~ 34.3), while in the other families the mean onset age of the proband was ~ 61.

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Sequencing of the β- and γ-synuclein genes was done as previously described.[14,15] No mutation was identified, within the coding sequence, in any of the probands with PD. However, we cannot exclude the occurrence of rare mutations undetected in our PD samples (ex: untested regulatory elements, deletions) or in other patients. Interestingly, it has been shown that α-synuclein frequently accumulates in the intracytoplasmic neuronal inclusions known as Lewy bodies in the brains of PD patients, suggesting that it plays an important role in the pathogenesis of the disease.[16,17] However, Spillantini et al. reported that, contrary to α-synuclein, β- and γ-synuclein are apparently not found in Lewy bodies or Lewy neurites.[18] In light of these findings, our results suggest that β- and γ-synuclein are not directly involved or have only a minor contribution in the genetics of PD.

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