Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology.

We have previously linked families with autosomal-dominant, late-onset parkinsonism to chromosome 12p11.2-q13.1 (PARK8). By high-resolution recombination mapping and candidate gene sequencing in 46 families, we have found six disease-segregating mutations (five missense and one putative splice site mutation) in a gene encoding a large, multifunctional protein, LRRK2 (leucine-rich repeat kinase 2). It belongs to the ROCO protein family and includes a protein kinase domain of the MAPKKK class and several other major functional domains. Within affected carriers of families A and D, six post mortem diagnoses reveal brainstem dopaminergic degeneration accompanied by strikingly diverse pathologies. These include abnormalities consistent with Lewy body Parkinson's disease, diffuse Lewy body disease, nigral degeneration without distinctive histopathology, and progressive supranuclear palsy-like pathology. Clinical diagnoses of Parkinsonism with dementia or amyotrophy or both, with their associated pathologies, are also noted. Hence, LRRK2 may be central to the pathogenesis of several major neurodegenerative disorders associated with parkinsonism.