

## Genetic studies of Parkinson's disease

Parkinson's disease is a neurodegenerative disorder characterised by bradykinesia, resting tremor, rigidity, and postural instability. The disorder results from degeneration of neurons within the substantia nigra, creating a deficiency in dopamine-mediated movement.<sup>1</sup> About 50-60% of the substantia nigral neurons can be lost without obvious clinical consequence.<sup>2</sup> It was previously thought that Parkinson's disease had little or no genetic component, however, in the last several years there has been a large focus on genetic approaches to identify loci and genes involved in Parkinson's disease. Genetic studies involving familial parkinsonism have advanced our molecular understanding of selective degeneration of dopaminergic neurons in the mid-brain. Thus far, eight loci have been identified from family linkage studies for parkinsonism; these include:

- Park 1 (alpha synuclein; 4q21-23)
- Park 2 (parkin; 6q25.2-27)
- Park 3 (2p13)
- Park 4 (4p14-16.3)
- Park 5 (UCH-L1; 4p14)
- Park 6 (1p35-p36)
- Park 7 (1p36)
- Park 8 (12p11.2-q13p.1)

The A53T mutation of the alpha synuclein gene is rare and originally described in an Italian kindred (the Contursi kindred) but has been found in other kindreds originating from Greece.<sup>3,4</sup> PD in these families phenotypically includes rigidity, hypokinesia, postural instability and resting tremor with a positive response to levodopa therapy and may be associated with cognitive decline, severe central hypoventilation, orthostatic hypotension, myoclonus and urinary incontinence.<sup>2,5</sup> Another mutation in the alpha synuclein gene, A30P was identified in one German family in a highly conserved genomic region with clinical features including all four cardinal PD signs (resting tremor, bradykinesia, postural instability, and rigidity).<sup>5</sup> Genetic studies have failed to find many families with the A53T or A30P muta-

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tions. More generally, alpha synuclein has been found to be the major component of Lewy bodies in more common sporadic PD; and has been shown to be one of the principal components of glial and neuronal cytoplasmic inclusions and the Lewy body like inclusions in synucleinopathies.<sup>7</sup>

Parkin (Park 2) has become an important gene for further research. This gene includes 12 exons and encodes for an E3 ubiquitin protein ligase involved in the ubiquitin proteasomal degradation pathway. Parkin mutations are prevalent; 50% of early onset, familial European PD cases and as many as 18% of sporadic, early onset PD cases are attributed to Parkin.<sup>8</sup> Parkin was first described in autosomal recessive juvenile parkinsonism (ARJP) cases. Clinically the phenotype of parkin is very broad, individuals with parkin mutations commonly have atypical features including dystonia at onset, hyper-reflexia, diurnal fluctuations, and sleep benefit.<sup>9</sup> Additionally, positive parkin cases with typical PD symptoms and older age of onset have been identified (>45 years).<sup>8</sup> Problems with the preliminary data of parkin were due to low amounts of sequencing performed on the parkin coding exons; currently the spectrum of parkin now involves at least 60 different mutations.<sup>2</sup> Several parkin substrates have been identified and are being followed increasing the focus on the ubiquitin-proteasome pathway and its role in familial and sporadic PD.

Recent reports on Park6 and Park7 suggest that gene mutations on chromosome 1p may account for a proportion of early onset Parkinson's disease. Park6, located on Chromosome 1p35-36 was first discovered in a large Italian kindred (Marsala Kindred). The phenotype of this family includes early disease onset (32-48 yrs), levodopa responsiveness, slow disease progression, and levodopa therapy associated dyskinesias.<sup>10</sup> Signs reported in autosomal recessive juvenile parkinsonism (ARJP) such as dystonia and sleep benefit are absent in the Marsala kindred. After initial reporting of the kindred, an additional eight families with Parkin negative ARJP from four different European countries were confirmed to have linkage to Park6.<sup>11</sup> The phe-

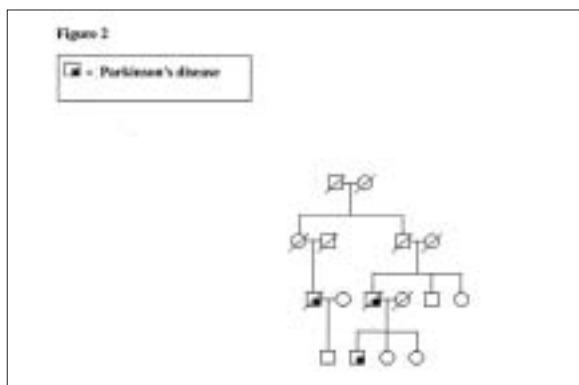
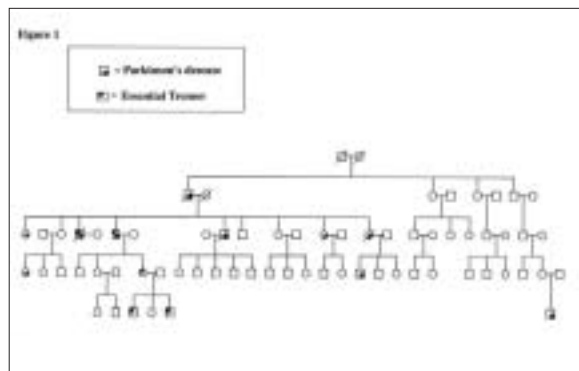
Gene	Chromosome Location	Clinical Diagnosis	Inheritance Pattern	Levodopa Responsive	Asymmetry	Resting Tremor	Dementia	Pathology
Park1 Alpha synuclein (A53T)	4q21-23	PD DLBD	AD	Y	Y	Y	Y	PD, DLB
Park1 Alpha synuclein (A30P)	4q21-23	PD	AD	Y	Y	Y	Variable	PD
Park2 Parkin (deletions or point mutations)	6q25.2-27	PD, dystonia	Variable; mostly recessive	Y	Variable	Variable	N	Neuronal loss in pigmented neurons (one lewy body report)
Park3	2p13	PD	AD, reduced penetrance	Y	Y	Y	Variable	PD
Park4	4p14-16.3	PD	AD, reduced penetrance	Y	Y	Y	Y	PD, DLB
Park6	1p35-36	PD	AR	Y	Y	Y	N	NA
Park7	1p36	PD	AR	Y	Y	Y	N	NA
Park8	12p11.2-q13.1	PD	?, possibly AD	Y	Y	Y	N	NA

notypes from these eight families overlap with that reported for European parkin cases, including a wide range for age of onset and additionally show slow progression of the disease. A second locus also located on chromosome 1 involved in autosomal recessive early onset parkinsonism, Park7, was discovered in a consanguineous family from an isolated community in the SW region of The Netherlands. The clinical phenotype of this family includes early onset parkinsonism and shows response to both levodopa and dopamine agonist therapy and slow progression of the disease.<sup>12</sup> Park 7 is 25cM telomeric to Park 6. Phenotypes of Park 6 and Park 7 are similar, however, focal dystonia appears as a symptom in Park 7 familial case.

Park 8 was mapped to Chromosome 12p11.2-q13.1 using linkage analysis in a large Japanese family with autosomal dominant PD. Clinical features are comparable to idiopathic PD including favourable response to dopaminergic agents. Neuropathological examination in four cases interestingly showed nigral degeneration without lewy bodies.<sup>13</sup> No other families have been found with the Park 8 locus to date. The Park 8 region contains several relevant genes and varies from any known hereditary PD locus.<sup>13</sup>

Genetics has revolutionised neurological research; our understanding of Parkinson's disease has been better characterised as a result of familial parkinsonism studies. In the future genetic studies will continue to expand our knowledge of parkinsonism and other neurodegenerative diseases and will be key in characterising the biochemical pathways of neurological diseases, which will help to pinpoint therapeutic targets and direct gene-environment interaction studies.

*The Laboratory of Neurogenetics (NIA) studies familial cases of parkinsonism and other movement disorders. We would be interested in collaborative efforts in cases with a strong family history of disease or early age of disease onset (<50 years). Examples of families we collect or would be interested in collecting are shown in Figures 1 and 2. Please contact Dr. John Hardy to discuss collaborations or direct interested participants to contact Melissa Hanson.*



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