

Parkinson Disease

Research Studies-Genetics of PD

1. PROGENI (Parkinsons Research: The Organized Genetics Initiative)
 - Sib pairs affected with Parkinson's disease
 - Sponsored by National Institutes of Health
 - <http://progeni.iu.edu>
2. Genetic analysis of Parkinson's disease
 - recruiting individuals from families with autosomal dominant Parkinsonism.
 - Sponsor National Human Genome Research Institute
 - http://clinicalstudies.info.nih.gov/detail/A_1997-HG-0078.html
3. Molecular Epidemiology of Parkinson's Disease
 - Affected individuals + unaffected siblings.
 - Sponsor National Institute of Environmental Health Sciences
 - <http://mayoresearch.mayo.edu/mayo/research/parkinsons/>

Support Groups/websites:

1. We Move
 - (p) 800-437-MOV2 www.wemove.org
2. Parkinson's Disease Foundation
 - (p) 800-457-6676 www.pdf.org
3. American Parkinson's Disease Association
 - (p) 800-223-2732 www.apdaparkinson.org
4. National Parkinson Foundation
 - (p) 800-327-4545 www.parkinson.org

Patient Reading:

1. Kathleen Biziere, Matthias Kurth. Living With Parkinson's Disease. Demos Vermande, 1997
2. David L. Cram. Understanding Parkinson's Disease :A Self Help Guide. LPC, 1999.

Family history clues

In a family history, the following may be clues to undiagnosed cases of Parkinsonism: tremor, shuffling gait, soft voice, small handwriting, dementia/personality changes, vivid dreams, postural instability, "masked" facies (loss of facial expression), depression/anxiety.

Diagnostic Criteria

Precise diagnostic criteria for Parkinson's disease remain elusive. It is important to distinguish idiopathic Parkinson's disease from the broader term "Parkinsonism." Numerous neurodegenerative diseases may include a Parkinson's-like clinical picture, including progressive supranuclear palsy and corticobasal degeneration. Parkinsonism can also be a secondary feature of stroke or exposure to toxins such as the recreational drug "ecstasy."

Pathology: Loss of pigmented neurons in the substantia nigra is a hallmark of Parkinson's disease. The presence of Lewy bodies is an important finding.

However, Lewy bodies may be seen in other neurodegenerative diseases, such as Alzheimer disease and multiple systems atrophy. Some forms of Parkinson's disease, such as Parkin-related disease, may lack characteristic Lewy bodies.

Clinical findings: The classic features of Parkinson's disease include:

Bradykinesia-difficulty initiating movements. Clinically evaluated by having patient perform rapid complex movements such as finger tapping, circling hands, etc.

Tremor-The presence of a tremor is commonly associated with Parkinson's disease. Many types of tremor, such as essential tremor, may be due to other causes. The tremor in PD is most often a "resting" tremor that may decrease during activity and be aggravated by stress.

Rigidity-involuntary stiffness of skeletal muscles. Can be elicited by moving large joints in the arm. "Lead pipe" and "Cog wheel" rigidity are terms used to describe the stiffness of the muscles.

Postural instability-patients begin to adopt a stooped, shuffling gait; falls occur later in the disease.

History: Many patients will report other symptoms including: small handwriting, vivid dreams, difficulty repositioning in bed, depression, anxiety,

Imaging findings: PET and SPECT scanning can support, but not confirm, a diagnosis of PD, and are considered "experimental".

Treatments/Intervention

1. Pharmacological-dopaminergic agents, such as levodopa, improve symptoms in Parkinson's disease. However, after many years this benefit comes with undesirable side effects such as dyskinesias (involuntary movements). There can also be significant fluctuations in the efficacy of the medicine. Some forms of Parkinsonism, such as progressive supranuclear palsy, may not respond well to these agents.
2. Surgical treatments include surgical destruction of portions of the globus pallidus or thalamus. This may improve some motor symptoms, but there is a significant risk of side effects.
3. Deep brain stimulation-implantation of an electrode to provide continual stimulation of globus pallidus, subthalamic nucleus, or thalamus. May improve motor symptoms and/or tremor.
4. Fetal stem cell transplantation is still considered research, and mixed results have been seen.

DNA testing options

Studies have identified numerous loci associated with a strong risk for developing PD.

These loci are:

PARK1-**Alpha synuclein** (autosomal dominant parkinsonism)

PARK2-**Parkin** (autosomal recessive early onset, possibly dominant in some families, may also be a modifying gene)

PARK3-unknown

PARK5-**UCHL1** (?susceptibility gene)

PARK6-**PINK1** (autosomal recessive early-onset parkinsonism)

PARK7-**DJ-1** (autosomal recessive early-onset parkinsonism)

PARK8-unknown (autosomal dominant parkinsonism)

In addition to these major loci, numerous candidate gene studies have suggested involvement of other loci in Parkinson's risk. These include polymorphisms in detoxification genes such as glutathione s-transferase and cytochrome p450 genes. Others have suggested a small increase in risk associated with the H1 haplotype of the tau gene. It is not yet clear how testing for such haplotypes/polymorphisms could be used clinically to predict risk for PD. Such testing is not clinically available.

As of the present time, the only clinically available genetic testing for Parkinson's disease is sequencing and dosage analysis of the Parkin gene (PARK2). While Parkin mutations are most frequent in autosomal recessive juvenile Parkinson's disease, mutations have been described in isolated early onset cases, later onset recessive cases, and even some apparently dominant pedigrees. Evaluation of the Parkin gene should include both sequencing and a quantitative analysis to look for genomic rearrangements. A significant percentage of Parkin mutations are large deletions that will not be detected by sequence analysis.

Review References

1. Albanese A (2003) Diagnostic criteria for Parkinson's disease. *Neurological Sciences* 24(supplement) s23-s26.
2. Bonifati et al. (2003) Mutations in the DJ-1 gene associated with autosomal recessive early-onset Parkinsonism. *Science* 299:256-259.
3. Dawson TM and Dawson VL (2003) Molecular Pathways of Neurodegeneration in Parkinson's disease. *Science* 302:819-822.
4. Farrer et al. (1999) The genetics of disorders with synuclein pathology and Parkinsonism. *Human Molecular Genetics* 8(10):1901-1905.
5. Hughes et al. (2002) The Accuracy of Diagnosis of Parkinsonian Syndromes in a Specialist Movement Disorder Service. *Brain* 125:861-70
6. Lucking CB et al (2000) Association between early onset Parkinson's disease and mutations in the Parkin gene. *New England Journal of Medicine* 342:1560-1567.
7. Marder K et al. (2003) Familial aggregation of early and late-onset Parkinson's disease. *Annals of Neurology* 54:507-513.
8. Paoline M et al. (2004) Parkinson's disease, pesticides and individual vulnerability. *Trends in Pharmacological Sciences* 25(3):124-9.
9. Rao G et al (2003) Does this Patient have Parkinson disease? *JAMA* 289(3):347-353.
10. Riess O et al. (2000) Genetic influence on the development of Parkinson's disease. *Journal of Neurology* 247 (supplement 2): s69-s74.
11. Valente EM et al. (2004) Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* Published online 4/15/2004.
12. West AB and Maidment N (2004) Genetics of Parkin linked disease. *Human Genetics* 114:327-336.