

Heredity in Parkinson's Disease: New Findings

Nirit Lev MD and Eldad Melamed MD

Department of Neurology, Rabin Medical Center (Beilinson Campus), Petah Tiqva, Israel

Key words: Parkinson's disease, heredity, parkin, alpha-synuclein, tau

IMAJ 2001;3:435-438

Parkinson's disease is a common progressive and disabling neurodegenerative disorder characterized clinically by resting tremor, rigidity, bradykinesia and postural instability. Its pathological findings include neuronal degeneration and gliosis in the substantia nigra and the locus ceruleus, and the presence of eosinophilic cytoplasmic inclusion bodies (Lewy bodies) in the substantia nigra.

Only a minority of Parkinson's disease patients has a clearly familial disease in which parkinsonism is inherited as a mendelian trait. While approximately 5% of parkinsonian patients have a family history of a similar disorder, most Parkinson's disease patients have a sporadic disorder. The primary cause of sporadic Parkinson's disease is still largely unknown despite ever-increasing intensive research. The ongoing debate is whether sporadic Parkinson's disease is caused by environmental agents, hereditary factors, or a combination of both.

In the nineteenth century Charcot had already speculated that Parkinson's disease may be an inherited disorder since many of his patients had positive family histories [1]. The pandemic of encephalitis lethargica (1918-1920) that resulted in postencephalitic parkinsonism in many survivors caused a reversal of opinion, with a shift to environmental factors as the main etiology of the disease [1]. In 1983 an outbreak of parkinsonism in California was found to be caused by heroin contaminated by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [2]. This simple pyridine moiety is capable of inducing all the motor features of Parkinson's disease by selectively destroying the substantia nigra pars compacta dopaminergic neurons. This lent further support to the possible importance of environmental toxic agents in the etiology of the illness.

Nonetheless, verifying that environmental factors are the cause of Parkinson's disease proves to be a difficult task. Although many factors have been suggested to enhance the risk of Parkinson's disease, the only unequivocally accepted risk factor identified to date is increasing age. Factors that have been suggested by epidemiological studies include rural living, farming, herbicide and pesticide exposure, and drinking well water. Only two specific suspicious agents have been identified, namely organochlorine pesticides and dithiocarbamates [1]. Interestingly, an inverse relationship between cigarette smoking and the risk for Parkinson's disease has been detected in a series of studies [1].

Most twin studies have shown a low concordance rate in monozygotic twins and thus could not establish a major genetic contribution to the etiology [3,4]. A recent study found a higher concordance rate in young-onset monozygotic twins [5], which suggests a substantial genetic determinant in this subgroup. Another study, using ^{18}F -dopa and positron emission tomography, showed a higher concordance for nigral pathology in monozygotic twins than in dizygotic twins [6]. This study allowed identification of subclinical disease and thereby demonstrated a much higher concordance rate in monozygotic twins than was found by clinical examination. Population-based epidemiological studies indicate that the risk of Parkinson's disease is at least doubled in first-degree relatives of patients compared with controls, while hospital-based studies suggest a higher risk [7-9].

It is currently believed that an interaction between genetic predisposition and environmental factors triggers the disease process. The existence of genetic susceptibility is strongly suspected, especially among patients with young-onset illness.

There are some families with a clear inherited form of Parkinson's disease, in which both autosomal dominant and autosomal recessive forms of inheritance have been identified. Two genes (alpha-synuclein and ubiquitin carboxy-terminal hydrolase L1) and two gene loci were implicated in the pathogenesis of autosomal dominant Parkinson's disease [10]. In autosomal recessive families with early-onset parkinsonism, mutations in the Parkin gene were recently identified [11].

Genetic investigation and molecular cloning of the disease genes in members of these families, together with investigation of the encoded proteins could contribute to the elucidation of the etiology and pathogenesis of the more common sporadic Parkinson's disease. Major breakthroughs were lately made in identifying genes involved in Parkinson's disease pathogenesis. The aim of this article is to review these new findings and to try elucidate the pathogenesis of Parkinson's disease via these new discoveries [Table 1].

Autosomal dominant parkinsonism

Alpha-synuclein gene mutations

The study of a large Italian family with Parkinson's disease, called the Contursi kindred, used a genome scan approach that led to mapping of a susceptibility gene to the chromosome 4q21-q23 region [12], to the same area of a gene encoding alpha-

synuclein. Initial symptoms in this kindred include resting tremor, bradykinesia, or gait disturbance. Dementia was not uncommon. There was a good response to levodopa treatment. The illness in the Contursi kindred is atypical only for its young average age of onset (45.6 years) and for its relatively rapid duration from onset to death (9.2 ± 4.9 years) [13,14]. Pathologically, neuronal degeneration and gliosis occur in the substantia nigra and the locus ceruleus; Lewy bodies are found in these locations as well as some cortical Lewy bodies [13,15].

Mutation analysis of the alpha-synuclein in these patients revealed a single missense mutation, i.e., G209A [14]. This mutation causes a replacement of Ala53Thr in the protein level. One additional mutation in the alpha-synuclein gene was found in a German family with autosomal dominant Parkinson's disease – C88G (Ala30Pro in the protein level) [15].

The normal alpha-synuclein (wild type) is an abundant presynaptic protein in human brain, widely expressed in cortical areas and in the basal ganglia [14]. It was found to be heavily deposited in the Lewy bodies of sporadic Parkinson's disease as well as in the cytoplasm and neuronal processes in close association with ubiquitin [14,16]. Interestingly, it also forms a component of amyloid plaques in Alzheimer's disease (NACP) [16], suggesting that this protein tends to form aggregates [14–16]. It is hypothesized that the mutations in the gene encoding for this protein may result in self-aggregation and/or decreased degradation of the protein, leading to development of inclusion bodies and eventually to neuronal death.

Familial frontotemporal dementia and parkinsonism

This is an autosomal dominant disorder that was linked to chromosome 17. It consists of behavioral changes, cognitive disturbances, dementia and parkinsonism [17]. Pathological features include neuronal loss and gliosis in the substantia nigra, locus ceruleus, pontine tegmentum, globus pallidus, subthalamic nucleus, pyramidal tracts, and cerebral cortex. Ballooned neurons with tau-positive inclusions are found in affected areas. There are no Lewy bodies or neurofibrillary tangles [15].

The gene encoding for tau protein is localized in the long arm of chromosome 17, and mutations in this gene were recently found in patients with this disorder. Five exonic and four

intronic mutations are presently known. Exonic mutations tend to cause dementia as the predominant clinical picture, while intronic mutations result in more prominent motor disturbances [15]. Tau is a microtubule-associated protein. Abnormal tau tends to form a filamentous structure that may lead to formation of neuronal inclusion bodies and cell death.

Chromosome 2-linked autosomal dominant Parkinson's disease

Gasser et al. [18] reported a susceptibility locus for Parkinson's disease in chromosome 2p13. They described families of European origin with typical clinical features of Parkinson's disease and good response to levodopa. The mean age of disease onset was 59 years. Pathology revealed nigral and locus ceruleus neuronal death and gliosis with Lewy bodies. In some families, there was also dementia with neurofibrillary tangles and senile plaques in the neocortex [15]. The gene involved in these families is still unknown.

Chromosome 4-linked autosomal dominant Parkinson's disease

Patients from a large American family known as the Iowanian family have early-onset autosomal dominant Parkinson's disease. The clinical features are generally similar to those of sporadic Parkinson's disease. Unique manifestations are the common presence of dementia and frontal release signs. Pathological features consist of neuronal degeneration, gliosis and Lewy bodies in the substantia nigra and locus ceruleus, as well as widespread cortical Lewy bodies. In addition, there is atrophy of the temporal lobe. This familial form was mapped to chromosome 4p15.1 [15] and may represent a familial form of diffuse Lewy body disease.

Ubiquitin carboxy-terminal hydrolase L1 gene mutation

To date there is only one family known to have this mutation. The family members are affected with early-onset levodopa-responsive parkinsonism. The disease is caused by a missense mutation in the ubiquitin carboxy-terminal hydrolase L1 gene, which is located at chromosome 4p14 [15,19]. Ubiquitin

Table 1. Summary of the known forms of hereditary parkinsonism

No.	Name	Mode	Location	Mutation	Clinical features
1.	Alpha-synuclein mutations	AD	4q21-q23	Alpha-synuclein (G209A,C88G)	Parkinsonism, dementia not uncommon
2.	Familial frontotemporal dementia & parkinsonism	AD	17	Tau protein gene mutations	Dementia, parkinsonism, behavioral changes
3.	Chromosome 2-linked parkinsonism	AD	2p13	?	Parkinsonism, Dementia in some
4.	Chromosome 4-linked parkinsonism	AD	4p15.1	?	Parkinsonism, dementia, frontal release signs
5.	Ubiquitin C-terminal hydrolase L1 mutation	AD	4p14	Missense mutation in the hydrolase gene (C277G)	Early-onset parkinsonism
6.	Parkin gene mutations	AR	6q25.2-27	Parkin gene mutations	Very early-onset parkinsonism

carboxy-terminal hydrolase L1 is one of the most abundant proteins in the brain and immunoreactivity to this protein was found in Lewy bodies [19]. The ubiquitin pathway is important in the elimination of damaged proteins. Proteins tagged with four or more ubiquitins are targeted for destruction, while the ubiquitin tag is recycled. Ubiquitin carboxy-terminal hydrolase L1 enzyme hydrolyzes terminal small adducts of ubiquitin and generates free monomeric ubiquitin. The missense mutation C277G (Ile93Met at the protein level) causes partial loss of its catalytic activity [15,19]. The reduced catalytic activity may result in accumulation of its substrate(s). It may also render the protein itself prone to aggregation or interfere in the ubiquitin pathway in another, yet unknown way.

Autosomal recessive Parkinsonism

Parkin gene mutations

Mutations in a gene, designated parkin, have recently been identified in families with autosomal recessive early-onset parkinsonism. The clinical features of this familial parkinsonism were first described in Japan [11,15]. It consists of early disease onset (usually in the second to third decades), typical motor signs of Parkinson's disease (tremor, rigidity, bradykinesia and postural instability), and good response to levodopa. Dystonic features, hyper-reflexia, sleep benefit, and tendency to develop motor fluctuations and dyskinesias under treatment with levodopa are also common. The rate of disease progression is slow [10,15,20]. However, European and North African patients with parkin mutations are clinically indistinguishable from patients with idiopathic Parkinson's disease [10]. Pathological changes include neuronal loss and gliosis in the substantia nigra and the locus ceruleus, but there are no Lewy bodies [15,20].

In normal brains, the parkin protein is more abundant in the substantia nigra than in other areas of the brain [15,21]. Intracellularly, it was located in the Golgi complex and the cytosol [21]. The parkin protein was not found in Lewy bodies. No parkin was expressed in brains of patients with autosomal recessive juvenile parkinsonism [21]. It is now thought to be part of the ubiquitin pathway and functions as a ubiquitin ligase.

The disease gene was mapped to chromosome 6q25.2-27 [22]. The gene cloned was about 1 Mb (the second largest gene next to the dystrophin gene) and consists of 12 exons [15,22]. Affected patients were found to have deletions or point mutations. Exons 3 to 7 appeared to be mutational hot spots [15]. This type of familial parkinsonism is now identified worldwide [15,23], including patients carrying these mutations in Israel.

Summary

Multiple factors have been hypothesized over the last century to be causative or contributory for Parkinson's disease. Hereditary factors have recently emerged as a major focus of Parkinson's disease research. Until recently most of the research on the etiology of Parkinson's disease concentrated on environmental factors, and the possibility that genetic factors contribute

significantly to the pathogenesis of Parkinson's disease has been neglected. However, it has become increasingly apparent that even in sporadic cases, the disease most likely reflects a combination of genetic susceptibility and an unknown environmental insult. Moreover, the identification of genes and proteins that may cause hereditary parkinsonism substantially contributes to our ability to understand the pathogenesis of Parkinson's disease and may help in the early identification of the disease and its treatment.

The discovery of alpha-synuclein mutations in families with autosomal dominant Parkinson's disease sheds light on its role in sporadic Parkinson's disease. It seems that this protein tends to aggregate when the cellular milieu is altered [14-16]. The question as to the exact changes that cause its deposition remains open. One of the major possibilities is oxidative stress [16]. The role of these aggregates in neuronal cell death is also still unclear. Transgenic mice expressing wild-type human alpha-synuclein developed progressive accumulation of alpha-synuclein and ubiquitin-immunoreactive inclusions in neurons in the neocortex, hippocampus and the substantia nigra. These alterations were associated with loss of dopaminergic terminals and motor impairments [24]. This finding suggests that accumulation of alpha-synuclein may play a causal role in sporadic Parkinson's disease as well.

The parkin protein seems to be a crucial survival factor for nigral neurons [15]. The parkin protein is related to the ubiquitin pathway, which is important in the elimination of damaged proteins. Ubiquitin-mediated degradation of proteins plays a central role in the control of numerous processes, including signal transduction, receptor and transcriptional regulations, programmed cell death, and breakdown of abnormal proteins that may interfere with normal cell functions. Further studies on the function of Parkin protein and its relation to the ubiquitin pathway could elucidate at least one of the molecular mechanisms of nigral neuronal death. A mutation in the ubiquitin carboxy-terminal hydrolase L1 gene also implies the importance of the ubiquitin pathway in Parkinson's disease.

Abnormal tau protein was found to be the cause of familial frontotemporal dementia and parkinsonism. It tends to form filamentous structures, which may lead to neuronal death. Elucidation of the molecular mechanism of neuronal death in this disease may contribute to our understanding of sporadic diseases with tau accumulation, such as corticobasal degeneration, progressive supranuclear palsy, Pick's disease, Alzheimer's disease and possibly also the pathogenesis of Parkinson's disease. Other genetic loci have been identified by linkage analysis of patients with familial parkinsonism. These loci conceal other genes and proteins that may be pivotal factors in the pathogenesis of Parkinson's disease.

The discovery of genetic mutations in patients with parkinsonism may offer us new insights into the understanding of the pathways leading to neuronal death and development of Parkinson's disease. It may also help in the early identification

of susceptible people to this disease and possibly in developing new treatment strategies.

Acknowledgement. Supported, in part, by the National Parkinson Foundation, USA.

References

- Langston JW. Epidemiology versus genetics in Parkinson's disease: progress in resolving an age-old debate. *Ann Neurol* 1998;44:S45–52.
- Langston JW, Ballard PA, Tetrund JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine analog synthesis. *Science* 1983;219:979–80.
- Gasser T. Genetics of Parkinson's disease. *Ann Neurol* 1998;44:S53–7.
- Vierregge P, Schiffke KA, Friedrich HJ, Muller B, Ludin HP. Parkinson's disease in twins. *Neurology* 1992;42:1453–61.
- Tanner CM, Ottman R, Ellenberg JH, Goldman SM, Mayeux R, Chan P, Langston JW. Parkinson's disease concordance in elderly male monozygotic and dizygotic twins. *Neurology* 1997;48:A333.
- Burn DJ, Mark MH, Playford ED, Maraganore DM, Zimmerman TR, Duvoisin RC, Harding AE, Marsden CD, Brooks DJ. Parkinson's disease in twins studied with ¹⁸F-dopa and positron emission tomography. *Neurology* 1992;42:1894–900.
- Jarman P, Wood N. Parkinson's disease genetics comes of age. *Br Med J* 1999;318:1641–2.
- Payami H, Larsen K, Bernard S, Nutt J. Increased risk of Parkinson's disease in parents and siblings of patients. *Ann Neurol* 1994;36:659–61.
- Vierregge P, Heberlein I. Increased risk of Parkinson's disease in relatives of patients. *Ann Neurol* 1995;37:685.
- Lucking CB, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Denefle P, Wood NW, Agid Y, Brice A. Association between early-onset Parkinson's disease and mutations in the Parkin gene. *N Engl J Med* 2000;342:1560–7.
- Nussbaum RL. Putting the Parkin into Parkinson's. *Nature* 1998;392:544–5.
- Polymeropoulos MH. Autosomal dominant Parkinson's disease and alpha-synuclein. *Ann Neurol* 1998;44:S63–4.
- Golbe LI, Di Iorio G, Bonavita V, Miller DC, Duvoisin RC. A large kindred with autosomal dominant Parkinson's disease. *Ann Neurol* 1990;27:276–82.
- Golbe LI, Di Iorio G, Sanges G, Lazzarini AM, La Sala S, Bonavita V, Duvoisin RC. Clinical genetic analysis of Parkinson's disease in the Contursi kindred. *Ann Neurol* 1996;40:767–75.
- Mizuno Y, Hattori N, Mori H. Genetics of Parkinson's disease. *Biomed Pharmacother* 1999;53:109–16.
- Mezey E, Dehejia A, Harta G, Papp MI, Polymeropoulos MH, Brownstein MJ. Alpha synuclein in neurodegenerative disorders: murderer or accomplice? *Nat Med* 1998;4:755–6.
- Foster NL, Wilhelmsen K, Sima AAF, Jone MZ, D'Amato CJ, Gilman S, Conference Participants. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. *Ann Neurol* 1997;41:706–15.
- Gasser T, Muller-Myhsok B, Wszolek ZH, Oehlmann R, Calne DB, Bonifati V, Bereznaï B, Fabrizio E, Vierregge P, Horstmann RD. A susceptibility locus for Parkinson's disease maps to chromosome 2p13. *Nat Genet* 1998;18:262–5.
- Leroy E, Boyer R, Auburger G, Leube B, Ulm G, Mezey E, Harta G, Brownstein MJ, Jonnalagada S, Chernova T, Dehejia A, Lavedan C, Gasser T, Steinbach PJ, Wilkinson KD, Polymeropoulos MH. The ubiquitin pathway in Parkinson's disease. *Nature* 1998;395:451–2.
- Hattori N, Kitada T, Matsumine H, Asakawa S, Yamamura Y, Yoshino H, Kobayashi T, Yokochi M, Wang W, Yoritaka A, Kondo T, Kuzuhara S, Nakamura S, Shimizu N, Mizuno Y. Molecular genetic analysis of a novel Parkin gene in Japanese families with autosomal recessive juvenile parkinsonism: evidence for variable homozygous deletions in the Parkin gene in affected individuals. *Ann Neurol* 1998;44:935–41.
- Shimura H, Hattori N, Kubo S, Yoshikawa M, Kitada T, Matsumine H, Asakawa S, Minoshima S, Yamamura Y, Shimizu N, Mizuno Y. Immunohistochemical and subcellular localization of Parkin protein: absence of protein in autosomal recessive juvenile parkinsonism patients. *Ann Neurol* 1999;45:668–72.
- Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the Parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 1998;392:605–8.
- Lucking CB, Abbas N, Durr A, Bonifati V, Bonnet AM, De Brouker T, De Michele G, Wood NW, Agid Y, Brice A. Homozygous deletions in parkin gene in European and North African families with autosomal recessive juvenile parkinsonism. *Lancet* 1998;352:1355–6.
- Masliah E, Rockenstein E, Veinbergs I, Mallory M, Hashimoto M, Takeda A, Sagara Y, Sisk A, Mucke L. Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. *Science* 2000;287:1265–9.

Correspondence: Dr. N. Lev, Dept. of Neurology, Rabin Medical Center (Beilinson Campus), Petah Tiqva 49101, Israel. Phone: (972-3) 937-6538/4, Fax: (972-3) 922-3352, email: niril@hotmail.com