

Genetics

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INTRODUCTION

Despite considerable progress in the understanding of clinical and pathological features of Parkinson's disease (PD), the etiology of this condition remains unknown (1,2). There are two major plausible explanations on which current working hypotheses are based. The "environmental hypothesis," widely propagated in the 1980s, appears to have had only limited influence (3). The scope of environmental factors on causation of PD is discussed in [Chapter 15](#). The "genetic hypothesis," which was popular in the 1990s, stemmed from significant progress in the development of new molecular genetic techniques and from the description of several large families with a phenotype closely resembling that of sporadic PD (4,5). However, genetic factors still do not explain the etiology of all cases of PD (6). It is reasonable to assume that a combination of environmental and inherited risk factors plays the crucial role in developing disease in most cases of parkinsonism. The era of exploration of these intermingling influences and factors is just beginning.

Understanding the etiology of PD is further complicated by a lack of *in vivo* biological markers for a diagnosis of PD, requiring reliance on

clinical or pathological criteria (7). In addition, PD is probably not a uniform clinical entity but rather represents a heterogeneous syndrome (8). In this chapter we will discuss the contributions of epidemiological, twin, kindred, and association studies to the support of the genetic hypothesis of PD and related parkinsonism-plus syndromes (PPS).

EPIDEMIOLOGICAL STUDIES

Epidemiological studies indicate a genetic contribution to the etiology of PD. According to a study conducted by Lazzarini and colleagues (9) in New Jersey, the chance of having PD at age 80 years is about 2% for the general population and about 5–6% if a parent or sibling is affected. However, if both a parent and a sibling are affected, the probability of having PD increases further, reaching 20–40%. Marder and colleagues (10) assessed the risk of PD among first-degree relatives from the same geographic region (northern Manhattan, New York). The cumulative incidence of PD to age 75 years among first-degree relatives of patients with PD was 2% compared with 1% among first-degree relatives of controls. The risk of PD was higher in male than in female first-degree relatives [relative risk, 2.0; 95% confidence interval (CI), 1.1–3.4]. The risk of PD in any first-degree relative was also higher for whites than for African-Americans and Hispanics (relative risk, 2.4; 95% CI, 1.4–4.1).

In an Italian case-control study (11), history of familial PD was the most relevant risk factor (odds ratio, 14.6; 95% CI, 7.2–29.6). In a Canadian study of PD patients (12), the prevalence rate of PD in first- and second-degree relatives was more than five times higher than that of the general population. Even patients who reported a negative family history of PD actually had a prevalence rate of PD in relatives more than three times higher than that in the general population. A study of the Icelandic population (13) revealed the presence of genetic as well as environmental components in the etiology of late-onset PD (onset at >50 years of age). The risk ratio for PD was 6.7 (95% CI, 1.2–9.6) for siblings, 3.2 (95% CI, 1.2–7.8) for offspring, and 2.7 (95% CI, 1.6–3.9) for nephews and nieces of patients with late-onset PD. The most recent epidemiological study, conducted by Maher and colleagues (14) on 203 sibling pairs with PD, also supported a genetic contribution to the etiology of PD. This study showed that sibling pairs with PD were more similar in age at symptomatic disease onset than in year of symptomatic disease onset. The frequency of PD in parents (7.0%) and siblings (5.1%) was greater than that in spouses (2%).

TWIN STUDIES

Studies of twins can provide a powerful confirmation of the genetic contribution to the etiology of a neurodegenerative condition. If a genetic component is present, concordance will be greater in monozygotic (MZ) than in dizygotic (DZ) twins. If a disorder is exclusively genetic in origin and the diagnosis is not compounded by age-associated penetrance or stochastic or environmental factors, MZ concordance may be close to 100%.

Although earlier twin studies in PD were inconclusive (15–17), the most recent twin study, conducted by Tanner and colleagues (18) on a large cohort of twins, demonstrated the presence of genetic factors in the etiology of PD if disease begins at or before age 50 years. This was a study of twins enrolled in the National Academy of Science/National Research Council World War II Veteran Twin Registry. No genetic component was evident when the onset of symptoms occurred after age 50 years. However, twin studies such as this one, which was based exclusively on clinical observations, may require extended longitudinal follow-up to confirm the presence of PD in a co-twin (19).

Positron emission tomography (PET) studies with [¹⁸F]6-fluorodopa (6FD) may in part circumvent the need for extended follow-up. Indeed, reduced striatal uptake of 6FD has been demonstrated in some clinically asymptomatic co-twins (20). Using longitudinal evaluation with measurement of 6FD, Piccini and colleagues (21) demonstrated 75% concordance of PD in MZ twins versus 22% in DZ twins.

EVALUATION OF KINDREDS

Kindreds with a parkinsonian phenotype have been reported in the world literature since the nineteenth century (22,23). In a review of literature in 1926, Bell and Clark (24) described 10 families with “shaking palsy” believed to exist on a hereditary basis. They also provided 20 references of earlier accounts of familial paralysis agitans. In 1937, Allen (25) detailed an additional 25 families with inherited parkinsonism and speculated that in approximately two thirds of these kindreds the inheritance was autosomal dominant and probably the result of a “single autosomal gene.” In 1949, a monograph by Mjones (26) detailed eight pedigrees with inherited parkinsonism, some with atypical features such as myoclonic epilepsy. In the levodopa era, a number of reports described families with PD and PPS (22), including two very large multigenerational kindreds known as Contursi and Family C (German-American) (27,28). With progress in molecular genetic techniques, the importance of collecting data from parkinsonian families with PD and PPS phenotypes has grown exponentially.

Table 1 summarizes the status of current knowledge of the genetics of PD and related conditions. It shows the types of inheritance and the location of known chromosomal loci and mutations. The key literature references are also provided.

ASSOCIATION STUDIES

Despite substantial progress in identification, the number of known large pedigrees with PD or PPS is still small. Furthermore, genetic linkage studies, which use “identity-by-descent” mapping, have been hampered because the amount of DNA available from affected pedigree members is limited, generally as a result of death, lack of consent, or geographic dispersion. Association or “identity-by-state” mapping is an alternate approach employing groups of unrelated individuals. Association studies measure differences in genetic variability between a group with the disease in question and a group of matched, normal individuals. This method is most powerful in implicating genes for multigenic traits in homogeneous population isolates. However, many past studies have been confounded by misconceived, a priori notions of disease etiology and by clinical, locus, and allelic heterogeneity. Studies must be reproducible, preferably in different ethnic populations, and the genetic variability should have some functional consequence (either directly or in disequilibrium) that alters gene expression or the resultant protein.

The genes for α -synuclein, ubiquitin C-terminal hydrolase, parkin, and tau harbor mutations that segregate with parkinsonism in large multiply affected kindreds (31,33,34,37,43) (Fig. 1). Although the relevance of these findings for sporadic PD is unclear, there is no doubt that these genes mark a pathway that is perturbed in both familial and sporadic PD. Understanding the components of this pathway and its regulation is the first step in elucidating the molecular etiology of parkinsonism (48). In some studies, common genetic variability in genes for α -synuclein (49,50), ubiquitin C-terminal hydrolase (51–53), and tau (54–56) has now been implicated in sporadic PD by association methods. It is clear that these genes contribute to risk in at least a subset of patients with idiopathic PD.

Other contributing genes are likely to be identified through family studies, ultimately facilitating molecular rather than clinicopathological diagnosis. Mutations in genes implicated in parkinsonism have already been used to create in vivo models that are providing powerful insights into neuronal degeneration (57–61). Much as in Alzheimer’s disease, these new tools bring the hope of novel therapies designed to address the causes rather than merely the symptoms of disease (62).

TABLE 1 Familial Parkinsonism with Reported Mutations/Loci

Chromosome	Gene	Locus	Age at onset, range, y(mean)	Phenotype	Response to levodopa	Ref.
Autosomal dominant						
1p32	Unknown	PARK9	NA (65)	PD, pathology unknown	Good	29
2p13	Unknown	PARK3	36–89 (58)	PD, with LBs	Good	28,30
4p14–15	<i>UCH-L1</i> (3 mutations)	PARK5	49–51 (50)	PD, pathology unknown	Good	31
4p15	Unknown	PARK4	24–48 (\approx 30)	PD and D, with LBs	Good	23,32
4q21	α -Synuclein (2 mutations)	PARK1	20–85 (46)	PD and D, with LBs	Good	33,34
12p11.2-q13.1	Unknown	PARK8	38–68 (53)	PD, pathology unknown	Good	M. Hasegawa, personal communication, 2001
12q23-24.1	<i>SCA2</i> (ataxin-2)	SCA2	19–61 (39)	PD, PD and A, without LBs	Fair	35
14q32.1	<i>SCA3</i> (ataxin-3)	SCA3	31–57 (42)	PD and A, without LBs	Good	36
17q21-22	<i>Tau</i> (>20 mutations)	FTDP-17	25–76 (49)	FTD, PD, PSP, CBGD, ALS with tau pathology	Poor	37,38
19q13	Unknown	DYT12	12–45 (23)	Rapid-onset dystonia—parkinsonism, pathology unknown	Poor	39

TABLE 1(continued)

Chromosome	Gene	Locus	Age at onset, range, y(mean)	Phenotype	Response to levodopa	Ref.
Autosomal recessive						
1p35-36	Unknown	PARK6	32–68 (45)	PD, probably with LBs	Good	40,41
1p36	Unknown	PARK7	27–40 (33)	PD, probably with LBs	Good	42
6q25.2–27	<i>Parkin</i> (>32 mutations)	PARK2	6–58 (26)	PD, sometimes with LBs	Good	43 (reviewed in Ref. 44)
X-linked recessive						
Xq13.1	Unknown	DYT3	12–48 (35)	Dystonia-parkinsonism, without LBs	Poor	45
Mitochondrial						
Complex 1	<i>ND4</i>	Unknown	(31)	PD, D, dystonia, and ophthalmoplegia without LBs	Fair	46
Complex 1	Unknown	Unknown	35–79 (42)	PD, pathology unknown	Good	47

A, ataxia; AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; CBGD, corticobasal ganglionic degeneration; D, dementia; FTD, frontotemporal dementia; FTDP-17, frontotemporal dementia and parkinsonism linked on chromosome 17; LBs, Lewy bodies; NA, not available; PD, Parkinson's disease; PSP, progressive supranuclear palsy; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.

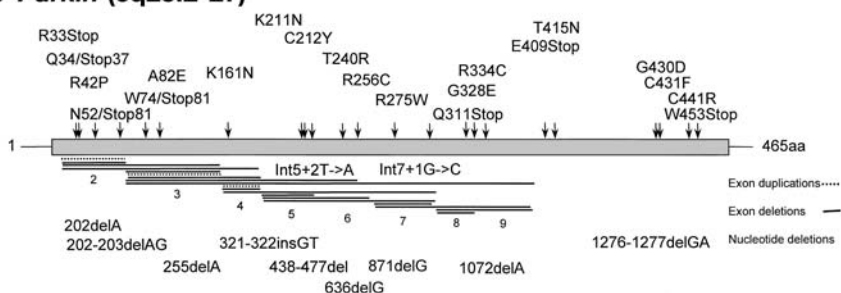
A *Ubiquitin C-terminal hydrolase (UCH-L1, 4p14-15)*



B *α-Synuclein (4q21)*



C *Parkin (6q25.2-27)*



D *Tau (17q21-22)*

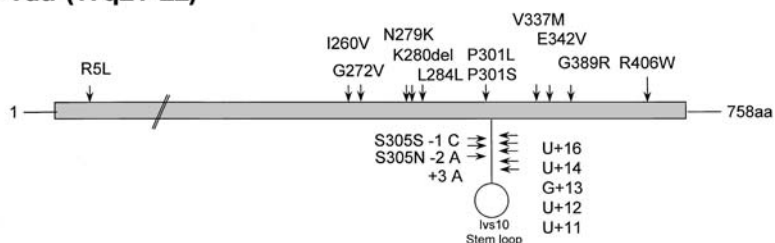


FIGURE 1 Genes and mutations associated with parkinsonism. Gene names are indicated in italics with their chromosomal assignment. (A) *Ubiquitin C-terminal hydrolase*; (B) *α-Synuclein*; (C) *Parkin*; (D) *Tau*. Boxes represent the coding sequence. Amino acids (aa) are shown N' to C' terminal. Coding mutations are indicated above; splice-site mutations and exonic and nucleotide deletions are represented below (not to scale). *Coding polymorphism associated with disease.

CLINICAL MOLECULAR GENETIC TESTING

At present, diagnostic molecular genetic testing is not commercially available and not clinically recommended for patients with sporadic PD or for those with a positive family history of PD. However, if patients express interest in research, they may be directed to centers where molecular genetic screening for PD is conducted. There are many such centers in the United States, Europe, Asia, and Australia.

SUMMARY

It is apparent that the genetics of PD and related conditions is complex, even in monogenic parkinsonism. The discovery of mutations in the genes for α -synuclein, ubiquitin C-terminal hydrolase, parkin, and tau has created a unique glimpse into the basic mechanisms responsible for neurodegenerative processes (43). Further genetic studies of already known PD/PPS loci will undoubtedly uncover more mutations. Subsequent clinical correlation aids in understanding the pathogenetic mechanisms and events that underlie cell dysfunction and death.

A large number of families have been described for which the genetic etiology is still to be explored. The study of these families—and those waiting to be discovered—will further enhance our knowledge of the biology of this neurodegenerative disease. Based on this background, an understanding of gene-gene and gene-environment interactions is also emerging. After almost 180 years, only short-term palliative remedies are presently available, but hope exists that this work will lead to curative treatments for PD and related conditions.

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