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Genetics of Parkinson's Disease - A Clinical Perspective

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Discovering genes following Medelian inheritance, such as autosomal dominant-synuclein and leucine-rich repeat kinase 2 gene, or autosomal recessive Parkin, P-TEN-induced putative kinase 1 gene and Daisuke-Junko 1 gene, has provided great insights into the pathogenesis of Parkinson's disease (PD). Genes found to be associated with PD through investigating genetic polymorphisms or via the whole genome association studies suggest that such genes could also contribute to an increased risk of PD in the general population. Some environmental factors have been found to be associated with genetic factors in at-risk patients, further implicating the role of gene-environment interactions in sporadic PD. There may be confusion for clinicians facing rapid progresses of genetic understanding in PD. After a brief review of PD genetics, we will discuss the insight of new genetic discoveries to clinicians, the implications of ethnic differences in PD genetics and the role of genetic testing for general clinicians managing PD patients. **Journal of Movement Disorders 2012;5:33-41**

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Parkinson's disease (PD) has become increasingly more prevalent as the population ages. Despite this, little is known about the etiology of the sporadic form of the disease. Considerable research into the etiology of PD, focusing on genetic and environmental factors, has occurred over the past few decades. Although progress has occurred, there is still no single factor that can account for most cases of sporadic PD. Recently, attention has been given to candidate genes, which, it is hypothesized, play a contributing (but not causative) role in sporadic cases of PD.

Although genetic factors are only implicated in a minority of cases of PD, the findings of genetic studies help us understand the pathophysiology of PD, which is especially true for the protein alpha-synuclein (*SNCA*, labeled PARK1) gene, the first identified genetic cause for familial Parkinsonism.[1] The localization of alpha-synuclein was found in the Lewy body, a pathologic hallmark of PD. Alpha-synuclein is regarded as a key molecule in the pathogenesis and progression of familial and sporadic cases of PD.[2]

The aim of this chapter is to provide a synopsis of the current state of knowledge in the genetic etiology of PD. And also, it will be illustrated how to apply this knowledge of genetics in the clinical assessment for the clinicians. Specific attention will be given to the ethnic difference of the prevalence of genetic mutations.

Although an increasing number of genetic factors appear to be associated with PD, we will focus on genes with a Mendelian inheritance (Table 1), including alpha-synuclein gene (*SNCA*, PARK1/4), parkin gene (*Parkin*, PARK2), P-TEN-induced putative kinase 1 gene (*PINK1*, PARK6), Daisuke-Junko 1 gene (*DJ-1*, PARK7), and leucine-rich repeat kinase 2 gene (*LRRK2*, PARK8), which have been conclusively proven as a monogenic etiology for familial parkinsonism.[3] Associated contributing genetic factors of PD, focusing on recent genome-wide association studies, will be also reviewed.

Park Genes Following Mendelian Inheritance

The loci, under the name "PARK gene," have been assigned to facilitate the diagnostic ap-

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Table 1. PARK genes

Locus	Gene	Inheritance	Clinical presentation	Pathology
Well-validated genes				
PARK1/4	*SNCA*	AD	Typical parkinsonism with early-onset, rapid progression, and sometimes associated with dementia	Lewy bodies
PARK2	*Parkin*	AR	Early-onset parkinsonism with very slow progression, sleep benefit, and sometimes dystonia	Usually no Lewy bodies
PARK6	*PINK-1*	AR	Early-onset parkinsonism with slow progression	Unknown
PARK7	*DJ-1*	AR	Similar to Parkin mutation	Unknown
PARK8	*LRRK-2*	AD	Typical parkinsonism (incomplete penetrance)	Usually Lewy bodies, sometimes tangles
PARK9	*ATP13A2*	AR	Early-onset parkinsonism with pyramidal sign, dementia, and gaze palsy	Unknown
PARK14	*PLAG2G5*	AR	Adult-onset parkinsonism with dystonia and pyramidal sign	Lewy bodies
Putative genes				
PARK3	Unknown	AD	Late-onset parkinsonism	
PARK5	*UCHL1*	AD	Late-onset parkinsonism	
PARK10	Unknown	Not clear	Late-onset parkinsonism	
PARK11	*GIGYF2*	AD	Late-onset parkinsonism	
PARK13	*Omi/HTRA2*	Not clear	Not clear	
PARK15	*FBXO7*	AR	Early-onset parkinsonism with pyramidal involvement	

AD: autosomal dominant, AR: autosomal recessive.

proach for the clinician. The phenotype of some of the PARK genes shows a rather limited resemblance to PD. For example, the *ATP13A2* gene (PARK9) is associated with recessively-inherited early-onset atypical parkinsonism, showing pyramidal signs of dementia and supranuclear gaze palsy.[4] A clinical presentation of the *PLA2G5* gene (PARK14) mutation carriers is adult-onset parkinsonism with dystonia and complicated pyramidal involvement.[5] Although these genes are of monogenic etiology under the PARK loci, we will focus on the conditions presenting symptoms and signs similar to classical parkinsonism.

SNCA, PARK1/4

SNCA is located in the long arm of chromosome 4, and three missense mutations have been identified in the etiology of dominantly-inherited familial parkinsonism: A53T, E46K, and A30P.[1,6,7] Carriers of A53T mutation experience an earlier onset of the disease, often presenting in their mid-forties, and demonstrate levodopa responsiveness, more severe and rapid progression of parkinsonian symptoms, frequent dementia, and prominent autonomic dysfunction in selected cases.[8]

Families with E46K mutations experience similar clinical pictures of dementia with Lewy Body disease, but A30P mutation carriers show typical late-onset parkinsonism with relatively mild dementia.[6,7]

Multiplications of *SNCA* (PARK4) have also been associated with PD.[9,10] The clinical phenotype of triplicated cases shows an earlier onset and more rapid course of the disease than that of duplicated families, suggesting a dosage effect of *SNCA*.[11] Penetrance in the families of abnormal *SNCA* is age-dependent and generally complete, but it appears to be slightly lower in A30P and duplicated cases.[12]

Lewy bodies and neurites are key pathological abnormalities of all cases with *SNCA* mutations, and they are found not only in the substantia nigra, but also in mesocortical and neocortical neurons in the autopsy of A53T cases. This is compatible with a diagnosis of Dementia with Lewy bodies.[8]

Alpha-synuclein is a 140-amino acid protein expressed presynaptically in neurons and is suggested to have a role in synaptic plasticity and neurotransmission.[13,14] Genetic alterations of *SNCA* lead to the formation of mutated alpha-synuclein proteins, which are more likely to oligomerise and aggregate, preventing degradation by the ubiquitine-proteasome pathway.[15]

Familial cases of *SNCA* mutation are extremely rare (up to 2.5% of all unrelated carriers), but findings of the alpha-synuclein protein as a principal component of key pathology and the pathogenic role of excessive wild-type alpha-synuclein have provided great insights into the pathogenesis of PD. Pathologic staging, based on the alpha-synuclein pathology, has been made, and it has proposed that the pathology spreads throughout the nervous system, possibly via the alpha-synuclein protein, as a seed molecule aggregated from mutated or excessive protein, like prion protein.[16,17]

Parkin, PARK2

The *Parkin* mutation was first described in young-onset

familial parkinsonism in Japan and has been regarded as the most common cause of autosomal-recessive juvenile parkinsonism.[18,19] The locus is mapped to the telomeric region of the long-arm of chromosome 6. More than 100 mutations are associated with *Parkin*, ranging from point mutations and deletions to rearrangements and duplications.[20,21] Clinically, affected families show parkinsonism similar to sporadic cases, except for the age of onset, which occurs from childhood to 40 years and is rarely seen in individuals over 50 years of age.[22] More symmetric motor symptoms, excellent levodopa responsiveness, frequent dystonia in the legs, hyperreflexia, diurnal fluctuation, sleep benefit, no dementia, mild autonomic symptoms, and severe treatment-related motor complications are also reported, but the general course of the disease looks more benign than typical PD.[19,23] Initial pathologic studies reported a selective loss of dopaminergic neurons of substantia nigra and a loss of adrenergic neurons of locus ceruleus without Lewy Body, but a few cases of Lewy pathology have been reported recently.[24-26]

The *Parkin* protein is a cytosolic protein and is associated with the cell membrane.[27,28] It is known that the protein functions as an E3 ubiquitin ligase, which tags dysfunctional or excessive proteins for degradation in the ubiquitin proteasome system.[27,29] The elimination of damaged mitochondria is one of the most important roles of *Parkin* protein.[30-32] *PINK1* and *Parkin* appears to act together in this pathway.[33,34] Mutations of *Parkin* induce loss or decrease in the role of protein degradation and mitochondrial maintenance, leading to the cytotoxic accumulation of abnormal proteins and mitochondrial dysfunction.

Homozygous *Parkin* mutations are found in most patients, but compound heterozygotes have also been reported. Because recessively inherited genetic disorders often appear sporadically, many sporadic cases of juvenile-onset appear to be associated with *Parkin* mutations.[35] A significant proportion of sporadic cases have been found to have heterozygous *Parkin* mutations, suggesting these mutations may be a disease-modifying risk factor.[36] This is supported by a report of decreased dopamine activity in striatum of mutation carriers.[37] However, a subsequent large case-control study found no significant difference in the frequency of heterozygous *Parkin* mutations in patients and controls.[38] Therefore, there is insufficient evidence that *Parkin* mutations are a risk for sporadic PD.

PINK1, PARK6

The *PINK1* mutation is another rare cause of autosomal-recessive early-onset parkinsonism. The *PINK1* gene is located in the short arm of chromosome 1.[39,40] The majority of the *PINK1* mutations associated with parkinsonism are missense or nonsense mutations, but rare deletion mutations are also reported.[41] Although the age of onset is between 20 and 50 years of age, most affected cases show phenotype of late-onset cases, such as the mild and slow progression of motor symptoms, good levodopa responsiveness, and mild dementia in some cases.[39,42,43] Atypical features, including dystonia and psychiatric disturbances, are also reported in a few families.[40,41] The pathology of *PINK1*-associated parkinsonism is still not known.

PINK1 protein is an active mitochondrial kinase, protecting cells against apoptotic or mitochondrial stressors and maintaining mitochondrial function.[33,44,45] The localization and function of *PINK1* in mitochondria is quite interesting in that PD has been assumed to be associated with mitochondrial dysfunction and oxidative stress. Phenotype due to loss of *PINK1* function is rescued by an over-expression of *Parkin*, suggesting that both proteins are involved in the same genetic pathway and *PINK1* is upstream of *Parkin*. The exact pathogenic mechanism is largely unknown, but recently it has been found that *PINK1* regulates mitochondrial Ca^{2+} efflux, and the loss of *PINK1* is associated with mitochondrial Ca^{2+} overload and dysfunction of mitochondria.[47] As with *Parkin*, heterozygous *PINK1* mutations may also be a genetic risk factor, based on the increased frequency of *PINK1* mutations in sporadic cases and decreased dopaminergic activity in healthy carriers, as shown in functional-imaging study.[48-50] Its exact role in sporadic PD also remains elusive, demanding further studies.

DJ-1, PARK7

DJ-1-associated parkinsonism is found in only a few families and is another rare cause of recessively-inherited parkinsonism.[51] The locus is mapped to the short arm of chromosome 1, and studies have found that missense mutations and whole exonic deletion are associated with parkinsonism.[51,52] The age of onset is from 20 to 40 years in most families, and the clinical phenotype of affected cases is similar to that of *Parkin* and *PINK1* cases.[53] In addition to parkinsonism, some patients showed peculiar characteristics, such as psychiatric symptoms, short statue, and brachydactyly.[54] Currently, there is no pathologic report of *DJ-1*-associated parkinsonism.

DJ-1 protein has H_2O_2 responsiveness, functioning as a sensor for oxidative stress, and is an antioxidant.[55,56] It has been suggested that *DJ-1* could be a part of novel E3 ligase complex with *Parkin* and *PINK1*, but the pathogenic role of *DJ-1* mutations is still unknown.[57] Both homozygous and compound heterozygous mutations are found in affected families, and the possibility of *DJ-1* as a risk factor for sporadic disease has also been suggested like other recessive genetic etiologies.[58]

LRRK2, PARK8

LRRK2 is another genetic cause of dominantly-inherited familial parkinsonism, and it is located in the short arm of chromosome 12.[59] *LRRK2* protein is a large, multi-domain

protein, and over 40 pathologic mutations have been reported, although only five missense mutations have been proven to have a causative role (R1441C, R1441G, Y1699C, G2019S and I2020T).[60-66] G2019S mutation is the most common, and the phenotype in families is similar to late onset sporadic cases. Onset occurs in patients aged in their 60s, with asymmetry of motor symptoms, and levodopa responsiveness is seen in two-thirds of cases, with slightly more frequent resting tremor (75%).[67] A more complex presentation of dystonia, amyotrophy, postural tremor, and restless legs syndrome is also described.[68] Most families with other mutations of *LRRK2* show a similar phenotype to typical sporadic cases.[69] However, the age at onset, as well as the severity of motor symptoms, may be highly variable, even within families.

The penetrance of the *LRRK2* mutation is age-dependent, but it is quite different according to mutations. The penetrance seems incomplete in the mutation of G2019S, which was reported at 28% at the age of 59 years, 51% at 69, 74% at age 79, and more than 90% at the age of 75 in R1441C.[69,70] It also appears to be varied between the ethnicities and is higher in Arab Berber than Ashkenazi Jews.[71,72] The penetrance reported in initial family-based studies may be overestimated, and the corrected overall penetrance is 67%.[73]

Although limited pathologic studies of *LRRK2* mutation carriers reported Lewy pathology, in most cases different *LRRK2* mutations showed variable results.[74,75] Autopsy of G2019S-mutations cases showed a relatively consistent pattern of neurodegeneration with Lewy bodies, but others (R1441C, Y1699C, and I2020T) showed pure nigral degeneration without Lewy pathology or pleomorphic findings, including tau pathology.[59,66,76,77] *LRRK2* is placed genetically upstream of deposited proteins, such as alpha-synuclein or tau, so mutations of *LRRK2* might induce different outcomes depending on the course the disease takes.[12,78] Although *LRRK2* protein is reported to have kinase and GTPase features, its pathogenic role in parkinsonism is largely unknown.[79,80] Evidences suggest that the mutant *LRRK2* impacts the morphology and the possible function of the neuritic/synaptic compartment.[81-83]

Monogenic Etiologies Other than PARK Genes

The naming of the PARK gene is historical, and there are currently no well-defined clinical or pathological inclusion criteria. Therefore, other genetic conditions, which can present primarily as parkinsonism, should be considered in the differential diagnosis.

Spinocerebellar ataxia (SCA) represents inherited ataxias encompassing a variety of clinical and genetic characteristics. There have been at least 29 gene loci reported to date, and parkinsonism has also been described in some genotypes.[84] Of the 29 reported gene loci, SCA2 mutations (CAG/CAA repeat) may cause levodopa-responsive parkinsonism, manifesting with resting tremors, rigidity, and bradykinesia as well as mild dysarthria and ataxic gait.[85,86] Most patients with an SCA2 mutation have a family history of ataxia with or without parkinsonism. Pure parkinsonian families are rarely reported.[87] It seems more frequent in families of Asian background, accounting for as high as 10% of familial parkinsonism.[86]

Monogenic forms of dystonia (dystonia-parkinsonism) can also show signs of parkinsonism, including DYT3 (X-linked dystonia-parkinsonism), DYT5 (dopa-responsive dystonia), and DYT12 (rapid-onset dystonia-parkinsonism). Of these, patients with DYT5 mutations can present as typical autosomal-recessive juvenile parkinsonism, because of mutations in the tyrosine hydroxylase (TH) gene (DYT5b).[88] Another condition associated with mutation in GTP cyclohydrolase 1 gene (GTPH1, DYT5a) may show more typical and late-onset parkinsonism.[89] The clinical phenotype of DYT5-mutation carriers includes early onset of dystonia, a diurnal fluctuation of symptoms, and an excellent response to low-dose levodopa.[90] Patients with *Parkin* mutations also frequently show early dystonia; however, a differential diagnosis based on a clinical phenotype can be difficult.[91] The DYT5 mutation is a biochemical defect in the pathway of dopamine synthesis, and does not cause widespread neurodegeneration, as shown in limited pathologic reports, with no evidence of Lewy Body pathology and a normal number of dopaminergic neurons (though severely hypomelanized).[92] Patients with the DYT5 mutation usually do not develop motor complications associated with dopamine replacement and show normal functional dopamine-imaging results, which is an important distinguishing feature when comparing patients with *Parkin* mutations.[93]

Genetic Risk Factors Associated with PD

Many genes have been studied to identify an association with sporadic and late-onset PD. Genetic polymorphisms increase the susceptibility of developing sporadic PD, but do not cause the disease. Associations can be established when polymorphisms in candidate genes are found in significantly higher rates in patients with classical PD. Efforts have failed to find conclusive evidences for an association of underpowered results in relation to the small increase in the risk of a small number of subjects or an arbitrary choice of candidate genes or genetic variants. It also remains to be elucidated if some of the monogenic etiologies for familial parkinsonism have a clear association with sporadic PD. Studies using advanced technologies overcoming the caveats of classical methods, such as genome-wide association studies, have confirmed already suggested associations and found several new genetic risk factors.

Proven Etiologies as a Genetic Risk

Polymorphisms in the non-coding promoter region (Rep1) and 3' end of the *SNCA* gene have been repeatedly associated with sporadic PD. There seem to be ethnic differences in Rep1 polymorphisms, which have found an association with allele length in Caucasians, but that neither the 259 nor 263 polymorphisms of Rep1 were associated with sporadic PD in Asians.[94,95] These polymorphisms of *SNCA* may correlate with higher expression of alpha-synuclein, and the lifetime risk of PD might be raised by 25% to 30% in carriers.

LRRK2 polymorphisms (G2385R and R1628P) are associated with sporadic PD in Asian populations but this finding has not been replicated in patients of European descent.[96,97] G2385R polymorphism was found in 6.7% of typical late-onset Japanese patients, 9.4% of early-onset patients, and 23.1% of familial patients (compared with 3% in controls).[98] This polymorphism has also been reported by other studies which found a prevalence of 8-9% in sporadic cases from East Asia and probably can explain 10% of the risk of sporadic PD in these countries.[99,100]

H1 haplotype of microtubule-associated protein Tau (MAPT; associated with Tau pathology) is also associated with PD, and it increases the disease risk by nearly 50% in populations of European ancestry.[101]

Parkinsonism has been reported in patients and carriers of Gaucher's disease (the most common lipid storage disease caused by homozygous glucocerebrosidase (GBA) mutation).[102] The loss of GBA function has been proven to be associated with PD (6.9% in PD vs. 1.3% in control), and loss of GBA function is especially prevalent in Ashkenazi Jews (19.3% vs. 4.1%).[103]

Genome-Wide Association Studies

In recent years, there have been efforts to overcome the caveats of the association studies, which usually require sufficient genetic variation around a specific gene to be measurable in a given population. Genome-wide association studies (GWAS) can genotype large numbers of common variations in a large numbers of cases and controls without any prespecification to a particular gene. GWAS has the potential to find loci where common, normal genetic variability contributes to disease risk. Several such studies have found that genes for α-synuclein, microtubule-associated protein tau, *LRRK2*, and HLA-DRB5 are associated with the PD.[104-106] Recent meta-analysis of GWAS involving 5233 cases and 12019 controls has confirmed the associations and identified several new loci.[107] We should be cautious not to ascribe disease risk to any specific gene suggested by such studies in the absence of further biological evidence. However, GWAS have revealed stronger genetic components in sporadic PD than our expectations, and there is hope to identify additional common genetic risks for PD.

Genetic Frequency and Ethnic Difference in PD

As we know, the first gene for PD, α-synuclein, was found in Italian families. Although several point mutations were discovered after the first report, these mutations are still rare (-2.5% of known unrelated, affected carriers), and this is definitely true for Asian populations.[108]

The most frequently found genetic cause in PD is *LRRK2*, corresponding to about 50% of all reported unrelated carriers of mutations, and 5% to15% of dominant families. Ethnic differences have been demonstrated more dramatically in *LRRK2*. The G2019S mutation is found in about 5% of familial Caucasian patients.[63] In contrast, it is much more prevalent in Ashkenazi Jews and African Arabs (20% and 40%, respectively).[71,109] The G2385R variant is more common in Asian populations (23.1% of familial PD and 6.7% of typical sporadic cases).[110]

Parkin mutations are also commonly found in genetic etiologies, especially in juvenile-onset cases. These mutations comprised 40% of reported unrelated mutation carriers, and more than 50% of cases onset before the age of 20.[19,111] Though mutations of the *Parkin* are more frequently reported in Asia, these mutations are also frequently found in Caucasian and Latin-American patients.

The other gene for PD that expresses dependency on ethnicity is *PINK1*. *PINK1* mutations account for approximately 6.5% of known unrelated mutation carriers, comprising 1% to 3% of early onset patients in Caucasian populations,[40,42] 9% of autosomal-recessive patients in Japanese families,[112] and 2.5% of early onset cases in a sample of Chinese, Malay, and Indian patients.[46] Relative frequencies of prevalent genes for PD according to ethnicity are summarized in Table 2.

Clinical Relevance of Genetics for the Diagnosis of PD

Genetic testing is not routinely performed in patients presenting to a clinician with symptoms and signs of PD. The yield is likely to be very low and hence, genetic testing is not currently recommended for patients with a negative family history.

The possibility of an underlying genetic etiology should also not influence therapeutic treatment options as patients with genetic monogenic etiologies or polymorphism associations typically demonstrate levodopa responsiveness although some genotypes, for example, *Parkin* mutations may be associated with a higher risk of treatment-related motor complications.

In patients with a positive family history, determination of

Table 2. Relative frequencies of genes dependent on ethnicity and familial history

Ethnicity		*SNCA* (%)		*LRRK2* (%)		*Parkin* (%)			*PINK1* (%)		*DJ-1* (%)	
		Classic	CNV	Classic	CNV	Classic	Mixed	CNV	Classic	CNV	Classic	CNV
Caucasian	F	4.13	2.07	67.36	0	10.12	3.51	7.44	3.93	0.21	0.83	0.41
	S	0.99	0.33	52.48	0	18.15	2.97	11.88	10.89	0.33	0.99	0.66
Asian	F	1.01	8.08	9.09	0	10.10	10.10	42.42	17.17	0	3.03	0
	S	0	3.13	10.42	0	28.13	1.04	38.54	17.71	1.04	0	0
Arab	F	0	0	88.61	0	1.27	1.27	3.80	3.80	1.27	0	0
	S	0	0	97.06	0	1.47	0	0.74	0	0	0.74	0
Latin-American	F	0	0	57.14	0	14.29	4.76	23.81	0	0	0	0
	S	0	0	41.67	0	41.67	0	8.33	0	8.33	0	0
Ashkenazi Jews	F	0	0	100.00	0	0	0	0	0	0	0	0
	S	0	0	98.04	0	0	0	0	0	0	1.96	0

CNV: copy number variation, F: familial cases, S: sporadic cases (adopted from Nuytemans et al., 2010[107]).

an underlying genetic etiology may be of value with family planning, understanding of prognosis and associated clinical features including rate of progression and risk of dementia.

It is expensive and time consuming to examine all possible mutant genes in a particular patient even if testing for mutations may be relevant. By utilizing the knowledge of frequency of genetic mutations among different ethnic groups, the pattern of inheritance and the clinical pattern in presentation, clinicians can limit the tests required to yield a specific answer relevant to the patient.

For example, we can consider *Parkin*/*PINK1*/*DJ-1* mutations in early-onset parkinsonism with slower disease course and *SNCA* mutations in a case with dementia and rapid progression in a Caucasian subject. In the case of typical parkinsonism with a positive family history in Asian populations, *LRRK2* mutations should be considered, and *Parkin*/*PINK1* can be considered in earlier-onset cases.

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