Clinicogenetics of Parkinson's disease: a drawing but not completed picture

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ABSTRACT

Parkinson's disease (PD) is a prevalent neurodegenerative disorder mainly affecting the population over the age of 60 years. The past decade has seen rapidly emerging data supporting a major importance of genetic factors in the development of PD. Increasing number of large-scale and replicating association studies has facilitated the confirmation of the possible predisposing factors to PD and the selection of genetic variants for risk prediction. While evidences are accumulating that variations within the *SNCA*, *LRRK2*, *MAPT* and *GBA* genes increase the individuals' vulnerability to PD, inconclusive or negative results have been reported for an association between PD and variants of the *parkin*, *PINK1*, *DJ-1*, *UCH-L1*, *Omi/HtrA2*, *GIGYF2*, *PLA2G6*, *VPS35*, *EIF4G1* and *BST1* genes. However, our understanding of the genetic picture of PD remains preliminary. Molecular diagnosis of the disease is only recommended for cases with clear family history, and currently, there is no ideal genomic biomarker available to predict the disease onset and progression, or to make a molecular classification of the disease. Efforts are expected to identify more genetic predisposing factors and to further clarify their roles in the mechanisms of PD.

Key words: Association, biomarkers, genetic variants, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a prevalent neurodegenerative disorder affecting 1-2% of the population over the age of 60 years.[1] The disease results mainly from progressive and profound degeneration of dopaminergic neurons in the substantia nigra with the presence of Lewy bodies containing aggregates of α-synuclein and other substances.[2,3] Although the etiology and mechanisms of PD remain largely unclear, the development of the disease is believed to be the combined results of three interactive events: genetic susceptibility, environmental exposures and the aging process.[4-8] The relative role of genetic and environmental factors has been debated for many years, however, evidences are rapidly accumulating that genetic risk factors are of major importance in the sporadic form of the disease, accounting for at least 10% of the general PD population.[1,9-11]

One important conceptual update of the genetic profiling of PD is that mutations or variations within causative genes for a minority of monogenic familial PD are also associated with sporadic PD. Studies in PD families have identified 11 (*a-synuclein*, parkin, *UCH-L1, PINK1, DJ-1, LRRK2, ATP13A2, OMI/HTRA2, FBX07, VPS35, EIF4G1*) causative genes and 4 loci of linkage across the genome (PARK3, PARK10, PARK12 and PARK16) pending characterization. Analysis of mutations or variations in many of these genes has been performed in recent years among diverse ethnic populations. In addition, the newly emerged genome-wide association studies (GWAS) have been used to identify novel genetic associations with the disease at the whole-genome level.[12-15] More recent progress has been made by the powerful technique of next-generation sequencing.[16,17] Further, more and more large-scale and multi-center collaborative analyses have been completed thanks to the improving analytic tools and the increasingly close international cooperation. The results published so far are consistent or conflicting with each other, reflecting confirmative, inconclusive or negative associations between genetic variants and PD. In this review, we give an up-to-date view of the genes that may have associations with the risk for PD and their implications in clinical

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practice, with emphasis on large-scale and multiethnic evidences, as listed in Table 1.

GENETIC VARIATIONS WITH WELL-EVIDENCED ASSOCIATIONS WITH PARKINSON'S DISEASE

SNCA

Genetic variability within the SNCA gene encoding α-synuclein is arguably the most reliable association of a common genetic risk factor with PD identified to date. Although mutations in this gene account for < 1% of PD in the general population, abnormal aggregation of the SNCA-encoding protein, α-synuclein, the principal component of Lewy bodies, is present in all patients with idiopathic PD.[16] In addition, association studies have repeatedly suggested the link of the SNCA variations to both familial and sporadic PD. Further, several most recently completed GWAS consistently showed strong linkage of the SNCA locus to PD across Western and Oriental populations.[12-15]

Although three missense mutations in SNCA were reported in families with PD inheritance[18-20] and thought to increase the aggregation of SNCA protein, point mutations have not been identified in sporadic PD,[21,22] and no several nonsynonymous (SNPs) have been found in the coding region, suggesting that disease-related amino acid changes in SNCA are unlikely in sporadic PD.[23] In contrast, multiplication, in particular triplication, of SNCA was revealed in both familial[24-29] and sporadic PD cases.[30] Due to the absence of point mutations in any of the copies of SNCA in these patients, the cause of PD appears to be the mere increase in α-synuclein levels. In support of this dosage effect, PD patients from families with two extra copies of SNCA have a more severe phenotype than PD patients with only one extra copy,[25,27,31] and SNCA mRNA levels in the brain from sporadic patients are increased.[32-35]

The pathogenicity of multiple SNCA gene copies and the apparent dosage effect of α-synuclein levels in both sporadic and familial PD highlight the clinical significance of the regulation of SNCA gene expression, which can take place at both transcriptional and posttranscriptional levels. Transcription of genes is mainly regulated by the promoter sequence. The first promoter variant reported in association with PD was the mixed dinucleotide repeat sequence (REP1), which resides approximately 10 kb 5′ to the translation start site of SNCA. Despite some negative results of association, the majority of individual studies[36-39] and a meta-analysis of data[40] from 18 sites across multiple ethnic populations have confirmed an association between risk for PD and the longer REP allele. In addition, variants other than REP1 in the promoter region, such as SNPs flanking the core promoter at the -770 and -116 positions, rs2583988, rs2619364, and rs2619363, were also reported to increase the susceptibility to PD in European population.[41] Posttranscriptional regulation of gene expression can be mediated by several elements, many of which are located in the 3'-untranslated region of mRNAs.[42,43] A series of studies reported an association of polymorphisms at the 3'-end of

Locus	Gene	Chromosome	Inheritance	Type of parkinsonism	Mutation/varaint type	Association with PD
PARK1/PARK4	SNCA	4q21	AD	LOPD/EOPD, dementia	Multiplication, point	Convinced
PARK2	Parkin	6q25-27	AR	EOPD	Re-arrangement, point	Re-arrangement: convinced; point: unconvinced
PARK3	Unknown	2p13	AD	LOPD	Point	Unconvinced
PARK5	UCHL1	4p14	AD	LOPD	Deletion, point	Unconvinced
PARK6	PINK1	1p36	AR	EOPD	Deletion, point	Unconvinced
PARK7	DJ-1	1p36	AR	EOPD	Deletion, point	Unconvinced
PARK8	LRRK2	12q12	AD	LOPD	Point	Convinced
PARK9	ATP13A2	1p36	AR	EOPD, Kufor-Rakeb syndrome	Point	Unconvinced
PARK10	Unknown	1p32	Unknown	LOPD	Point	Unconvinced
PARK11	GIGYF2	2q37	AD	LOPD	Point	Unconvinced
PARK12	Unknown	xq21-25	X-linked	LOPD	Point	Unconvinced
PARK13	HTRA2	2p12	AD	LOPD	Point	Unconvinced
PARK14	PLA2G6	22q13	AR	EOPD, dystonia-parkinsonism	Point	Unconvinced
PARK15	FOXB7	22q12-13	AR	EOPD, pallido-pyramidal syndrome	Point	Unconvinced
PARK16	Unknown	1q32	Risk	LOPD	Point	Unconvinced
PARK17	VPS35	16q11	Risk	LOPD	Point	Unconvinced
PARK18	EIF4G1	3q27	Risk	LOPD	Point	Unconvinced
-	GBA	1q21	Risk	LOPD	Point	Convinced
-	BST1	4p15	Risk	LOPD	Point	Unconvinced
-	MAPT	17q21	Risk	LOPD	Haplotype	Convinced
-	ATXN2	12q12	Risk	LOPD	Trinucleotide expansion	Unconvinced
-	ATXN3	14q32	Risk	LOPD	Trinucleotide expansion	Unconvinced

AD: autosomal dominant; AR: autosomal recessive; EOPD: early-onset Parkinson's disease; LOPD: late-onset Parkinson's disease; PD: Parkinson's disease

SNCA (e.g. rs356165 and rs356219) with sporadic PD, especially those from Southern Germany and Asian.[44-47] Although molecular details are not clear, the 3'-variants have been shown to increase the expression of α-synuclein.[48]

LRRK2

The discovery of mutations in the LRRK2 gene as the cause of PD in the families linked to the PARK8 locus (12q12) was probably the most important step forward since the α-synuclein discovery.[49,50] LRRK2 is a very large gene that contains 51 exons, and over 30 sequence variants have been linked to autosomal-dominant Parkinsonism. However, only five (R1441C, R1441G, Y1699C, G2019S, and I2020T) have been shown or be clearly pathogenic, and two substitutions (G2385R, R1628P) have been associated with an increased risk for sporadic PD.

The most common LRRK2 mutation is Gly2019Ser. It is detected in about 5% of familial and 1-2% of sporadic European PD patients[51,52] and up to 30% of patients with PD from North African and 10-40% of Middle Eastern populations.[53-56] One intriguing feature of this mutation is its association with both familial and sporadic PD. However, the penetrance of this mutation is relatively low. By analyzing the pooled data of 24 populations worldwide (including 19,376 unrelated patients with PD), the International LRRK2 Consortium reported the risk of PD for a person who inherits the LRRK2 G2019S mutation was 28% at age 59 years, 51% at 69 years and 74% at 79 years. Although motor and nonmotor symptoms of LRRK2-associated PD were more benign than those of idiopathic PD, the core features (asymmetrical, tremor predominant parkinsonism with bradykinesia and rigidity that responded to dopamine) of the patients with LRRK2 G2019S-associated PD are indistinguishable from patients with idiopathic PD, again implying a critical contribution of LRRK2 to the PD pathogenesis.[57]

Although the G2019S is prevalent in PD patients in the above-mentioned populations, it does not occur at appreciable frequency in control cohorts from these populations and is strikingly rare in Chinese[58,59] and South African.[60] Therefore, it is more a population-specific mutation than a popular susceptibility variant. In contrast, two variants reported from Asian populations appear to be true risk variants for PD. The first G2385R was initially described in a Taiwanese family.[61] Assessment of this variant in large Asian populations showed association with risk for disease in Taiwanese, Japanese, Hong Kong Chinese and mainland Chinese populations.[61-63] In general this variant is present in about 10% of PD populations and

0.5-5% in controls and confers at least two-fold risk for the chance of PD. Given that this association appears robust across Asian populations, this risk allele is an underlying factor in a very large number of PD cases worldwide. More recently a second LRRK2 risk allele, also identified within Asian PD populations has been described.[64,65]

Microtubule associated protein tau

The microtubule associated protein tau (MAPT) gene encodes MAPT. Tau modulates the assembly, dynamic behavior, and spatial organization of microtubules, and is a major protein component of neurofibrillary tangles, a hallmark lesion of Alzheimer's disease (AD). Mutations in the MAPT gene were identified to cause autosomal dominant frontotemporal dementia with parkinsonism linked to chromosome 17.[66] In addition to rare causal mutations, common variability in MAPT has been linked to disease such as progressive supranuclear palsy, AD and PD. The most frequently reported variation is caused by a common genomic inversion within a large block (approximately 1.6 Mb in length) containing the MAPT locus that shows reduced recombination and high levels of linkage disequilibrium. This phenomenon results in two common Caucasian haplotype groups across this locus, often termed H1 and H2. Association between MAPT H1 and risk for PD has been tested by many groups,[67,68] and the results in general show a consistent association with the disease. Moreover, patients carrying the H1 allele present in their fifth decade either with behavioral/cognitive changes or with rapidly progressive and poorly levodopa-responsive parkinsonism. A recent follow-up study demonstrated that 17% of incident PD patients developed dementia over 5 years, and the MAPT H1/H1 genotype was an independent predictor of dementia risk (odds ratio = 12.1).[69] The results also suggested that Lewy body deposition in posterior cortical areas, which is influenced by MAPT genotype and the aging process are associated with subsequent global cognitive decline and dementia. However, the H1 haplotype may not be a universal risk allele because the H2 haplotype is almost exclusively Caucasian in origin, and its prevalence in other populations is essentially zero.[70]

In addition to the H1 haplotype, a subhaplotype within the H1 clade composed of two "H1-SNPs" (rs242562 and rs2435207) spanning MAPT exons 1-4 was also significantly overrepresented in cases versus control subjects.[71,72] However, except for in one Greek and one Nowegian study, the association of H1-subhaplotype with PD was not well replicated in other Caucasian studies, and Taiwan Chinese,[68,73,74] and it has not been tested whether this subhaplotype is associated with PD in populations that possess merely the H1 clade.

Glucocerebrosidase

The glucocerebrosidase (GBA) gene encoding a lysosomal enzyme called glucocerebrosidase that hydrolyses the beta-glycosidic linkage of glucosylceramide, a ubiquitous sphingolipid present in the plasma membrane of mammalian cells.[75] Over 200 mutations have been described in GBA, including point mutations, deletions and recombination alleles derived from the pseudogene sequence.[76] These mutations usually cause a recessive lysosomal storage disorder - Gaucher disease (GD), which is characterized by macrophages enlarged with deposits of glucosylceramide.

The initial recognition of an association between PD and GBA mutations came from the clinical observations of parkinsonian manifestations in genotypically heterogeneous patients with GD.[77] Moreover, brain samples from autopsy-confirmed PD cases revealed significantly higher carrier frequencies (14%) than the estimated GBA mutation carrier frequency in the general population (0%).[78] The frequency and distribution of GBA mutations in PD vary among populations. Ashkenazi Jewish PD patients have the highest carrier frequency with a range 13.7-31.3%, compared with 4.5-6.2% in controls.[79,80] It was lower in nonAshkenazi-Jewish populations, ranging 2.8-12%, compared with 0.2-5.3% controls from the same populations.[81-83] Among all the mutations, L444P and N370S turned out to be the most frequently identified in PD patients. Although N370S is also common in European populations, it has not been encountered among Asians.[84] In contrast, L444P was believed as a panethnic mutation associated with PD.[85,86] A most recent multi-center study including 5691 patients and 4898 controls from 16 centers revealed that either mutation was found in 15% of patients and 3% of controls among Ashkenazi Jewish subjects, and in 3% of patients versus 1% of controls among nonAshkenazi Jewish subjects.[87] The odds ratio for any GBA mutation in patient's versus controls was 5.43 across centers, which is the highest effect size conferred by the known risk variants for PD. There is preliminary evidence that, overall, mutation carriers have an earlier age at onset (AAO), more atypical clinical manifestations, more cognitive changes and more likely to have affected relatives.[82,88]

GENETIC VARIANTS IN INCONCLUSIVE OR NEGATIVE ASSOCIATION WITH PARKINSON'S DISEASE

Parkin

The most frequent mutations in early-onset PD (EOPD) (AAO ≤ 50 years) patients are those identified in the parkin gene, which account for up to 50% of autosomal recessive juvenile parkinsonism (AR-JP) and 15-20% of sporadic EOPD.[89-91] Over 100 types of mutations including sequence substitutions, insertions and exonic deletions/duplications (or dosage mutations) in the parkin gene have been described in diverse ethnic groups.[92] While homozygous or compound heterozygous mutations are causative, heterozygous mutations have been suggested to increase the risk for PD.[93,94] The predisposing effects of heterozygote were, however, soon questioned by other studies in which they were reported as common in control subjects as in PD patients.[95,96] These conflicting observations, as suggested by some studies, may come from the heterogeneous effects of different types of mutations, which may have different origins and pathogenic effects. For example, a haplotype analysis for a European EOPD family series demonstrated that exonic rearrangements occurred independently whereas point mutations may have been transmitted by a common founder.[97] In addition, some studies suggested that dosage mutations are more pathogenic than sequence mutations in the development of familial PD.[98,99] However, these results remain to be confirmed by large-scale studies, and it is unclear whether the dosage mutations are associated with typical sporadic PD.

PINK1

Mutations in the PTEN-induced putative kinase 1 (PINK-1) gene are the second common cause of autosomal recessive EOPD after parkin. The gene resides on chromosome 1p35-36 (PARK6) and encodes a protein locating on mitochondria.[100-102] Evidences are gathering that PINK-1 is crucial for the normal functions of mitochondria and might participate in the detoxification of proteins.[103] Different PINK-1 mutations including missense, nonsense, splice site mutations and entire PINK-1 gene deletion have been identified in both familial[104] and sporadic EOPD cases,[105,106] with a frequency ranging from 1% to 8%. However, single heterozygous PINK-1 mutations have also been reported in healthy controls and large-scale case-control studies confirming the association between PINK-1 mutations, and sporadic PD are not available.

DJ-1

The DJ-1 gene (PARK7) encodes a protein belonging to the DJ-1/Thi/PfpI protein super family. It was initially described in association with oncogenesis and male rat infertility,[107,108] and later found to be associated with autosomal recessive EOPD.[109,110] DJ-1 is proposed to play a role in protecting neurons from oxidative stress and protecting against mitochondrial damage.[111] A few PD-causing mutations have been identified, including exon deletions, truncations, homozygous and heterozygous point mutations, which predominantly result in loss of function.[109,112] However, there is currently a lack of information about the frequency of

mutations, including single heterozygous mutation, for DJ-1 in both familial and sporadic parkinsonism, especially in large population samples. Moreover, in a recent complete mutational analysis of DJ-1 coding sequence in a large cohort of familial and sporadic PD cases from 12 countries, none had causative mutation in DJ-1, suggesting its mutations are very rare in either familial or in sporadic parkinsonism.[113]

UCH-L1
The *UCH-L1* gene (PARK5) encodes the ubiquitin carboxy-terminal hydrolase L1, which is a component of LB and possesses both a hydrolase activity to generate the ubiquitin monomer and a ligase activity to link ubiquitin molecules to tag proteins for disposal.[114] The detection of an Ile93Met mutation in the UCH-L1 gene in a German family with autosomal dominant PD[115] suggested a role for an impaired ubiquitin-proteasomal activity in PD pathogenesis. In contrast, a Ser18Tyr polymorphism affecting mainly the ligase activity has been suggested to have a protective effect in PD in some association studies.[116] However, a subsequent large case-control study involving 3,044 PD cases and 3,252 controls, failed to replicate the association.[117]

Omi/HtrA2
The gene Omi/HtrA2 (PARK13) encodes a serine-protease with pro-apoptotic activity containing a mitochondrial targeting sequence at its N-terminal region.[118] Several lines of evidence in the literature support a role for Omi/HtrA2 in neurodegeneration.[119,120] The first pathogenic mutation (G399S) a risk variant (A141S) for PD were identified in a German cohort.[121] However, a later case-control study screening the whole coding region of Omi/HtrA2 revealed that neither of the two variants was overrepresented in the patients.[122] Although another mutation, R404W, was found in Belgian PD patients,[123] it is not clear whether it is associated with PD patients in other populations. Further, the most recent large-scale analysis of the five most informative SNPs spanning the Omi/HtrA2 gene in a cohort of 6,378 cases and 8,880 controls from 20 sites worldwide again confirmed the lacking of association of Omi/HtrA2 variants with PD.[124] Therefore, the genetic basis for the involvement of Omi/HtrA2 is still not conclusive at this point.

GIGYF2
Recently, it has been proposed that the GIGYF2 gene corresponds to the PARK11 locus causes a form of autosomal-recessive familial PD.[125,126] In two independent French and Italian familial PD populations, 10 changes in 16 unrelated PD patients were found in the shortest form of GIGYF2, yielding a mutation frequency of 6.4%.[127] However, no disease-causing mutations were found in other European populations[128]

and in recent months, over 10 replication studies have provided conflicting data, casting considerable doubt on the causal role of GIGYF2.[129] In addition, a pooled analysis of over 4,500 PD and 5,500 controls revealed that the estimated frequency of GIGYF2 mutations in the entire replication cohort was only about 0.001%.[127] Furthermore, the presence of mutations in healthy population controls or within asymptomatic family members of PD patients argues against causality even if longitudinal data are not available. Thus, unless new information emerges to suggest otherwise, it is reasonable to conclude that GIGYF2 does not play a major role in PD.

VPS35
The most recently described cause of monogenic PD is the mutations of a gene encoding vacuolar protein sorting-associated protein 35 (VPS35), which were identified by the next-generation of sequencing technique.[130,131] Vilariño-Güell *et al*.[130] described the identification of the p.D620N mutation in VPS35 within affected members of a Swiss kindred and three other families with late-onset, autosomal dominant PD, and in one sporadic PD case. At the same time, Zimprich *et al*.[131] published the identification of the p.D620N mutation in a large multigenerational Austrian family with PD and in two additional families screened for VPS35 mutations. Both groups also identified additional mutations in VPS35; however, the pathogenicity of these additional variants remains unknown. Moreover, VPS35 mutations have been detected only in whites with PD. Studies in both Chinese and Japanese have excluded an association between VPS35 mutations and sporadic PD.[132-134]

PLA2G6
Mutations in phospholipase A2, group VI (PLA2G6)[135] usually cause an early-onset recessive degenerative disorder with spasticity, ataxia and dystonia; however, later adult onset forms of the disease can present with a dystonia predominant parkinsonism.[136] The patients with PLA2G6 homozygous mutations presented in their 20s with slowly progressive gait problems, clumsiness, imbalance, hand tremor, cognitive decline and dysarthria. Most patients with Parkinsonism are Levodopa-responsive at first, but this usually lasts only 1-2 years. PLA2G6 mutations have been screened for both early- and late-onset PD. Although SNPs have been identified in PD patients, none of these has been convincingly associated with the risk for PD.[137,138]

EIF4G1
Most recently, translation initiator mutations in EIF4G1 were genetically linked to autosomal dominant late-onset PD with brainstem Lewy body pathology.[139] EIF4G1 is a central component of the EIF4F complex

that regulates translation of mRNAs with highly structured 5'-sequences. The most popular mutations, p.Ala502Val and p.Arg1205His mutation were found to be with PD in some population. However, later replication studies in multiple ethnicities failed to confirm EIF4G1 mutations as a cause or a susceptible factor for familial or sporadic PD.[133,140,141]

BST1

Recently, GWAS in PD have provided association evidence at 16 loci, including a region encompassing a gene encoding bone marrow stromal cell antigen 1 (BST1) on 4p15.[142] Interestingly, all PD-associated single-nucleotide polymorphisms (SNPs) on the BST1 locus lie within linkage disequilibrium blocks containing only the BST1 gene.[142] However, by direct sequencing of the entire coding region of BST1, we did not reveal a variant associated with PD.[143]

CONCERNS ON THE TRANSLATION OF GENETIC INFORMATION INTO CLINICAL APPLICATIONS

Molecular diagnosis of Parkinson's disease: possibilities and concerns

As mutations in several genes are able to cause monogenic forms of PD, molecular diagnosis using these mutations for familial PD is possible. However, cautions must take before extensive applications of these mutations to genetic counseling, because most of our knowledge about the genetic basis of PD remains preliminary. According to the latest European Federation of Neurological Societies guidelines on the molecular diagnosis of PD,[144] for mutations that are detected in rare familial forms of PD, such as point mutation or multiplication of SNCA in familial PD, molecular diagnosis should be considered only for clearly familial cases. Even for the LRRK2 genes in which mutations are much more prevalent in Europeans, molecular testing is only recommended for cases with dominant inheritance of parkinsonian syndromes, and testing for the G2019S mutation is only recommended for familial and sporadic patients in the Ashkenazi Jews or North African Arabs. Similarly, testing for mutations in recessive PD-genes (parkin, PINK-1, DJ-1) is only recommended for families suggestive of recessive inheritance (affected sib pairs) or sporadic patients with very early onset (< 35 years). For most of the other mutations, using of them for genetic testing should wait until their causative role in the disease is convincingly established.

Use of genetic variation as predictive biomarkers for Parkinson's disease: is it possible now?

A biomarker is a substance used as an indicator of normal biologic and pathogenic processes, or responses to a therapeutic intervention. Biomarkers for PD may be directed at disease risk, disease progression, or both. A mutation or genetic variant can be considered a risk biomarker for PD if it is associated with the disease. The discovery of mutations that cause monogenetic forms of PD has allowed clinical investigators to determine the cause of the disease and to predict the risk for developing the disease. However, at least two factors have to be simultaneously considered before defining such mutations as biomarkers: the penetrance of the mutations and the variability of AAO of PD caused by the mutations. Mutations that confer high risk of developing a disease usually display a high penetrance (> 80%), and the variability of AAOs of patients carrying such mutations is usually low. In autosomal dominant form of PD, the most affirmatively causative mutations are those within the SNCA and LRRK2 genes. Point mutations, duplications, and triplications of SNCA cause PD with high penetrance. However, the AAO of each mutation type in this gene is associated with a fairly high variability among cases (ranging from mid- 30s to late 80s), making it difficult to use these mutations to predict the onset and course. On the other hand, although the causative role of the LRRK2 G2019S mutation is not in question, and the AAO is less variable (usually at 60s), it is clear that the penetrance of this gene is only 30-40%. Therefore, carrying this mutation does not unequivocally predict development of PD during a lifetime.[145] The situation for the risk variants associated with the onset and progression of sporadic PD are even more complicated and puzzling as it may involve multiple independent and interactive factors. Thus, the value of a genetic biomarker in predicting an individual's risk of developing the disease is questionable at the current stage.

Can genetic variations help in molecular classification of Parkinsonian disorders?

Parkinsonian disorders are a group of clinically and pathogenically diverse disorders. For diagnostic and therapeutic purposes, it has long been expected to classify this clinical complex further. Currently, the classification of these disorders is mainly based on pathological findings. According to autopsy findings, the histological characteristics in the patients' brain have been classified as α-synucleinopathies and non-α-synucleinopathies, the latter including tauopathies, TDP-43 proteinopathies and nonspecific degeneration in the pars compacta of the substantia nigra (SNPc).[146] However, this classification is made postpartum and, therefore, less useful for preclinical and clinical diagnosis. Interestingly, studies have demonstrated that similar pathologies might result from the influence of mutations in genes that are part of the same pathways.[11,147] For example, PD cases with mutations in SNCA, LRRK2 and GBA genes usually display a common α-synuclein pathology,

while those with mutations in the MAPT gene tend to possess both α-synuclein and tau pathologies. In contrast, except for nonspecific neuronal loss and gliosis, no histopathological hallmark was revealed in most of the AR-JP patients caused by mutations in the parkin gene.[146] Moreover, many variations in these genes are not only associated with increased risk for PD, but strongly correlate with certain profiles of the disease. Hence, it is reasonable to assume that genetically determined loci, especially when combined with pathological and clinical information, can help in establishing a classification for PD. In a recent study, we have investigated clinical profiles of PD related to LRRK2 (LRRK2-PD), GBA (GBA-PD) variant, or none of the variants (idiopathic PD, IPD).[148] As a result, LRRK2-PD is largely similar to IPD, while GBA-PD patients had an earlier onset and more frequent and severe nonmotor symptoms. These results favor the feasibility of genetic classification of PD. However, since much of our knowledge about the genetic-pathologic-clinical axis of parkinsonism is quite limited so far, there is still a long way ahead before a rational nosology for parkinsonian disorders linked to their genetic underpinnings is made and before the classification becomes a practice guideline.

CONCLUDING REMARKS AND FUTURE RESEARCH CONCERNS

The past decade has been an exciting time for investigators involved in genetic research in PD. The rapidly emerging evidences of the genetic contribution to PD have changed the way we think about the disease. However, we are still not able to see a complete genetic picture of the disease. Many concerns remain to be addressed. First, the highly genetic heterogeneity among populations reminds us that the genetic information of a gene or locus provided by current studies for certain populations is limiting and segmentary. For example, although the link of the LRKK2 G2019S mutation to PD in multiple populations has been well-established, it provides little information for Eastern Asians. The emerging evidences for the contribution of another variant, G2385R, residing in a different domain of the protein may suggest a yet-unknown, but sharply different story of LRRK2 from that of the G2019S mutation. Thus, before characterizing the roles played by G2385R or other potential significant variants, a complete genetic behavior of LRRK2 should not be described merely by the G2019S information, nor should it be applied extensively to clinical practice. Similarly, it is not reasonable to overestimate the genetic contribution of the H1 haplotype of MAPT gene because the homozygous H1 allele is dominant while the H2 haplotype lacks in Asians. These problems necessitate clinical and genetic studies surrounding

the population-specific variants. Second, most of the current genetic studies are focused on sequence variations (i.e. point mutations or SNPs) and much less have been directed to copy-number variations (CNVs), whose pathogenic or predisposing effects sometimes are even more evident and important. Dosage mutations of the parkin gene, for instance, have been suggested to be more pathogenic than the sequence mutations for familial PD among Europeans. Therefore, large-scale and multi-central analysis of CNVs are urgently needed to improve the image of risk genetic variants for PD. Third, the work on genetic mechanisms underlying PD is far away from just identifying mutations or risk variants. We have to figure out how these variants act on the disease, e.g. how they interact with other genes and/or environmental factors, and how they are linked to pathophysiological pathways involved in PD. In addition, prospective studies of presymptomatic carriers of mutations or risk genetic variants of PD genes are necessary to confirm their genetic roles in the disease development and progression.

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