Parkinson's Disease: From Genetics to Clinical Practice

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Abstract: Breakthroughs in genetics over the last decade have radically advanced our understanding of the etiological basis of Parkinson's disease (PD). Although much research remains to be done, the main genetic causes of this neurodegenerative disorder are now partially unraveled, allowing us to feel more confident that our knowledge about the genetic architecture of PD will continue to increase exponentially. How and when these discoveries will be introduced into general clinical practice, however, remains uncertain. In this review, we provide a general summary of the progress in the genetics of PD and discuss how this knowledge will contribute to the diagnosis and clinical management of patients with, or at risk of this disorder.

INTRODUCTION

Dissection of the genetic architecture of any complex disorder like Parkinson's disease (PD) is paramount to understanding its biological basis, assess the individual predisposition of disease, and evaluate the capacity of novel therapeutic interventions in early, even pre-symptomatic stages. A striking progress in genetics of PD during the last decade has led to the identification of a substantial number of Mendelian genes and loci, as well as a large list of genes with significant effects on disease risk. In order to make an apprehensible description of what has been discovered during the last 15 years, we have performed a summary divided into three main topics: Mendelian genes, well established genes related to sporadic forms of disease, and genes with low risk effects resulting from genome-wide association analyses. We also discuss the usefulness and limitations of genetic testing.

1. MENDELIAN GENES

PARK1 (PARK4): α-Synuclein; Chromosome 4q21-23

Three missense mutations (p.A30P, p.E46K, and p.A53T) in the gene encoding for α-synuclein (*SNCA*), the main protein that aggregates in Lewy bodies, have been reported in families with autosomal dominant forms of PD [1]. Broadly, these point mutations range from a relatively typical levodopa-responsive PD to a disorder reminiscent of diffuse Lewy body dementia, with a relatively early age at onset (mean age of 45 years). In 2003, a genomic triplication of 1.5 million base-pairs that includes the entire *SNCA* gene was found to segregate with disease in a large family called the "Iowa kindred" [2, 3]. Additional families with either

SNCA triplication or duplication mutations were later discovered [4, 5]. In these cases, the α-synuclein gene is normal in sequence but abnormal in dose. Interestingly, duplication of the *SNCA* locus more closely resembles idiopathic PD, whereas patients with four copies of the gene tend to present an earlier onset and a more aggressive clinical course, including cognitive decline and shorter survival.

PARK2: Parkin; Chromosome 6q5.5-q27

Mutations in *PARK2* are the leading cause of autosomal recessive early-onset PD. They account for up to 10% of patients with PD onset before 50 years [6, 7] and as high as 77% of patients with onset at 20 years or younger [8]. Since *PARK2* was identified in 1998, a wide variety of mutations, including exon rearrangements, single base pair substitutions, and small deletions or insertions of one or several base pairs, have been identified in nearly all populations studied, regardless of ethnic origin. Patients with mutations present a clinical syndrome that is indistinguishable from that of idiopathic PD, with a good response to levodopa. Brain autopsy studies in *PARK2* cases have shown pathological heterogeneity. Although the majority of reported cases present substantia nigra degeneration without neuronal inclusions of alpha-synuclein [9-11], other patients have been described with Lewy bodies (LB) in the nigra and locus coeruleus [12], basophilic LB-like inclusions in the pedunculopontine nucleus [13], or neurofibrillary tangle pathology in the cerebral cortex and brainstem nuclei [14].

Interestingly, carriers of heterozygous *PARK2* mutations are at risk to develop PD [15-17], and some coding polymorphisms appear to be risk factors for sporadic and familial PD [18]. The role of heterozygous *PARK2* mutations as a PD risk factor has been supported by positron emission tomography (PET) scanning studies showing preclinical changes in striatal structures in asymptomatic heterozygous mutation carriers [19, 20].

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PARK6: PINK1; Chromosome 1p36

PTEN-induced putative kinase 1 gene (*PINK1*) is the second most frequent causative gene in early onset autosomal recessive PD. Homozygous and compound heterozygous mutations comprising nonsense, missense and small deletions, have been described in patients with a slowly progressive levodopa-responsive phenotype. Intriguingly, several alterations in imaging biomarkers have been reported in patients carrying a single *PINK1* mutation. For example, a low uptake of the tracer iodine-123 metaiodobenzylguanidine in myocardial muscle [21], and a 20 to 30% reduction in caudate and putamen F-dopa have been shown in *PINK1* mutation carriers [20]. Nonetheless, there is no clear evidence that *PINK1* heterozygosity increases susceptibility to idiopathic PD [22].

PARK7: DJ1; Chromosome 1p36

Homozygous and compound heterozygous mutations in *DJ1* are rare causes of early onset PD with a recessive inheritance [23]. Although patients with *DJ1* mutations present a clinical picture of idiopathic PD with L-dopa responsiveness, three cases from the same family have been reported to have a phenotype comprising early-onset parkinsonism, dementia, and amyotrophic lateral sclerosis [24].

PARK8: LRRK2; Chromosome 12p11.2-q13.1

The most frequently mutated gene in PD is the gene encoding for the Leucine-rich repeat kinase 2 (*LRRK2)* [25, 26]. Mutations in this gene lead to an autosomal dominant PD with onset in the sixth decade of life. Although more than 250 aminoacid substitutions have been reported in this gene [27], genetic evidence for pathogenicity by cosegregation with disease within families has only been proven for six variants: p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.G2019S, and p.I2020T. Among these mutations, p.G2019S is the most common, with a worldwide frequency ranging from 1% of patients with sporadic PD to 4% of patients with familial PD. These frequencies vary in different populations, however. It is present in ~40% of North African Berber Arabs with PD, in 28% of Ashkenazi Jews with hereditary disease (and in 10% with sporadic disease), and in less than 0.1% of Asians [28]. The age-related penetrance of the p.G2019S mutation has been estimated to be 28% at 59 years, 51% at 69 years, and 74% at 79 years. Patients harboring the p.G2019S mutation are clinically indistinguishable from those with idiopathic PD. Nonetheless, mutation carriers can present a more benign progression and less prevalence of dementia during the course of PD course than non-carriers.

PARK9: ATP13A2; Chromosome 1p36

A syndrome appearing at very young ages, between 11 and 16 years, was first described in 1994 in a consanguineous Jordanian family originating from a small community named Kufor-Rakeb [29]. This form of the disease consists of akinetic-rigid parkinsonism with concomitant bradykinesia, progressive spasticity, supranuclear upgaze paresis and dementia. It has a good response to L-dopa. The gene was mapped to the short arm of chromosome 1 (1p36) in 2001 [30], and the responsible gene (ATPase type 13A2, *ATP*

13A2) was cloned soon afterwards [31]. Since then, few families have been described worldwide and mutations in *ATP13A2* seem to be a very rare cause of Parkinsonism.

PARK14: PLA2G6; Chromosome 22q13.1

Mutations in the *PLA2G6* gene, encoding for the phospholipase A2, group VI (cytosolic, calcium-independent) gene, typically lead to a recessive degenerative disorder characterized by motor and cognitive regression starting at the first or second year of life [32]. Cerebellar cortical atrophy and basal ganglia iron accumulation are prominent radiologic features in these patients, and spasticity, dystonia and cerebellar features are also evident in mutation carriers [33]. It is important to note that patients with homozygous *PLA2G6* mutations can also present with adult-onset levodopa-responsive complicated parkinsonism without brain iron accumulation on MRI. However, a clinical phenotype comprising slowly progressive gait problems, cognitive decline, clumsiness, hand tremor, bradykinesia, dysarthria and dystonia has also been described [34].

PARK15: F-box protein 7; Chromosome 22q12-q13

Pyramidal signs with an onset within the third decade of life, followed by L-dopa responsive extrapyramidal symptoms, were first described in a large Iranian family with an autosomal recessive pattern of inheritance [35]. The authors cloned the *FBXO7* gene as the genetic cause of this disorder. A handful of families with early-onset, progressive parkinsonism with associated pyramidal tract signs due to *FBXO7* homozygous and compound heterozygous mutations have since been reported in Italy, Turkey, the Netherlands and Pakistan [36, 37]. Clinical features such as bulbar signs, supranuclear gaze palsy and cognitive deterioration have been reported in some of these families, expanding the heterogeneity related to *FBXO7* mutations.

PARK17: VPS35; Chromosome 16q12

The recent finding of *VPS35* is a good example of how targeted enrichment of genomic DNA and next-generation sequencing are powerful tools for the discovery of Mendelian genes. This gene encodes for the vacuolar protein sorting 35 homolog (S. cerevisiae), and is the causal gene for some forms of late-onset, autosomal dominant PD. The gene was found in 2011, when two independent groups performed a caption of the ~180,000 exons that represent 22,000 genes of the human genome and sequenced all the resulting fragments by means of next generation sequencing systems in families with autosomal dominant PD from Switzerland and Australia [38, 39]. A missense mutation (p.D620N) in the *VPS35* gene was found in both families. Subsequent analyses disclosed families from Tunisia, Israel and Austria carrying the same mutation. Although other missense mutations were found by both groups, the pathogenicity of these additional mutations remains unknown.

2. *SNCA*, *GBA* AND *MAPT* AS WELL ESTABLISHED GENES RELATED TO PD

SNCA Genetic Variation and PD Risk

In 1999, certain alleles of the polymorphic complex repeat site NACP-Rep1 (D4S3481), which is composed of a

mixed length of contiguous dinucleotides, and located ~10Kilobases upstream of the transcriptional start site of the *SNCA* gene, were associated with an increased risk of sporadic PD [40]. Subsequent analyses trying to replicate this finding were not always successful. In 2006 however, a large study that included 2,692 PD cases and 2,652 controls and incorporated previous analyses but also added novel data revealed compelling evidence that NACP-Rep1 was associated to PD risk [41]. The biological link between this microsatellite and PD has been supported to some degree by functional data, which suggest that α-synuclein levels could be influenced by NACP-Rep1 alleles through a regulation of *SNCA* gene transcription [42]. The role of *SNCA* in sporadic forms of PD has been fueled by different genome-wide association studies. These analyses indicate that common polymorphisms located downstream of the gene (more than 125 Kb away from the NACP-Rep1 microsatellite) might also contribute to PD risk [43-45]. Whether the NACP-Rep1 variant, located upstream of *SNCA*, or biallelic polymorphisms located downstream of the gene are independent association signals is still a matter of controversy [46, 47].

GBA Mutations and PD Risk

Homozygous mutations in the glucocerbrosidase (*GBA*) gene lead to Gaucher disease, the most common lysosomal storage disorder. The presence of progressive parkinsonian features in some patients with Gaucher disease was a key element in identifying mutations in *GBA* as an important risk factor for PD. Since the first discovery that resulted from the analysis of Ashkenazi Jewish patients, [48] many studies worldwide have replicated this finding [49-54]. In 2009, a multicentric international analysis that included 5,691 patients and 4,898 controls indicated that *GBA* mutations may be present in 3%-10% of PD patients from a non-Ashkenazi Jewish origin, and carriers of a *GBA* mutations have a five-fold increased risk to develop PD compared to noncarriers [55]. The clinical phenotype associated to a *GBA* mutation is indistinguishable from idiopathic PD. However, bradykinesia, resting tremor, rigidity and symmetric onset have been reported to be more frequent features in patients carrying a *GBA* mutant allele. A remarkable characteristic in patients harboring a *GBA* risk allele is the greater prevalence of cognitive decline and dementia during PD course [52, 56, 57], and carriers might have a six-fold increased risk to dementia compared to noncarriers [58].

MAPT H1 Haplotype and PD Risk

In 2002, the first genetic association between MAPT H1 halpotype (an extended haplotype that results from a common genomic inversion of approximately 800 kb in the large arm of chromosome 17 containing the *MAPT* gene) and PD risk was reported through a limited number of cases and controls [59]. With more than 20 studies performed to date, *MAPT* seems to be undoubtedly associated with PD risk in populations with European ancestry but not in Asians (http://www.pdgene.org) [60]. The MAPT H1 haplotype is present in all human populations, whereas the inverted haplotype (named H2) is mainly found in southwest Asian and southern European populations, with frequencies ranging from 21% to 32% [61, 62]. Interestingly, a longitudinal study performed in 2003 revealed that PD patients with the H1 variant followed for 3.5 years had a greater risk of cognitive decline than noncarriers [63]. A subsequent comprehensive analysis from same authors concluded that the *MAPT* H1 variant was the strongest independent predictor of dementia among PD patients, with an odds ratio of 12 over 5 years of follow-up [64]. Data originated in our and other's centers have provided compelling evidence that the *MAPT* H1 variant leads to an increased risk of cognitive decline and dementia in PD patients [65-67].

3. GENES WITH LOW RISK EFFECTS: RESULTS FROM GENOME WIDE ASSOCIATION STUDIES (GWAS)

In 2005 the first genome-wide association study of PD was performed in 443 sibling pairs discordant for PD, and a second tier of 332 patients and controls [68]. In 2006 a subsequent study that included 537 samples was not able to replicate previous findings and proposed that there are no common genetic variants with high risk effects on PD [69]. Three years later, two studies from Japan and Europe used more powerful sample sizes that evidenced the association with *SNCA*, *MAPT*, *LRRK2*, and disclosed novel loci in chromosome 1 (PARK16) and chromosome 4p15 (close to the *BST1* gene) [70, 71]. In that same year, a similar study comprising 857 PD patients with a family history of PD and a similar number of controls disclosed a 112 kb region on the short arm of chromosome 4 that contained the genes *GAK* and *DGKQ* [72]. Additional analyses with similar sample sizes combined with data released from previous studies supported these genetic associations, [73-76] and yielded novel loci, like the human leukocyte antigen (HLA) region in choromosme 6p21.3 (which was designated PARK18) [74, 75]. In 2011 a meta-analysis of datasets from five PD GWAS was conducted by the International Parkinson's Disease Genomics Consortium (IPDGC). This study, which included a discovery phase with 5,333 cases and 12,019 controls, and a replication phase consisting of 7,053 cases and 9,007 controls, revealed five novel loci (*ACMSD*, *STK39*, *MCC1/LAMP3*, *SYT11*, and *CCDC62/H1P1R*) with subtle but significant risk effects [45]. A follow-up analysis performed by the same consortium revealed five additional PD risk loci that comprised the previously detected region in chromosome 1q32 (PARK16) and variants located close to the genes *STBD1*, *GPNMB*, *FGF20*, and *STX1B* [77]. Together with this study, an analysis performed by the Personal genetics company 23andMe, that incorporated over 3,400 cases and 29,000 controls, confirmed the outcomes from the IPDGC and yielded significant signals near *SREBF1/RAI1* and *SCARB2* genes [43]. Most recently, a meta-analysis was performed from data at the freely available online database "PDGene" (http://www.pdgene.org), which contains a comprehensive collection of all public genetic association studies performed on PD. It confirmed the existence of eleven loci previously shown to increase or decrease PD risk and revealed a novel association with an intronic polymorphism in *ITGA8* gene on chromosome 10p13 [44].

4. MOLECULAR GENETIC TESTING

Up to 40% of PD patients with age at onset of less than 30 years and 17% of those with age at onset of less than 50 yeas will probably have a mutation in one of the known
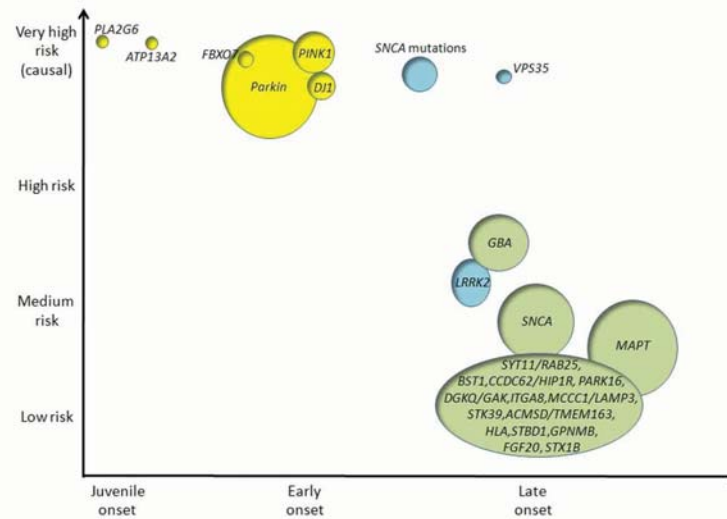
Fig. (1). Schematic representation of the genetic architecture of PD. The Y axis shows the strength of genetic effects and the X axis indicates the age at onset of disease. Autosomal recessive genes are presented in yellow; autosomal dominant genes in blue and risk loci in green. The size of each circle is an approximation of the population attributable risk (PAR), that is, the proportion of PD that is ascribable to a mutation or a genetic risk variant at any gene. Percentages of PAR in genetic risk loci are based on references 56, 59 and 79. For genes related to monogenic forms of disease *(PLA2G6, ATP13A2, FBOX7, PARK2, PINK1, DJ1, SNCA* and *VPS35)* % of PAR have limited value due to the rarity of the deleterious alleles in the population and therefore the circle size represents an approximation of the % of cases due to known genetic causes. Relative risks for each loci are based on evidence from the PD gene database (www.pdgene.org).

Mendelian genes linked to PD [78]. Therefore, genetic testing for diagnostic purposes in families with a Mendelian aggregation of disease is a very powerful tool and may be appropriate in many instances. Due to the increasing number of genes related to PD, genetic diagnostic process can be long, expensive and complex using classic Sanger-based sequencing approaches. The advent of next-generation sequencing (NGS) tools will allow a rapid, efficient and cost-effective process to test for genetic alterations in genetic forms of PD. Implementing NGS in diagnostic services, however, can be challenging. First, the large amount of data resulting from NGS can complicate the interpretation of pathogenic variants. Second, large gene dosage alterations (such as deletions and insertions) can be missed with NGS technologies. Finally, genomic regions with enriched G-C stretches are typically poorly captured and therefore mutations within these regions could be omitted. In any case, although genetic testing can be conducted in a successful and widely available manner, they should be performed in a multidisciplinary setting supported by personnel with expertise in this area. The reason for this multifaceted approach in genetic counseling is the possible ethical, social, psychological and legal consequences of a potential positive result from the test.

Genetic counseling and risk evaluation in sporadic, late onset PD, however, is likely of limited clinical utility at the present time. Predictive accuracy is poor due to the small effect sizes of genetic variants that have been associated with PD risk. As most of these genetic variants only explain a small proportion of the disease (Fig. **1**), caution should be taken when interpreting this kind of genetic data for counseling purposes.

The determination of genetic causes contributing to the modification of disease (modifier genes) is of extraordinary importance in terms of clinical follow up and management. *GBA* mutation or *MAPT* H1 allele status, for example, might be an independent risk factor for cognitive impairment in patients with PD and could therefore have strong implications in the disease course and therapeutic treatments [52, 56, 58, 64, 65].

Further insights into the genetic causes of PD are warranted, and an overwhelming amount of new data will probably come to light in coming years. How these data are handled in terms of genetic counseling and therapeutic interventions is a major responsibility that governments, scientists, the biotechnology industry, and civil society must approach with sensitivity, objectivity and rigor.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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