

Review

Usefulness of Genetic Testing in PD and PD Trials: A Balanced Review

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Abstract. An increasing proportion of the individual and population risk to develop Parkinson's disease (PD) can be explained by genetic variants of different effect strength, forming a continuum from rare high penetrance gain or loss of function mutations to relatively common genetic risk variants that only mildly modify disease risk. In the coming years, further advances in molecular genetic technologies, in particular the increasing use of next generation sequencing, is likely to generate a wealth of new knowledge about the genetic basis of PD. Although specific treatments for PD based on the underlying genetic etiology will probably not be available in the near future, genetic testing is therefore likely to play an increasing role, both in the counselling of individual patients and their families with respect to the expected disease course and recurrence risks, and in the stratification of patient groups in clinical trials. Thus, the usefulness of genetic testing strongly depends on question asked and needs to be considered within each particular setting.

Keywords: Parkinson's disease, genetics, mutation, risk variant

INTRODUCTION

Until about 20 years ago, Parkinson's disease (PD) was considered the textbook example of a "non-genetic" disorder. With the identification of an increasing number of disease-causing mutations and a host of genetic risk factors, this view has fundamentally changed [1]. Nevertheless, the known monogenic forms of PD are rare and all together account for less than 5 to 10% of PD cases in most populations. Many of the recently discovered genetic risk alleles, on the other hand, are much more common, but have a relatively weak effect, increasing the likelihood to develop sporadic PD only by the factor 1.2–2.0 (Fig. 1). Thus, in contrast to high-penetrance mutations, these small-

effect risk factors are not useful to predict an individual risk to develop PD.

The usefulness of genetic testing in PD keeps evolving along with our growing knowledge of the genetic architecture of this complex disorder. Today, clinical genetic testing targeting the major known PD genes (Table 1) is only helpful in a very limited proportion of cases with typical PD in whom one of the rare forms of the disease with Mendelian inheritance is suspected based on family history or age-at-onset [2]. In atypical parkinsonian syndromes and more rarely in typical PD, however, genetic testing can occasionally also reveal unsuspected mutations in genes that are more often associated with other inherited diseases such as the spinocerebellar ataxias of the frontotemporal dementias.

Finally, in a research setting, stratification of patient populations according to genetic mutations and risk factors is likely to become an important feature of clinical trials aimed at the modification of the disease

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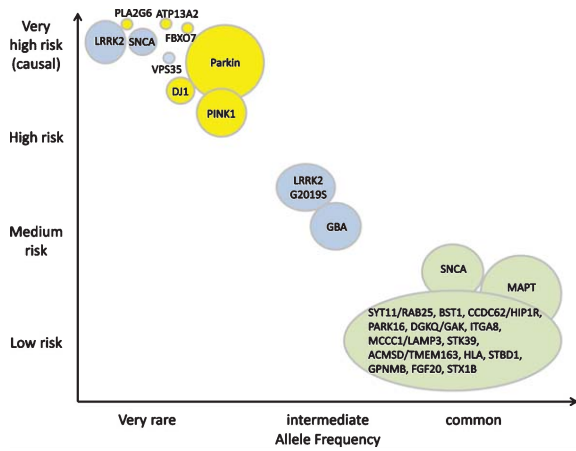


Fig. 1. Genetic architecture of Parkinson's disease. Continuum of variants of different effect strengths and allele frequencies. The size of the bubbles roughly corresponds to population allele frequencies. Colors symbolize modes of inheritance: dominant (blue), recessive (yellow), risk loci (green). Modified from [35] and [36].

course. Each of these situations has to be considered separately to fully assess the usefulness of genetic testing in PD.

GENETIC ARCHITECTURE OF PD

A minority of patients with the typical clinical picture of PD have a positive family history compatible

with a Mendelian (autosomal dominant or autosomal recessive) inheritance.

Autosomal dominant forms of mendelian PD

The exchange of a single basepair in the α -synuclein (*SNCA*) gene leading to an alteration of the amino-acid sequence (A53T) of the encoded protein was the first disease-causing PD mutation found in a large family of Italian origin (Contursi kindred) with an autosomal dominant pattern of inheritance [3]. Later, a few additional missense mutations were recognized [4, 5], but the results of large screening studies of several thousands of patients suggest that the overall frequency of *SNCA*-mutations is below 0.1% [6, 7]. Since 2003 [8], duplications and triplications of the *SNCA* gene are also recognized as a rare cause of autosomal-dominant PD (called PARK4, because the disease-locus in the first triplication family was erroneously mapped to a different part of chromosome 4).

A more common form of monogenic PD with dominant inheritance is caused by mutations in the gene for leucine-rich repeat kinase 2 (*LRRK2*) [9, 10]. The pathogenicity of several rare point mutations is supported by co-segregation in large families (p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.I2020T), but a specific and much more common variant, p.G2019S, also occurs in 2 to 7% of sporadic Caucasian PD patients, and, due to a founder effect, even in up

Table 1
Monogenic forms of Parkinson's disease

	Gene	Chromosomal position	Clinical characteristics
Autosomal-dominant PD			
PARK1	<i>SNCA</i>	4q21	<ul style="list-style-type: none"> • Different point mutations • Parkinsonism and dementia • Onset early (A53T) to late (A30P) depending on mutation
PARK4	<i>SNCA</i>	4q21	<ul style="list-style-type: none"> • duplication or triplication of the wild-type gene • parkinsonism and dementia • onset early (triplication) to late (duplication)
PARK8	<i>LRRK2</i>	12q12	<ul style="list-style-type: none"> • point mutations
PARK17	<i>VPS35</i>	16q11	<ul style="list-style-type: none"> • similar to sporadic PD, mostly late onset • similar to sporadic PD
Autosomal-recessive PD			
PARK2	<i>Parkin</i>	6q25	<ul style="list-style-type: none"> • nonsense and missense mutations, deletions, duplications • dystonia and dyskinesias common, slow progression
PARK6	<i>PINK1</i>	1p35	<ul style="list-style-type: none"> • similar to <i>parkin</i>-associated PD
PARK7	<i>DJ-1</i>	1p36	<ul style="list-style-type: none"> • similar to <i>parkin</i>-associated PD
Complex syndromes with parkinsonism			
PARK9	<i>ATP13A2</i>	1p36	<ul style="list-style-type: none"> • Parkinsonism, pyramidal syndrome, dementia
PARK14	<i>PLA2G6</i>	22q13.1	<ul style="list-style-type: none"> • dystonia-parkinsonism, pyramidal syndrome, dementia
PARK15	<i>FBXO7</i>	22q12	<ul style="list-style-type: none"> • parkinsonism, pyramidal syndrome, dementia
n.a.	<i>DNAJC6</i>	1p31.3	<ul style="list-style-type: none"> • parkinsonism, pyramidal syndrome, cognitive impairment, seizures
n.a.	<i>SYNJ1</i>	21q22.11	<ul style="list-style-type: none"> • parkinsonism, cognitive impairment, seizures

to 25% of patients from Ashkenazi Jewish or North African Berber ancestry. Due to reduced age-related penetrance, estimated between 25 and 70%, many of those patients do not have a very clear family history of the disease.

Overall, LRRK2 mutations account for 5 – 15% of dominant familial [11], and 1–3% of sporadic PD cases [12], whilst another mutation, the R1441G variant, is a Basque founder mutation with a prevalence of 15% in patients with PD from this region [13, 14].

Other, less common dominant mutations have been found in the genes for *VPS35* [15], and, recently in *DNAJC13* [16], the latter one still unconfirmed by other studies.

Autosomal-recessive forms of mendelian PD

Several genes cause recessively inherited early-onset PD by loss-of-function mutations. The two most common ones are *parkin* (PARK2) [17] and *PINK1* (PARK6) [18], both of them likely to be critically involved in mitochondrial maintenance and quality control. Different types of mutations (nonsense and missense point mutations, deletions, duplications) have been found in both genes, suggesting a loss-of-function mechanism. In the homozygous or compound heterozygous state they cause an early-onset form of PD with dystonia as a relatively common early feature. Dopamine-loss is severe and most patients develop early and marked levodopa-induced motor-fluctuations and dyskinesias, although the disease progresses only slowly with a low prevalence of dementia. Among families with early-onset PD under the age of 30, 49% of the patients with an affected sibling and about 10% of cases without positive family history had *parkin* mutations [19]. Whether heterozygous *parkin* mutations increase the susceptibility to late-onset PD is widely discussed and still unresolved.

An increasing number of other, less common recessive mutations are identified as a cause of early-onset PD, in some cases with more or less atypical clinical and imaging features. The first of these rare recessive genes, *DJ-1*, was found in 2002 [20] and has a similar phenotype as described in patients with *parkin* and *PINK1* mutations. More recently, however, the use of next generation sequencing, in particular in consanguineous families, has facilitated the discovery of several new genes for early-onset recessive parkinsonism in rapid succession, including *DNAJC6* [21] and *SYNJ1* (auxilin, synaptojanin1) [22, 23]. The frequency of these mutations has not yet been fully assessed, but it can be expected that individually,

each will account only for a very small minority of patients.

It should be noted that a number of nominated Mendelian loci have not yet been confirmed independently as disease genes and that the pathogenicity of several suggested mutations could so far not be unequivocally confirmed. Some of these genes and loci have been assigned a “PARK” designation (PARK3, *UCHL1* - PARK5, PARK10, *GYGYF2* - PARK11, *OMI/HTRA2* - PARK13, *EIF4G1* - PARK18). The link of these genes to PD remains uncertain and thus any result with respect to these genes obtained through genetic testing has to be interpreted with great caution.

RISK FACTORS OF INTERMEDIATE STRENGTH IN PD

Heterozygous mutations in the gene for glucocerebrosidase (*GBA*), which cause Gaucher’s disease in the homozygous or compound heterozygous state, have been identified as a relatively frequent risk factor for PD [24]. *GBA* mutation carriers have an increased risk to develop PD by a factor of ~5, compared to the general population (corresponding to a reduced age-dependent penetrance of about 30% by the age of 70 [25]). Some mutations are particularly prevalent in specific ethnic groups, such as the N370S mutation amongst Ashkenazi Jewish, where *GBA* mutations are found in 15 to 30% of sporadic PD cases. Clinically, patients with *GBA* mutations have typical PD with a slightly earlier onset age, and a higher prevalence of autonomic and other non-motor manifestations and cognitive impairment [26]. The LRRK2 G2019S variant discussed above can also be considered to be a risk factor of this category, rather than a high penetrance mutation.

COMMON GENETIC RISK FACTORS FOR PD OF WEAK EFFECT-STRENGTH

Genome-wide association studies (GWAS) to date have led to the discovery of as many as 28 genetic risk loci for sporadic PD [7]. The associated risk variants can be common in the population (with allele frequencies up to 35 or 40%), but convey only a mildly (1.2 to 1.5 fold) increased risk to develop the disease. Even if all known risk factors are considered together, they are only associated with an odds ratio of 3 to 4 [7] and thus explain only a part of the expected heritability of PD [27]. This could be due to the fact that many of the rarer risk variants are

probably still unknown, or that “balancing protective” factors are not yet accounted for. Interestingly, common risk variants occur in some of the same genes that had been identified as Mendelian disease genes, such as *SNCA* (alpha-synuclein), *LRRK2* or *MAPT* (microtubule-associated gene tau), emphasizing shared pathogenic pathways between inherited and sporadic forms of PD.

COMPLEX SYNDROMES WITH PARKINSONISM AS PART OF THEIR CLINICAL SPECTRUM

Mutations in several genes can cause rare syndromes of a more complex phenotype with parkinsonism representing only one of several clinical features. Some of them have been designated as “PARK”-genes (*ATP13A2* - PARK9, *PLA2G6* - PARK14 and *FXBOX* - PARK15), but others have not (e.g. *DCTN1*, responsible for Perry syndrome, or *MAPT* or *PRGN*, which cause frontotemporal dementia (FTD), which can occur with or without parkinsonism). Even elongated repeat expansions in the *SCA2* gene have been described in patients with parkinsonism and no overt ataxia [28].

The exclusion of these genes from further consideration in this review article is somewhat arbitrary. The developments of recent years clearly show that genotype-phenotype correlations are much more variable than anticipated, and the increasing use of exome sequencing will further increase this diversity. However, due to space limitations, this important topic cannot be discussed here in depth.

GENETIC TESTING IN PD IN A CLINICAL SETTING

Genetic testing in an affected individual or at-risk person in a clinical setting can serve several purposes. If a causal treatment results from the molecular confirmation of a diagnosis, ideally even before development of overt symptoms, as can be the case in Wilson’s disease, the motivation to pursue genetic testing is obvious. However, also in the absence of clear therapeutic consequences, a patient or an at-risk relative may have well justified reasons to ask for genetic testing. The patient may simply look for a definitive diagnosis, a final explanation of his or her symptoms and complaints. This is often particularly true for young patients, who struggle with the diagnosis of a neurodegenerative disorder usually considered a

disease of late life. In such a case, a genetic diagnosis may end an odyssey of hospital visits and costly, sometimes invasive or risky clinical tests.

Life or family planning may be another reason, usually in the setting of a strong dominant family history. A study exploring the attitudes of patients and their families towards genetic diagnosis indicates a high level of interest, but a lack of knowledge about genetic testing [29], clearly indicating an unmet need of patient and caretaker education.

It always has to be kept in mind that the diagnosis of a genetic disorder, in particular one with a dominant or X-linked pattern of inheritance, is always a diagnosis that affects not only the patient or at-risk individual, but the entire family. The patient therefore should be objectively counseled about the risk of transmission, questions of penetrance and expressivity and about potential therapeutic or preventive aspects. Genetic counselling should always be non-directive, aimed at giving the patient the information that is necessary to take an educated decision about the genetic test offered.

In clinical practice, genetic testing should only be performed if there is a clear wish of the patient, following genetic counselling, and a reasonable probability of a conclusive result. Thus, knowledge about the complex genetic architecture of PD as described above is a prerequisite for the appropriate use of genetic testing. This is reflected in the recommendations published jointly by the European Federation of Neurological Societies (EFNS) and the Movement Disorders Society – European Section (MDS-ES) [30]. According to these recommendations, clinical genetic testing in PD should be limited to testing for mutations in *SNCA* and *LRRK2* in patients with typical PD and a clear dominant family history; for mutations for the recessive genes parkin, PINK1, and DJ-1 in patients with typical PD, and either a family history compatible with recessive inheritance (affected siblings, unaffected parents) AND an age of onset below 50, or sporadic patients with typical PD AND an age of onset below 40. Testing for mutations with reduced penetrance, such as *GBA*-variants or the *LRRK2* G2019S-variant, should be limited to patients from the appropriate founder populations. Testing for the many very rare genes causing atypical forms of parkinsonism can be offered based on a case-by-case decision or in a research setting.

It is expected that in the future genetic testing will be used much more liberally. So-called “panel sequencing”, i.e. the simultaneous determination of genetic variability in a large number of genes more or less

strongly associated with the phenotype under study, or even exome sequencing in a clinical setting, will probably become much more common. This will on the one hand result in a higher number cases, where rare mutations in genes not primarily suspected to be causative in this particular disorder will be identified, broadening the range of phenotypes associated with particular genes and mutations. On the other hand, it will produce a large number of variants of unknown significance, which will necessitate stringent criteria to assess pathogenicity [31] and pose a major challenge to genetic counselling.

GENETIC TESTING IN CLINICAL TRIALS

Genetic testing will also play an increasingly important role in clinical trials. Genetic stratification – with or without disclosure of the test results to the patient – will be crucial in trials that test strategies of disease course modification, targeting specific molecular pathways. Focusing on genetically defined patient groups reduces etiologic heterogeneity and allows to start interventions in mutation carriers very early, ideally in the presymptomatic phase. This approach has been pursued for Alzheimer's disease in the DIAN trial (Dominantly Inherited Alzheimer's Network), by ascertaining and characterizing a cohort of symptomatic and presymptomatic carriers of dominant mutations in the presenilin genes (*PSN1* and 2) or the gene for the amyloid precursor protein (*APP*) [32]. A first interventional trial using immunization against aggregating A β -proteins in presymptomatic mutation carriers has been initiated (<http://www.nia.nih.gov/alzheimers/clinical-trials/dominantly-inherited-alzheimer-network-trial-opportunity-prevent-dementia>).

Another emerging option is to stratify patients with sporadic PD according to genetic risk factors with intermediate or even low effect strength. This strategy will also allow to reduce heterogeneity of patient cohorts, both with respect to underlying pathogenic pathways and clinical features. For example, it has been shown that non-motor features including autonomic signs and cognitive dysfunction are more common in patients with *GBA*-mutations [26]. Similarly, common risk SNPs, such as rs356165 in the 3'-untranslated region of the alpha-synuclein gene have been associated with a higher disease risk, an earlier onset and more rapid progression [33], and the ApoE4 allele is a major determinant for the development of dementia in PD [34]. Stratifying the patient population in trials

aimed at these different aspects of PD may significantly increase the power of clinical trials.

In conclusion, genetic testing in PD will play an increasing role in clinical practice and research. Due to the complexity of the disease however, the interpretation of test results will become a major challenge for clinical neurologists and geneticists alike.

CONFLICT OF INTEREST

The author reports no conflicts of interest.

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