Genetic Insights into Early-onset Parkinson’s Disease

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Abstract

Early-onset Parkinson’s disease (EOPD) is defined as disease onset before 40 or 50 years of age. The clinical characteristics of EOPD are very similar to those of late-onset PD, but dystonia is more often a presenting symptom, dementia is rare, and disease progression may be slower. Mutations in several genes have been described in cases with EOPD, often with strong family history, including mutations in α-synuclein (SNCA), DJ-1, PTEN-induced kinase-1 (PINK-1), and ATP13A2. However, the most common mutations identified in EOPD are in Parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2), and glucocerebrosidase (GBA). With the exception of SNCA and ATP13A2 carriers, mutation carriers are often indistinguishable from non-carriers. Large series of EOPD cases that are not ascertained by family history estimate mutation frequency at 4–16%. Given that the frequency of positive family history is much higher, we believe that many genetic risk factors are yet to be discovered.

Keywords

Parkin, SNCA, DJ1, PINK1, LRRK2, GBA, phenotype, early-onset Parkinson’s disease (EOPD)

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Parkinson’s disease (PD) is the second most common neurodegenerative disorder, affecting up to 1.5% of the American population. It has been estimated that up to 10% of the affected population develops the disease by 40 years of age. The definition of early-onset PD (EOPD) varies among studies, and usually ranges between 40 and 50 years of age. While familial clustering of PD has been well described, it is only as recently as 1997 that the first gene associated with PD was identified. To date, all of the genes associated with PD have also been identified in people who developed PD before 50 years of age (i.e. EOPD) and, with the exception of the leucine-rich repeat kinase 2 (LRRK2), mutations are more often identified in people who develop EOPD rather than late-onset PD.

EOPD is considered to be a complex disorder, which means that it is associated with the effects of multiple genes in combination with lifestyle and environmental factors. In EOPD, traditional genetic definitions of autosomal dominant and autosomal recessive may not fully apply. Most of the carriers of autosomal dominant mutations do not develop the disease, i.e. incomplete penetrance (e.g. LRRK2 and possibly synuclein), and some of the autosomal recessive genes may actually increase the risk for EOPD even when only a single copy of the mutated gene is inherited (e.g. Parkin [PRKN], PTEN-induced kinase 1 [PINK-1]). Several genes and chromosomal loci have been associated with EOPD and were designated PARK1 to PARK14 (see Table 1). In this article we will summarize the available data on each separate gene.

PARK1, PARK4—α-synuclein

α-synuclein (SNCA) was the first gene identified as a cause of EOPD in 1997. The gene encodes for synuclein, which has since been found to comprise a major component of Lewy bodies, which are the pathologic hallmark of PD and EOPD. Gain-of-function mutations, duplications, and triplications have all been found in EOPD patients, most often in those with a strong family history. However, very few cases have been described in the literature and penetrance estimations vary. Only 33% of duplication carriers in a single family developed PD in one report. Unfortunately, carriers of gain-of-function mutations and copy number variation (CNV) in the gene may also develop dementia.

Gene dosage may dictate the severity of the EOPD phenotype according to one report. Carriers of triplications were more likely to develop EOPD and dementia, while carriers of duplications were more likely to develop late-onset PD. Interestingly, single-nucleotide polymorphisms (SNPs) in the promoter region of SNCA were implicated by genome-wide association studies (GWAS) in the pathogenesis of PD. Whether these SNPs are also associated with EOPD is unknown.

PARK2—Parkin

Mutations in the PRKN gene are the most common genetic risk factors for EOPD. The relationship between PRKN mutations and EOPD
was discovered in 1998. PRKN mutations were initially identified in familial cases of EOPD, which were usually indistinguishable from idiopathic PD.

PRKN-associated EOPD was initially thought to present with dystonia and brisk reflexes. Subsequent studies comparing PRKN carriers with other patients with EOPD demonstrated that carriers develop the disease at a younger age compared with non-carriers, require less levodopa treatment, and present with a similar frequency of brisk reflexes or dystonia to non-carriers after adjustment for age at onset. Therefore, presentation with dystonia was associated with younger age at onset rather than with PRKN mutation status.

Many of the phenotypic features of PRKN carriers may be explained by the early age at onset rather than by the genetic mutation status. Given the early age at onset of PRKN carriers, many ultimately require surgical intervention in the form of deep brain stimulation (DBS). Data suggest that mutation carriers benefit from DBS, but the clinical response is not superior to that of non-carriers.

The likelihood that EOPD patients will carry a PRKN mutation is higher in Hispanic people, but mutations have been described in multiple ethnicities. Many mutations have been identified in the PRKN gene, and include point mutation and CNV. There is an ongoing academic controversy as to whether PRKN mutations are a risk factor for ‘Parkinson’s disease’ or whether they are the cause of a similar disease that can be named ‘Parkin disease.’ Autopsies provide conflicting data. Only six carriers of two PRKN mutations—homozygotes or compound heterozygotes—have been described. Two had Lewy bodies and four did not. Furthermore, impaired olfaction, which is frequently seen in EOPD and idiopathic PD, is not present in most PRKN patients.

Another uncertainty with regard to PRKN mutations is the role of heterozygote mutations. While traditionally considered an autosomal recessive disease, even the earliest reports of PRKN mutations reported carriers of a single mutation. While a comprehensive study showed a similar frequency of heterozygous point mutations in PD cases and controls, positron-emission tomography (PET) studies show reduced fluorodopa uptake in nigrostriatal terminals in the caudate and posterior putamen of both symptomatic and asymptomatic PRKN heterozygotes compared with controls. This was similar to the reduction found in sporadic PD. Regardless of the risk conveyed by a single PRKN mutation, carriers of a single PRKN mutation often develop EOPD with a later age at onset than carriers of two mutations.

PARK3
The PARK3 locus was mapped to chromosome 2p13; however, the associated gene has not yet been identified and disease onset is described as late-onset PD.

PARK4—see PARK1

PARK5—Ubiquitin C-terminal Hydrolase L1
Mutations in ubiquitin C-terminal hydrolase L1 (UCHL1) were described in a German family. Of the two siblings described, one was 49 years of age and the other 51 years of age at disease onset. The disease course of both was indistinguishable from idiopathic PD.
**PARK6—PTEN-induced Kinase-1**

*PINK-1* was initially described in three consanguineous families from Italy in 2001.40,41 Like *PRKN*, carriers of two mutations, either homozygotes or compound heterozygotes, develop EOPD. *PINK-1*-related EOPD is very similar to *PRKN*-related EOPD: carriers often report positive family history and the disease course has been described as slowly progressive, with early onset of drug-induced dyskinesias.42,43 Like *PRKN* carriers, *PINK-1* carriers may benefit from DBS; however, in contrast to *PRKN*, *PINK-1*-related EOPD may be associated with psychiatric symptoms including affective and delusional disorders.44 Furthermore, *PINK-1*-related EOPD is associated with impaired olfaction45 and, in one report, with Lewy body pathology at autopsy.46

Mutation frequency has been estimated to be very low (ranging from 0 to 8%, including heterozygous carriers) in samples of EOPD cases from different ethnicities, including Caucasian,47-50 Indian,51 Taiwanese,52-54 Korean,55 and Japanese patients.56

As with *PRKN*, the role of heterozygous carrier status as a risk factor for EOPD is controversial.57-59 Most family studies support the hypothesis that even a single *PINK-1* mutation conveys a risk for PD,60-62 but a couple of studies reported conflicting evidence.63-64 Imaging and psychophysical studies support the hypothesis that *PINK-1* heterozygotes compensate for mild dopamine deficiency even when no motor signs of PD are apparent.65,66

**PARK7—DJ-1**

The association between *DJ-1* mutations and EOPD was discovered in 2003 in two European families: a Dutch family and an Italian family.67 Mutations in *DJ-1* are less common than *PRKN* or *PINK-1*,68 and are very rare in Asian patients with PD.69 When 89 American EOPD cases were genotyped for *DJ-1* mutations, a single heterozygote was identified.69

*DJ-1*-associated EOPD is described as being similar to *PRKN* and indistinguishable from idiopathic EOPD. One study reported normal olfaction in *DJ-1* carriers similar to *PRKN* carriers, but the number of mutation carriers was small.70

**PARK8—Leucine-rich Repeat Kinase 2**

The association between leucine-rich repeat kinase 2 (*LRRK2*) mutations and PD was discovered in 2004.71 In contrast to the other PARK genes, the frequency of *LRRK2* mutations is similar in EOPD and late-onset PD.72,73 The most frequently reported *LRRK2* mutation, G2019S (nt. 2877510G→A), is found in up to 1% of sporadic and 4% of familial PD cases worldwide.74 However, up to 39% of Northern African Arab75 and 18.3% of Ashkenazi Jewish76-78 individuals with PD carry the mutation. Additional mutations, including the i2020t in Japanese patients79 and the R1441C, Y1699C in Caucasians,72 have been described.

The presentation of *LRRK2*-related PD is heterogeneous,79-82 but it is usually associated with good response to treatment with levodopa and dopamine agonists, and may be complicated by dyskinesias.83 Thirty-four *LRRK2* G2019S carriers were compared with 891 non-carriers in a study of EOPD cases. Disease characteristics between the groups were similar, except that *LRRK2* carriers were less likely to suffer from tremor and were more likely to manifest the postural instability gait difficulty motor phenotype (PIGD).84 There were no other clinical differences between carriers and non-carriers, including other manifestations of PIGD (e.g. worse motor performance and cognitive impairment).85

Gan-Or and others also found that carriers of G2019S mutations were more likely to present with gait impairment compared with glucocerebrosidase (*GBA*) mutation carriers.86 Studies of *LRRK2* carriers (not restricted to EOPD cases) reported impaired olfaction.87 There were variable findings on pathology, but most cases demonstrated Lewy body pathology.72,88

In summary, while not restricted to early-onset illness, the *LRRK2* mutation is among the most common genetic mutation that can be identified in EOPD cases with and without a family history of PD.72

**PARK9—ATP13A2**

Mutations in *ATP13A2* were identified in 2006 in consanguineous Jordanian families with Kufor Rakeb syndrome.89 In contrast to the rest of the genetic forms of EOPD, carriers of *ATP13A2* have a distinct phenotype, different from non-carriers.

The Kufor Rakeb syndrome is associated with juvenile, atypical parkinsonism, usually rapidly progressive with only transient response to levodopa treatment.90 The syndrome is inherited in an autosomal recessive fashion and presents with dementia and spasticity in addition to parkinsonism. Magnetic resonance imaging (MRI) findings suggest iron accumulation; however, autopsy data are not available.91

**Glucocerebrosidase**

While *GBA* mutations are among the most frequently recognized genetic mutations in EOPD, a PARK assignment was never made for this gene. Case series have reported early-onset parkinsonism in Gaucher disease patients who, by definition, carry two *GBA* mutations.92 Even a single mutation in *GBA* may increase the risk for PD. Case-control studies have shown that carrying a single *GBA* mutation (heterozygous) is more common among PD patients than among healthy controls.93 As many as 8.3% of Ashkenazi Jews and up to 1% of non-Jews carry a mutation.94

Among PD patients, *GBA* mutations have been associated with earlier age at onset.95 One study suggested that carriers of severe *GBA* mutations (e.g. L444P) may have a higher risk for PD than carriers of milder mutations (e.g. N370S).96 Most studies assessing the *GBA* mutation carriers did not distinguish between EOPD and late-onset PD. In 699 EOPD cases, including 37 *GBA* carriers, mutation carriers were more likely to self-report cognitive impairment than non-carriers. However, no difference on cognitive screening with the Mini-Mental State Exam (MMSE) was noted.97

Two independent autopsy studies suggest that *GBA* carriers are more likely to have cortical Lewy bodies associated with dementia with Lewy bodies.98,99 Therefore, it is possible that EOPD *GBA* carriers are more likely to develop cognitive impairment.
Summary

In summary, EOPD is a complex disorder likely caused by an interaction between genetic and environmental factors. The overall genetic contribution to EOPD has received limited analysis. Mellick and others looked at 74 EOPD participants and found a mutation frequency of 7%.26 Macedo and others looked at 187 EOPD participants in The Netherlands and reported a mutation frequency of 4%.27 More recently, a study from 13 movement disorder centers in the US reported a mutation frequency of 16%. There are several reasons for the higher rate of mutation carriers in this latter study. They included genotyping of common GBA mutations, L44P and N370S, which were not analyzed in the other studies, and they used participants from diverse ethnicities including Ashkenazi Jews and Hispanic patients, in whom mutation frequency is higher (G2019S in Ashkenazi Jews and PRKN in Hispanics). While much has been discovered during the past decade, most risk factors for EOPD remain unknown.