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Genetics of Parkinson disease and essential tremor

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Abstract

Purpose of review—Elucidating the genetic background of Parkinson disease and essential tremor is crucial to understand the pathogenesis and improve diagnostic and therapeutic strategies.

Recent findings—A number of approaches have been applied including familial and association studies, and studies of gene expression profiles to identify genes involved in susceptibility to Parkinson disease. These studies have nominated a number of candidate Parkinson disease genes and novel loci including *Omi/HtrA2*, *GIGYF2*, *FGF20*, *PDXK*, *EIF4G1* and PARK16. A recent notable finding has been the confirmation for the role of heterozygous mutations in *glucocerebrosidase* (*GBA*) as risk factors for Parkinson disease. Finally, association studies have nominated genetic variation in the *leucine-rich repeat and Ig containing 1* gene (*LINGO1*) as a risk for both Parkinson disease and essential tremor, providing the first genetic evidence of a link between the two conditions.

Summary—Although undoubtedly genes remain to be identified, considerable progress has been achieved in the understanding of the genetic basis of Parkinson disease. This same effort is now required for essential tremor. The use of next-generation high-throughput sequencing and genotyping technologies will help pave the way for future insight leading to advances in diagnosis, prevention and cure.

Keywords

essential tremor; genetics; *LINGO1*; PARK16; Parkinson disease

Introduction

Parkinson disease and essential tremor are prevalent age-related conditions whose clinical manifestations worsen over time, eventually impacting on patients' quality of life [1,2]. Even though Parkinson disease and essential tremor are traditionally viewed as sporadic diseases, about 15% of patients with Parkinson disease report an affected first-degree relative, and up to 50% of cases with essential tremor display familial aggregation [3,4]. Individuals with Parkinson disease present with various combinations of motor (rest tremor, bradykinesia, rigidity and postural instability) and nonmotor (hyposmia, autonomic dysfunction, sleep disorders, cognitive impairment and depression) symptoms, whereas the main clinical feature in essential tremor consists of action (postural and kinetic) tremor.

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Motor symptoms respond to dopaminergic agents (Parkinson disease) and various pharmacologic treatments including beta-blockers (essential tremor), and are amenable to surgical treatment with deep-brain stimulation (Parkinson disease and essential tremor).

Despite therapeutic advances aimed at symptomatic control, no proven treatment currently exists that alters the course or prevents the occurrence of either Parkinson disease or essential tremor. Understanding the genetic basis of disease may provide us with the knowledge and tools to design future therapeutic strategies targeting the very molecular events leading to neuronal loss/dysfunction. The purpose of this review is to discuss recent advances in the genetics of Parkinson disease and essential tremor, as well as their significance for future research.

Causal mutations and risk-modifying variants in Parkinson disease

Since the discovery of the first disease-causing mutation in the *α-synuclein* gene (*SNCA*), a number of genes and loci have been implicated in Parkinson disease (Table 1). Those genes harboring mutations that cause late-onset dominantly inherited Parkinson disease include *SNCA* and *leucine-rich repeat kinase 2* (*LRRK2*), whereas early-onset recessive parkinsonism is associated with homozygous and compound heterozygous mutations in *parkin* (*PRKN*), *Pten-induced kinase 1* (*PINK1*) and *Oncogene DJ-1* (*DJ-1*) [5]. Of note, these genes were identified by family-based 'traditional' linkage studies, whereas large population-based genome-wide association studies (GWAS) have been largely confirmatory so far (see below).

Despite their importance in identifying key players in the pathogenesis of Parkinson disease, mutations in those genes associated with Mendelian-inherited disease remain relatively rare and account for only a fraction of familial cases. However, there are marked population-specific differences, for example the most common *LRRK2* mutation in populations of European descent (Lrrk2 p.G2019S) causes late-onset Parkinson disease that is clinically similar to idiopathic Parkinson disease [6•]. Prevalence rates of Lrrk2 p.G2019S in Parkinson disease range from 1–2% (sporadic patients) to 4–5% (familial patients) in populations of European descent, whereas figures rise to 30–40% among North African Arabs and Ashkenazi Jews, and the mutation is virtually absent in Asians [6•,7–10]. By contrast, two coding variants in Lrrk2 (p.G2385R and p.R1628P) have been shown to significantly alter risk for Parkinson disease, however, only in populations of Asian descent, further emphasizing differences due to ethnicity [11–17,18•]. Although over 100 variants have been identified in the *LRRK2* gene, pathogenicity had been established for only six causal mutations (p.R1441C, p.R1441G, p.R1441H, p.G2019S, p.I2020T and p.Y1699C) and two risk factors (p.G2385R and p.R1628P) [19]. Recently, however, a novel pathogenic coding mutation (p.N1437H) was identified to segregate with disease in a large Norwegian family with dominantly inherited, early-onset Parkinson disease [20•]. The Lrrk2 p.N1437H mutation was also identified in one other Norwegian patient with familial Parkinson disease and not in 623 controls. Additionally, in-vitro evidence showed the Lrrk2 p.N1437H mutation enhances GTP-binding and kinase activity, which further supports pathogenicity.

Perhaps one of the most surprising findings has been the discovery that heterozygous mutations in the *glucocerebrosidase* gene (*GBA*) significantly alter risk for sporadic and familial Parkinson disease as well as for diffuse Lewy body disease [21–24]. Homozygous or compound heterozygous mutations in *GBA* cause Gaucher's disease which does not share clinical or pathological features with Parkinson disease. A recent multicenter collaborative study that included 5691 patients with Parkinson disease and 4898 controls from Europe, the US, Israel and Asia found much higher rates of *GBA* mutations among patients with Parkinson disease (15% in Ashkenazi Jews, 3% in non-Ashkenazi Jews) compared with

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controls (Ashkenazi Jews: 3%; non-Ashkenazi Jews: <1%) [25••]. This study demonstrates that *GBA* mutations represent a rather strong [odds ratio (OR) ~10–15] risk factor for Parkinson disease particularly prevalent among Ashkenazi Jews, but also present in populations of European and Asian descent.

In addition to risk-modifying variants and mutations in *LRRK2* and *GBA*, the most robust and consistent associations with Parkinson disease have been with *SNCA* and *microtubule-associated protein tau* (*MAPT*) [26,27]. The fact that mutations in *LRRK2*, *SNCA* and *MAPT* also cause dominantly inherited forms of parkinsonism emphasizes the importance of studying monogenic forms in order to understand the pathogenesis of Parkinson disease. It also indicates that genetic factors determine both sporadic and familial forms of Parkinson disease, and that the degree of disease heritability depends on the combination and penetrance of such variants. One noteworthy study of *SNCA* multiplication patients in Japan demonstrated that reduced penetrance is also a feature of this form of parkinsonism and reminds us that age remains the greatest risk factor for late-onset neurodegenerative disorders such as Parkinson disease and essential tremor [28•].

Linkage, association and expression: different paths to the same goal

At the 18th WFN World Congress on Parkinson's Disease and Related Disorders held in Miami, FL (USA) in December 2009, a presentation by Dr Matthew J. Farrer of the Mayo Clinic announced the discovery of a mutation (p.R1205H) in *eukaryotic translation initiation factor 4G1* (*EIF4G1*) that segregates with disease in a large French family with autosomal dominant, late-onset Parkinson disease [29•]. The p.R1205H mutation was also found in three smaller families from Ireland, Italy and the US but not in 4000 control individuals. Whereas these findings clearly warrant replication, *EIF4G1* may represent yet a novel gene implicated in Parkinson disease. The eIF4G1 protein helps regulate translation of specific mRNAs in response to stress, growth factors and nutrient availability. Generally, depletion of eIF4G1 impairs nutrient sensing and mitochondrial bioenergetics while promoting autophagy, which would complement known mechanisms in Parkinson disease pathogenesis.

Recently, Elstner and colleagues [30•] reported an association between genetic variation in the *pyridoxal kinase* gene (*PDXK*) and risk for Parkinson disease. They used an innovative approach by examining the whole-genome expression profile in isolated cells from the substantia nigra in patients with Parkinson disease and controls, followed by an association study. However, a replication study in six independent patient–control series of European ancestry (n =3884) could not confirm an association with risk for Parkinson disease; therefore further studies are required to establish the role of *PDXK* in Parkinson disease [31].

An association between variation in the *fibroblast growth factor 20* gene (*FGF20*) and risk for Parkinson disease was reported in populations of European and Asian descent [32,33]. Furthermore, in-vitro evidence suggested that *FGF20* SNP rs12720208 modifies risk of Parkinson disease by disrupting a micro-RNA (miRNA-433) binding site, thereby altering levels of the FGF20 and α-synuclein proteins [32]. However, replication studies have failed to confirm the association as well as the effect on levels of α-synuclein [34–36]. Mutations in the *Omi/HtrA2* gene (PARK13) had previously been implicated in Parkinson disease [37,38]; however, a large replication study performed by the GEO-PD consortium on 6378 patients and 8880 controls failed to identify an association with risk for Parkinson disease [39], supporting earlier studies [40,41]. Mutations in the *GIGYF2* gene were suggested to account for linkage within the PARK11 locus [42]. A remarkable effort was put into trying to replicate and extend these findings, yet studies performed in several populations of European and Asian descent, including those patients in which the PARK11 locus was

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originally identified, have largely disproved this hypothesis and shown *GIGYF2* variants are unlikely to play a role in Parkinson disease susceptibility [43–46].

Genome-wide association studies in Parkinson disease

Genome-wide association studies have emerged as a powerful and unbiased analysis tool utilizing high-density single-nucleotide polymorphism (SNP) chips. However, early findings in Parkinson disease have fallen short of expectations with the identification of known Parkinson disease genes/loci, or the nomination of novel genes/loci subsequently not replicated [36,47,48]. Possible explanations for these results include heterogeneity of Parkinson disease, sample size issues, and the fact that only common variants are examined that have to be highly correlated (i.e. in high degree of linkage disequilibrium) with disease-associated variants in order to be identified.

Recently two large GWAS in Parkinson disease have been completed in populations of European and Asian descent [49••,50••]. Simon-Sanchez and colleagues [49••] examined a series of 1713 patients and 3978 controls of European ancestry in the GWAS phase (3452 patients and 4756 controls for subsequent replication) and found genome-wide significant associations with Parkinson disease for only two previously identified loci, *SNCA* and *MAPT*. The study by Satake and colleagues [50••] included 1078 patients and 2628 controls from Japan in the GWAS phase, and two independent sets for replication (combined: 937 patients and 15 753 controls). The combined analysis of all Japanese series identified four loci that associated with Parkinson disease at the genome-wide level, including *SNCA*; one novel locus on 1q32 (designated PARK16); a second novel locus on 4p15 that contains one gene (*BST1*); and one locus on 12q12 (upstream from *LRRK2*) [50••]. Replication attempts in the European series found nominal significance for disease association with PARK16, supporting it as being a potential risk factor for Parkinson disease in both Asian and European populations [49••]. In contrast, there was no association with the 4p15 locus in the European series. As expected no association with *MAPT* was observed in the Japanese series (the *MAPT* H2 allele is on the whole absent in Asian populations), further emphasizing population-specific differences in genetic factors implicated in Parkinson disease.

Linkage, genome-wide association studies and the genetic factors implicated in essential tremor

Despite its high prevalence and degree of inheritability, essential tremor has proven more challenging than Parkinson disease with regard to the identification of its genetic determinants. This may in part reflect methodological issues relating to the lack of a reliable diagnostic biomarker. Three loci (ETM1, ETM2 and ETM3) were nominated through genome-wide linkage studies in families with essential tremor. However, no mutation has been replicated in candidate genes within these loci, including *dopamine D3 receptor* (*DRD3*) and *HS1-binding protein 3* (*HS1BP3*) [51].

Last year, Stefansson and colleagues [52••] completed the first GWAS in essential tremor, using an Icelandic series of 452 patients and 14 378 controls (discovery phase). Two SNPs located in intron 3 of the *leucine-rich repeat and Ig domain containing 1* gene (*LINGO1*) displayed nominal association with risk for essential tremor. When combining the discovery and replication samples (752 patients and 15 797 controls from Iceland, Austria, Germany and the US) the authors found a genome-wide significant association between *LINGO1* SNP rs9652490 and risk for essential tremor. We and others confirmed this finding in populations of European and Asian descent, showing *LINGO1* is likely a risk factor for essential tremor with widespread distribution [53•,54]. Furthermore, an extended multicenter study investigating *LINGO1* and its paralog *LINGO2* by means of gene sequencing and an

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association study using haplotype-tagging SNPs distributed across both genes identified six novel coding variants in *LINGO1* and *LINGO2* that may be pathogenic, as well as polymorphisms nominally associated with risk for essential tremor [55]. These findings warrant further studies to establish the role of *LINGO1* and *LINGO2* in essential tremor, identify the variants/mutations responsible for the association and understand the pathogenic mechanisms involved.

Parkinson disease and essential tremor: is there a connection?

Whereas Parkinson disease and essential tremor are rightfully regarded as distinct entities, clinical evidence suggests there is considerable overlap, including a fourfold increase in risk of Parkinson disease in patients with essential tremor, the presence of action tremor often preceding the onset of Parkinson disease symptoms, and an increased prevalence of essential tremor in relatives of patients with Parkinson disease [56]. Additionally, brainstem Lewy bodies have been identified in a number of essential tremor cases, and imaging studies have found signs of dopaminergic deficiency in some patients with essential tremor [57].

Therefore we investigated the role of *LINGO1* in Parkinson disease by genotyping rs9652490 in 1044 patients with Parkinson disease of Caucasian ancestry (426 from North America and 618 from Norway) and in 1030 ethnically and sex-matched controls. An association between rs9652490 and risk for Parkinson disease was identified in the US and Norwegian populations as well as in the combined series [OR 1.8; 95% confidence interval (CI) 1.3–2.7] [53•]. Given the association of *LINGO1* with risk for essential tremor, this provides the first evidence of a genetic link between Parkinson disease and essential tremor and opens new avenues in the understanding of mechanisms implicated in both conditions. Our follow-up study extended this observation to other variants in *LINGO1* as well as in its paralog *LINGO2*, and identified additional polymorphisms nominally associated with risk for Parkinson disease and essential tremor [55]. Two subsequent studies investigated the role of *LINGO1* in Parkinson disease in populations from Austria and Poland [58,59]. Whereas both studies performed on relatively small samples did not confirm an association with risk of Parkinson disease, a meta-analysis supported a role for *LINGO1* in Parkinson disease [58]. Therefore these negative results may relate to power issues and further studies of larger populations are warranted to investigate the role of *LINGO1* in Parkinson disease.

The way ahead

Despite recent progress in unraveling the genetic factors that determine risk for Parkinson disease and essential tremor, mutations and variation in known genes account for only a fraction of the genetic risk and more genes remain likely to be identified. Apart from the recently nominated loci (PARK16 and 4p15) which await confirmation, GWAS have fallen short of identifying novel genes and loci in Parkinson disease. It has been suggested that complex traits such as Parkinson disease and essential tremor may be influenced by the combined effect of rare variants rather than by a few common variants [60–62]. Therefore approaches that detect rare variants may be needed, which include high-throughput next-generation sequencing of all exons within genome (exome sequencing) or the whole genome itself. Sequencing technology for this is readily available and rapid reduction of costs will soon allow performing studies on a large scale, which will likely help expand our knowledge of the genetic background of Parkinson disease and essential tremor.

Conclusion

Over a decade after the discovery that mutations in *SNCA* cause Parkinson disease, tremendous progress has been achieved that has shed light on molecular mechanisms

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implicated in Parkinson disease and less so for essential tremor. However, more effort needs to be put into collecting large samples of familial and sporadic patients from different ethnicities, in order to further understand disease pathogenesis. With the use of novel technologies we will likely see more genes being identified that will pave the way for future targeted therapeutics aimed at disease prevention and cure.

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Table 1

Genes implicated in monogenic forms of Parkinson disease and parkinsonism-plus syndromes

Gene	Locus/disease	Mode of inheritance	Phenotype	Onset age (years)
SNCA	PARK1/4	AD	PD, PDD, DLB	20–85
PRKN	PARK2	AR	EOPD	16–72 (mean 30)
PINK1	PARK6	AR	EOPD	20–40
DJ1	PARK7	AR	EOPD	20–40
LRRK2	PARK8	AD	PD	32–79
ATP13A2	PARK9/KRS	AR	P, D, O, S	11–16
NR4A2/NURR1	–	Unknown	PD	45–67
POLG	–	Unknown	PD	20–26
FBXO2	PARK15/PPS	AR	P, S	10–19
GRN	FTDP-17	AD	FTD, FTD-MND, P, CBS	45–83
MAPT	FTDP-17	AD	FTD, P, O, CBS	25–76
DCTN1	Perry syndrome	AD	P, Dep, H, WL	35–61

AD, autosomal dominant; AR, autosomal recessive; CBS, cortico-basal syndrome; D, dementia; Dep, depression; DLB, dementia with Lewy bodies; EOPD, early-onset Parkinson disease; FTD, frontotemporal dementia; FTD-MND, frontotemporal dementia – motor neuron disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; H, hypoventilation; KRS, Kufor-Rakeb syndrome; O, oculomotor signs; P, parkinsonism; PD, Parkinson disease (dopa-responsive parkinsonism); PDD, Parkinson disease – dementia; PPS, pallido-pyramidal syndrome; S, spasticity; WL, weight loss.