Parkinson disease is the second most common neurodegenerative disorder after Alzheimer disease. The average age at onset is between 60 and 80 years, and ~1% of the general population older than 65 is affected.12,89 Although PD appears to be sporadic in most cases, linkage and positional cloning studies were instrumental in the identification of certain genes that cause familial forms of the disease that feature autosomal dominant or autosomal recessive inheritance. These genes include alpha-synuclein, parkin, PINK1, DJ-1, LRRK2, and ATP13A2. The monogenic variants are important tools in identifying cellular pathways that shed light on the pathogenesis of this disease. Certain common genetic variants are also likely to modulate the risk of PD. International collaborative studies and meta-analyses have identified common variants as genetic susceptibility risk/protective factors for sporadic PD. (DOI: 10.3171/2009.10.FOCUS09220)

**Key Words**
- Parkinson disease
- genetic association study
- polymorphism
- gene mutation

**Abbreviations used in this paper:**
- DBS = deep brain stimulation
- PD = Parkinson disease
- SNP = single nucleotide polymorphism
flect on dopaminergic neurons.\textsuperscript{18} Alpha-synuclein monomers interact under certain circumstances to form protofibrils or fibrillar \( \beta \)-pleated sheets.\textsuperscript{84,86,89} Toxicity caused by protofibrils may involve the leakage of dopamine from synaptic vesicles because of perforation of the vesicular membranes by these protofibrils.\textsuperscript{29} This may account for the selective toxicity of alpha-synuclein in the dopamine-producing neurons of the substantia nigra.\textsuperscript{13,56,84}

Parkin (PRKN, PARK2) was the first gene identified for an autosomal recessive form of PD.\textsuperscript{1,5,35,40,83} Parkin protein localizes, although not predominantly, to the synapse and associates with membranes. Its main function is as an ubiquitin ligase in the cellular ubiquitination protein degradation pathway. Severe and selective degeneration in the substantia nigra pars compacta but without Lewy bodies has been described, suggesting that the disease may differ in some important ways from typical idiopathic PD.\textsuperscript{35,68,83,91} Parkin mutations turned out to be a very common cause of parkinsonism.\textsuperscript{13,56,84} Par

The third locus for autosomal recessive juvenile parkinsonism was mapped also to chromosome 1p36, and the gene was identified as the oncogene DJ-1 (PARK7).\textsuperscript{6} The function of the DJ-1 protein is not entirely clear. The main hypothesis is that it acts as a sensor for oxidative stress, providing neuroprotection in situations of increased demand.\textsuperscript{7,93} Parkinson disease causing DJ-1 mutations is rare and accounts for only ~1–2% of early-onset autosomal recessive PD cases. The phenotype closely resembles that found in patients with parkin and PINK1 mutations.\textsuperscript{6} The associated pathological characteristics are still unknown, because no autopsies have been reported.

Mutations in LRRK2 (PARK8) have been found in a large number of patients with PD.\textsuperscript{63,94} More than 40 different variants, almost all missense mutations, have been reported.\textsuperscript{3,37} The G2019S mutation in particular was detected in 5–6% of autosomal dominant familial PD cases and in 1–2% of sporadic cases.\textsuperscript{28,46,62,80} Specific populations such as Ashkenazi Jews and North African Arabs

<table>
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<tr>
<th>Locus</th>
<th>Gene</th>
<th>Inheritance &amp; Comments</th>
<th>OMIM No.</th>
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<td>SNCA</td>
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<td>PINK1</td>
<td>AR; 2nd most common cause of recessive juvenile PD</td>
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<td>DJ-1</td>
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<td>LRRK2</td>
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<td>FBXO7</td>
<td>AR; PD plus dementia &amp; spasticity</td>
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* AD = autosomal dominant; AR = autosomal recessive; OMIM = Online Mendelian Inheritance in Man; ? = controversial or unidentified.
Genetic basis of Parkinson disease

were found to have an even higher prevalence. The LRRK2 is a large protein with multiple protein interactions and catalytic domains that have possible roles in intracellular signaling pathways. Some pathogenetic mutations seem to be associated with an increase of kinase activity, which appears to be necessary for neurotoxicity in vitro. Although LRRK2 was not found to interact with either alpha-synuclein or tau, the identification of Lewy body or neurofibrillary tangle pathological features in patients with LRRK2 mutations suggested a possible common role of LRRK2 in the processing of those two proteins. The phenotype of LRRK2 mutation carriers is that of idiopathic PD, although the whole clinical picture is more benign.

Other Genes and Loci

The ATP13A2 gene is mapped at the PARK9 locus and is responsible for Kufor-Rakeb disease, a recessive, juvenile-onset, atypical Parkinsonism with pyramidal degeneration and cognitive dysfunction. The ATP13A2 gene encodes a large lysosomal P-type adenosine triphosphatase, which is involved in the lysosomal degradation pathway that clears SNCA aggregates. Lysosomal dysfunction caused by mutations in this gene might contribute to the pathogenesis of parkinsonism.

A heterozygous missense mutation in the ubiquitin carboxy-terminal hydrolase L1 gene (UCHL1, PARK5), which is located on chromosome 4p, has been identified in a single affected family of German ancestry. However, whether UCHL1 is really a PD gene is not clear yet.

Mutations in the glucocerebrosidase gene (GBA) (which has not been assigned a PARK locus yet) are the cause of a recessive lysosomal storage disorder—Gaucher disease. More than 200 mutations have been described in GBA. Phenotypes of Gaucher disease and PD do not overlap significantly, but the first indication for a relationship between the two actually came from clinical descriptions. Mutations in GBA have a conspicuously high prevalence in patients with PD. Between 2 and 4% of Caucasian patients with PD have been found to have mutations in GBA. Those variants are likely to act as risk factors rather than as high-penetration disease genes. The nature of the association between PD and Gaucher disease remains elusive. However, the pathogenetic mechanisms leading to PD in carriers of mutant GBA may be related to the faulty processing of toxic proteins, aggravated by the relative decrease in GBA activity and accumulation of glucocerebrosidase. Moreover, recent findings indicate that Gaucher disease and PD share pathophysiological features.

Other mendelian forms of PD remain to be identified. Either the causal genes at several loci have not yet been identified (PARK12), or the role of the candidate genes at these loci is still controversial (PARK3, PARK10, PARK13). Two novel genes, the FBX07 (PARK15), a member of the F-box family of proteins active in the ubiquitin-proteasome protein degradation pathway, and the PLA2G6 gene (PARK14) on chromosome 22, have also been identified in families with atypical PD.

Neurosurgical Treatment in Familial PD

The identification of inherited forms of PD has also helped in developing a more appropriate application of neurosurgical treatments of the disease. Deep brain stimulation provides symptomatic benefits to patients with idiopathic PD in terms of both motor activity and quality of life. In hereditary PD, DBS is an efficacious symptomatic treatment for patients with parkinsonism and mutation of the parkin and PINK1 genes. Patients with parkin mutations are specifically expected to be very good candidates for DBS and to benefit more and longer than other patients because of their younger age at onset, lower daily doses of levodopa, and slower disease progression. The response to DBS among patients carrying mutations of the LRRK2 gene is not well established. There are some studies that show that the response to DBS was worse among patients with the R1441G mutation in LRRK2 compared with patients with idiopathic PD.

Based on the aforementioned findings, we conclude that the effectiveness of DBS in different genetic forms of PD has not been studied adequately. The main reason for this is that patient selection is based predominantly on clinical criteria. A multidisciplinary approach involving a neurosurgeon, a neurologist, and a neuropsychologist is important to determine the appropriate surgical candidate. The best prognostic indicator of a patient’s suitability for DBS surgery is his/her response to levodopa. The patient’s age also is another major factor determining how an individual will cope with the surgical procedure and behave postoperatively. Based on these criteria, many patients with genetic forms of the disease who have a sustained response to levodopa or atypical symptoms are excluded from this procedure. As a result, it is impossible, based solely on clinical characteristics of monogenic PD forms, to study the effectiveness of DBS in these patients. Another reason for this is that most patients who have undergone DBS surgery are not screened for mutations in various genes responsible for monogenic forms of the disease.

The detailed evaluation of these patients and the genetic analysis based on criteria such as the family history, phenotype, age at onset, and response to levodopa are of great importance. However, larger series of patients with mutations and longer follow-ups will be needed for evidence of specific genotype-related differences.

Another matter worth discussing is that there are also no studies showing the optimal DBS target based on genetics. Generally the literature demonstrates a trend that the subthalamic nucleus may be more efficient in managing the symptoms of PD, based on institutional experience, surgical and programming management, lower current requirements, and significant reduction in dopaminergic medication. For these reasons, all of the previous studies in patients with mutations have referred to the effectiveness of DBS of the subthalamic nucleus. Maybe the genetic forms of the disease with the different neuropathological characteristics will enable deciphering of the mechanisms of DBS on the basis of the function and pathophysiological characteristics of the
Genetic Susceptibility Factors in Sporadic PD

Monogenic forms represent < 10% of cases of PD. Common PD, on the other hand, is thought to result from complex interactions involving genetic and environmental risk factors. The discovery that 1-methyl-4-phenyl tetrahydropyridine, a contaminant of a synthetic opiate, can cause parkinsonism through its neurotoxic metabolite, 1-methyl-4-phenylpyridinium, stimulated interest in environmental chemical exposures as risk factors for PD.\textsuperscript{44} Many studies have investigated the association between PD and pesticide use, and some, but not all, have found an association.\textsuperscript{22,70,95} Use of well water, rural living, and agricultural employment have also been implicated as risk factors, although studies have given conflicting results.\textsuperscript{45,55}

On the other hand, the extent of the genetic component remains elusive. Common genetic variations (mainly SNPs) may be either susceptibility factors or disease modifiers, affecting penetrance, age at onset, severity, or disease progression.

Genetic association studies that compare the frequency of putative risk alleles in cohorts of patients and controls are controversial because they have failed to reproduce the initial positive findings most of the time. Almost 800 genetic association studies have been performed so far on more than 500 genes regarding PD (see www.pdgene.org). The vast majority of genetic association studies have focused on candidate genes involved in detoxification of metabolites, dopamine metabolism, mitochondrial function, and familial PD.\textsuperscript{78} Some of these findings were exciting at the beginning because the encoded proteins of these genes appear to be closely linked to the pathophysiological mechanisms of PD; however, none of these candidate gene variants have been consistently replicated since then. Thus, theoretically attractive, broad-based meta-analyses yielded no true common genetic risk variant. Potential biases include population stratification, small sample size, misclassification, and inappropriate statistical methods.\textsuperscript{46}

Nevertheless, specific polymorphic variants have been validated as genetic susceptibility factors. The Rep 1, a mixed nucleotide repeat in the promoter region of SNCA, has been confirmed as a risk factor.\textsuperscript{11,34,35,55,60,64} A polymorphism in microtubule-associated protein tau has also been detected.\textsuperscript{26} The combination of risk genotypes in SNCA and microtubule-associated protein tau doubles the risk of PD.\textsuperscript{27,31} Two variants in the LRRK2 gene, G2385R and R1628P, confer susceptibility to PD in Asian populations.\textsuperscript{19,21,24,80} An S18Y variant of the UCHL1 gene has been demonstrated to be protective against PD in some association studies and meta-analyses.\textsuperscript{5,79} The number of polymorphisms that have been studied until now is very large, but so far these are some of the main risk alleles for sporadic PD that seems to be robustly reproducible.

With the completion of the human “HapMap” project and the availability of the SNP databases, there is increasing interest in using the whole-genome association approach to unravel genetic susceptibility factors. Genome-wide association studies of PD, which use haplotype tagging strategies to study variation across the entire human genome, provided little evidence until now about genetic variants that influence the risk for disease. A 2-stage genome-wide association study with a 200-SNP map, and a 1-stage study with more informative markers found no positive associations.\textsuperscript{16,54} The most strongly associated SNPs identified in the 2-stage study were not replicated in a subsequent association study with a large number of participants.\textsuperscript{16,54} However, the combination of genome-wide databases with meta-analytical techniques can improve the detection of genetic variants with small effect sizes. The GAK-DGKQ region on chromosome 4 has been identified by this strategy, albeit not replicated in a recent report.\textsuperscript{19,20} The genomic pathway approach that combines SNPs with axon guidance pathway genes has also been applied to genome-wide association studies, with one positive result,\textsuperscript{48} but again without replication.\textsuperscript{48}

Genome-wide association studies require large sample series and international collaborations, so probably we will have to wait for a few years to identify possible common genetic risk variants and clearly understand their role in the disease.\textsuperscript{20,25,36,47,54}

Conclusions

It is hoped that an understanding of the genetic basis of PD will allow us to identify upstream key facts of the pathogenesis and lead to new targeted therapeutic strategies in the future. Large-scale multicenter collaborations, public availability of the International HapMap Project, and genome-wide association PD databases will hopefully arm researchers with information that could be used for modifying the natural course of the disease.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: E Dardiotis. Analysis and interpretation of data: E Dardiotis, V Tsimourtou, PM Koutra, KN Paterakis, EZ Kapsalaki. Study supervision: KN Fountas, G Xiromerisiou, GM Hadjigeorgiou.

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