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REVIEW

IMAGING THE IMPACT OF GENES ON PARKINSON'S DISEASE

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Abstract—Although Parkinson's disease (PD) has traditionally been considered to be a non-genetic disorder, recent progress in the neurogenetics of PD provided converging evidence that genetic factors play a relevant role in the etiology of PD. The strongest case for a genetic contribution to PD was made by the discovery of mutations in single genes that can cause autosomal dominant (α-synuclein (SNCA)) and leucine rich repeat kinase 2 (LRRK2) gene) or recessive (Parkin, PTEN-induced putative kinase 1 (PINK1), DJ-1, and ATP13A2 gene) forms of PD. Here, we review how structural and functional neuroimaging of individuals carrying a mutation in one of the PD genes has offered a unique avenue of research into the pathogenesis of PD. In symptomatic mutation carriers (i.e. those with overt disease), brain mapping can help to link the molecular pathogenesis of PD more directly with functional and structural changes in the intact human brain. In addition, neuroimaging of presymptomatic (i.e. non-manifesting) mutation carriers has emerged as a valuable tool to identify mechanisms of adaptive motor reorganization at the preclinical stage that may prevent or delay clinical manifestation. In addition to mutations causing monogenic forms of PD, common polymorphisms in genes that influence mono-aminergic signaling or synaptic plasticity may have modifying effects on distinct aspects of PD. We also discuss how functional and structural neuroimaging can be used to better characterize these genotype-phenotype correlations.

Key words: magnetic resonance imaging, Parkin, PINK1, parkinsonism, positron emission tomography, single photon emission computed tomography.

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Parkinson's disease (PD) is the second most common neurodegenerative disorder (de Lau and Breteler, 2006). The traditional view dictates that affected patients present with a variable combination of motor symptoms, including bradykinesia, rigidity, resting tremor and—in later stages of the disease—also with postural instability. However, it is becoming increasingly clear that these "traditional" motor impairments represent just the tip of the iceberg, and that these are typically accompanied (or indeed, even preceded) by a variety of nonmotor symptoms, including hyposmia, cognitive decline, mood disorders, pain, autonomic dysfunction and sleep disorders (Langston, 2006). In this review, we will focus on the pathophysiology of the motor impairments in PD, and how these are linked to the underlying genetic abnormalities that can be found in subgroups of patients with parkinsonism. We have limited ourselves to the motor manifestations of PD as they represent the best "accessible" outcome measures in imaging and genetic studies.

The motor impairments in PD result mainly from progressive neuronal loss of dopaminergic neurons in the substantia nigra pars compacta and can improve markedly with dopaminergic drugs (Gibb, 1991; Gibb and Lees, 1991; Damier et al., 1999). Interestingly, the motor system has a substantial potential to cope with the slowly progres-

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Abbreviations: AADC, aromatic 1-amino-acid decarboxylase; ADC, apparent diffusion coefficient; BOLD, blood oxygen level dependent; COMT, catechol-*O*-methyltransferase; DAT, dopamine transporter; DTI, diffusion tensor imaging; ERPs, event-related cortical potentials; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; LRRK2, leucine rich repeat kinase 2; met, methionine; MRI, magnetic resonance imaging; PD, Parkinson's disease; PET, positron emission tomography; PINK1, PTEN-induced putative kinase 1; PMd, dorsal premotor cortex; SMA, supplementary motor area; SNCA, α-synuclein; SPECT, single photon emission computed tomography; TRAP1, tumour necrosis factor receptor-associated protein 1; val, valine; VBM, voxel-based morphometry; VMAT2, vesicular monoamine transporter type 2; [^{18}F]F-DOPA, 6-[^{18}F]fluoroL-3,4-dihydroxyphenylalanine.

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sive degeneration of the nigrostriatal dopaminergic projections. Clinical symptoms only emerge when around 70%–80% of nigrostriatal nerve terminals have undergone degeneration (Bernheimer et al., 1973). The logical implication is that for most patients, the neurodegenerative process has likely started well in advance of the first overt clinical motor symptoms, although the length of this presymptomatic period remains unknown. Indeed, postmortem histological examinations have identified individuals who show Lewy neurites and Lewy bodies (the histological hallmarks of PD) in various brainstem areas but who had never developed parkinsonism during their lifetime (Braak et al., 2003, 2004).

It has been a widely held notion that PD is mainly caused by environmental factors, with genetic factors playing only a very minor role in the pathogenesis. This "environmental" theory was supported in particular by the identification of "selective" nigrostriatal neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which can cause parkinsonian symptoms with a remarkable resemblance to idiopathic PD in rodents, primates and even in humans (Langston et al., 1983; Bloem and Roos, 1995). However, the ideas about the etiology of PD have changed considerably in the last decades. Advances in neurogenetics have provided strong evidence that what clinicians perceive as "idiopathic PD" can in fact be genetically determined. There are converging sources of supporting evidence (Martin et al., 1973; Tanner et al., 1999; Warner and Schapira, 2003), but the case is certainly strongest for monogenic forms of familial PD that are caused by mutations in specific genes (Gasser, 2007; Klein and Schlossmacher, 2007).

Although monogenic forms account for only a small fraction of PD patients (perhaps around 3% to 5% of all cases), they have considerably stimulated the field of PD research. For example, the cellular pathways that are affected by monogenic variants of PD have provided important clues regarding the molecular pathogenesis in typical sporadic PD (Gasser, 2007). In this review, we will focus on another important research area that greatly benefited from the advances in PD genetics, namely the field of neuroimaging. Specifically, we evaluate the structural and functional brain mapping studies that have been performed in individuals carrying a mutation in a specific PD gene, and discuss how this "neurogenetics-neuroimaging approach" provides unique means to tap into important pathophysiological aspects of PD.

Monogenic forms of PD

The genes and chromosomal loci linked to familial forms of PD have been designated as PARK1–13. These loci include six autosomal dominant (PARK1 (=4), 3, 5, 8, 11 and 13), four recessive (PARK2, 6, 7, and 9), one X-linked (PARK12), and one form with an as yet unknown mode of transmission (PARK10) (Table 1). Mutations in the leucine rich repeat kinase 2 (LRRK2), Parkin and PTEN-induced putative kinase 1 (PINK1) genes are the clinically most relevant types because they are relatively frequent and their clinical phenotype shows substantial overlap with that of sporadic (non-familial) PD. A detailed description of the genetics of PD is beyond the scope of this paper and has been covered in several recent reviews (Shadrina and Slominskii, 2006; Gasser, 2007; Klein and Lohmann-Hedrich, 2007; Klein et al., 2007; Klein and Schlossmacher, 2007; Tan and Skipper, 2007; Belin and Westerlund, 2008). Here we will rather focus on a short description of well-established forms of genetic PD for which neuroimaging data have become available, i.e. PARK1(=4), PARK2, PARK6, PARK7 and PARK8 (Table 1). In the following sections, these monogenic forms of parkinsonism will be grouped according to their mode of inheritance. This is in agreement with functional findings that suggest a gain-of-function mechanism for dominant and a loss-of-function mechanism for recessive forms. However, things appear to be more complex as penetrance (percentage of mutation carriers that actually develop the disease) is remarkably reduced in dominant forms. Conversely, a putative role of single heterozygous mutations as a suscepti-

Table 1. Synopsis of well-established forms of genetic PD

Acronym	Mode of inheritance	Locus	Gene/protein	Main clinical features	OMIM #
PARK1/PARK4	Autosomal dominant	4q21-q23	*SNCA (alpha-Synuclein)*	Early-onset parkinsonism (~40 years), dementia, reduced life span	168601
PARK8	Autosomal dominant	12q12	*LRRK2 (Leucine-rich repeat kinase 2)*	Classical parkinsonism	607060
PARK2	Autosomal recessive	6q25.2-q27	Parkin	Early onset (~30–40 years), rarely juvenile, slow disease progression, exquisite response to L-DOPA	600116
PARK6	Autosomal recessive	1p35-p36	*PINK1 PTEN-induced putative kinase 1*	Early onset (~30–40 years), rarely juvenile, slow disease progression, exquisite response to L-DOPA, frequently psychiatric features	605909
PARK7	Autosomal recessive	1p36	*DJ-1*	Early onset (~30–40 years), rarely juvenile	606324

OMIM=Online Mendelian Inheritance in Man.