Genetics of Parkinson’s disease: LRRK2 on the rise

Our view of the pathogenic mechanisms of Parkinson’s disease has greatly changed over the past decade with the identification of several genes implicated in Mendelian forms of this disorder (Corti et al., 2005; Gasser et al., 2005). Parkin, DJ-1 and PINK1 are responsible for autosomal recessive forms, usually with early onset, that are not associated with Lewy bodies. α-Synuclein was considered to be the major gene responsible for autosomal dominant forms until late 2004, when the LRRK2 gene was identified (Paisan-Ruiz et al., 2004; Zimprich et al., 2004a). Despite their rarity, the discovery of α-synuclein mutations or multiplications led to the demonstration that α-synuclein is the major component of Lewy bodies, and clearly illustrated the gene dosage effect resulting from gene multiplications; duplications of the α-synuclein gene are responsible for a late-onset typical Parkinson’s disease (Chartier-Harlin et al., 2004; Ibanez et al., 2004), whereas triplications result in an early-onset and rapidly progressive dementia with Lewy bodies (Singleton et al., 2003), indicating the importance of the number of functional copies of this gene. It now turns out that LRRK2 is much more frequent and also has interesting features.

The LRRK2 gene encodes a putative protein kinase named dardarin from dardara, the Basque term for tremor. From previous reports of LRRK2 families, it is known that the phenotype is mostly that of typical late-onset dopa-responsive Parkinson’s disease, but with some intrafamilial variability (Funayama et al., 2002; Nicholl et al., 2002; Zimprich et al., 2004b). The most striking variability concerns the neuropathological features. Although the dopaminergic neurons of the substantia nigra degenerate in all patients in association with gliosis, other pathological markers vary, even within the same family (Wszołek et al., 2004). Several patients have the pathological hallmark of Parkinson’s disease: α-synuclein-positive Lewy bodies in the brainstem which may extend to the cerebral cortex as in diffuse Lewy body disease. Others have tau pathology as in progressive supranuclear palsy, and still others may have neither α-synuclein nor tau deposits, but nigral degeneration without any distinctive histopathological features. Finally β-amyloid deposits or anterior horn cell loss with axonal spheroids have been found in several cases. These observations show that the same disease can have multiple pathological expressions, challenging the accepted neuropathological criteria for Parkinson’s disease. Another recent finding is the frequency of the G2019S LRRK2 mutation, which accounts for 3–41% of familial Parkinson’s disease (Di Fonzo et al., 2005; Kachergis et al., 2005; Lesage et al., 2005a; Mata et al., 2005; Nichols et al., 2005; Zabetian et al., 2005). A north–south gradient of distribution is suspected because the frequency of this mutation is low in Northern Europe, increasing in Southern Europe and exploding in North Africa. The G2019S mutation is also found, although at a lower rate (1–2%), in apparently sporadic cases from Europe (Bras et al., 2005; Farrer et al., 2005; Gilks et al., 2005; Hernandez et al., 2005; Zabetian et al., 2005) but not from Asia (Tan et al., 2005). Interestingly, this mutation is associated with the same haplotype in different populations, indicating the existence of a common founder which probably lived in the 13th century (Kachergis et al., 2005; Lesage et al., 2005b).

In this issue of Brain, three papers extend our knowledge of several features of LRRK2 gene mutations (Adams et al., 2005; Berg et al., 2005; Khan et al., 2005). The first provides information on brain metabolism with TEP studies in affected and unaffected members of two families with LRRK2 mutations (Adams et al., 2005). The other two report clinical and genetic findings in new LRRK2 positive families (Berg et al., 2005; Khan et al., 2005). In their series of 51 families with Parkinson’s disease, mostly from Germany, Berg et al. (2005) identified 7 families with LRRK2 mutations, 4 of which had novel missense mutations, but the common G2019S mutation was not found. In contrast, Khan et al. (2005) found 6 out of 118 families with LRRK2 mutations: 2 with novel missense mutations and 3 with the G2019S mutation. There are now 16 identified LRRK2 mutations. Interestingly, all but one of these mutations are missense and all but 2 are located in functional domains of the protein (Fig. 1). In accordance with previous series of families mostly from Europe, LRRK2 accounted for 5–10% of familial cases (Zimprich et al., 2004a; Mata et al., 2005). Age at onset varied within families, as already observed for the G2019S mutation, where it ranges from 28 to 86 years. Furthermore, penetrance is age-dependent and might also be reduced. In a family with the Q930R mutation, an obligate carrier died at the age of 90 years with no sign of parkinsonism (Berg et al., 2005), similar to a healthy octogenarian recently described with the G2019S mutation (Kay et al., 2005). This growing list of examples shows that being identified as a carrier does not imply that there is a 100% risk of developing the disorder. In the future, an estimate of the penetrance of the different mutations will be crucial for appropriate genetic counselling, particularly in at-risk individuals who want presymptomatic testing. In contrast, an affected member of an LRRK2 family may not always have the mutation.
already reported for the G2019S mutation (Lesage et al., 2005; Nichols et al., 2005), affected relatives of LRRK2 carriers may represent phenocopies (phenotype of the disease but absence of the mutation) (Berg et al., 2005; Hernandez et al., 2005; Khan et al., 2005). This also has implications for genetic counselling and testing. Accordingly, in LRRK2 families, offspring of patients cannot be considered at-risk with certainty until their affected parent has been genetically confirmed. Conversely, analysing a single patient may not be sufficient to exclude LRRK2 mutations in a family.

These two studies also help to refine the LRRK2 phenotype (Berg et al., 2005; Khan et al., 2005). In spite of its name, dardarin, tremor might be absent in authentic LRRK2 cases. Additional features such as orthostatic hypotension, dementia and hallucinations are not frequent. One might find, however, mild signs of executive dysfunction. In addition, despite the observation of Lewy bodies in the olfactory bulb of an LRRK2 case, olfactory dysfunction seems to be less frequent than in idiopathic Parkinson’s disease. Finally, as in idiopathic Parkinson’s disease, sleep disturbances and behavioural disorders are frequent.

If LRRK2-associated Parkinson’s disease is clinically indistinguishable from idiopathic Parkinson’s disease, have TEP studies detected differences? Following the study of Hernandez et al. (2005), both Adams et al. (2005) and Khan et al. (2005) have analysed 18F-dopa uptake in LRRK2 patients. It turns out that patients have the typical pattern seen in idiopathic Parkinson’s disease: significant reduction of 18F-dopa uptake in the striatum compared with controls, asymmetry and a rostrocaudal gradient of severity with the putamen more severely affected than the caudate. These findings are consistent with the common neuropathological finding of nigral degeneration. One of the studies also documented a reduction in the binding of both 11C-d-threomethylphenidate (11C-MP) and 11C-(-/+)α-dihydrotetabenazine (11C-DTBZ), which label the membrane dopamine transporter (DAT) and the vesicular dopamine transporter (VMAT2), respectively (Adams et al., 2005). However, the most exciting observations were made in asymptomatic LRRK2 carriers. Although none of them had decreased striatal 18F-dopa uptake, two out of six, both over 55 years of age, showed decreased 11C-MP binding and one showed decreased 11C-DTBZ binding. Moreover, 4 years after normal scans, two still asymptomatic carriers had significantly reduced 11C-MP binding and one had decreased 11C-DTBZ binding. 18F-dopa uptake was in the normal range in both. Decreased 11C-DTBZ binding in asymptomatic carriers suggests early nerve terminal loss. In contrast, the normal 18F-dopa PET indicates that dopa uptake, decarboxylation and storage as dopamine are maintained and these prevent the symptoms. The differential involvement of the three presynaptic markers reflects compensatory changes that maintain adequate dopaminergic transmission. These observations indicate that further TEP studies in clinically normal carriers may provide a unique opportunity to approach the presymptomatic phase of the disorder in order to analyse the compensatory mechanisms that retard or prevent symptoms and to evaluate the rate at which presynaptic dysfunction progresses.

It already is evident that LRRK2 represents an important fraction of Parkinson’s disease. These and ongoing genetic studies will help better to evaluate its relative frequency according to the geographical origin and its associated transmission parameters (e.g. penetrance). They will also generate a precise inventory of the associated clinical and neuropathological phenotypes. However, the major challenge now is to elucidate the normal and pathological functions of...
this putative protein kinase that may target α-synuclein and tau.

Alexis Brice1,2,3,4
1INSERM U679 (former U289),
2Département de Génétique, Cytogénétique et Embryologie,
3Fédération de Neurologie and
4Faculté de Médecine Pierre et Marie Curie,
Groupe hospitalier Pitié-Salpêtrière, AP-HP,
47 boulevard de l’Hôpital,
75013, Paris, France
E-mail: brice@ccr.jussieu.fr

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