Unlocking the genetics of paroxysmal kinesigenic dyskinesia

Paroxysmal kinesigenic dyskinesia (PKD, or paroxysmal kinesigenic choreoathetosis) is a rare and remarkable hereditary disorder that was recognized as early as 1892 and defined more precisely during the 20th century (Mount and Reback, 1940; Kertesz, 1967; Richards and Barnett, 1968; Lance, 1977; Kato et al., 2006). Patients with PKD experience recurrent and brief episodes of dystonic or choreoathetotic involuntary movements that are induced by sudden motion, such as standing up quickly or being startled (Bruno et al., 2004; Bhatia, 2011). Although this disorder can be very disabling if undiagnosed, its outcome is usually benign when treated with low doses of anti-convulsants such as carbamazepine or phenytoin. Most patients with primary idiopathic forms of PKD report a family history of the disease compatible with autosomal dominant inheritance. The first locus for PKD, identified in 1999 on chromosome 16p11.2-q12.1 (EKD1, Fig. 1) overlaps with another locus identified for infantile convulsions and paroxysmal choreoathetosis (ICCA) (Szepetowski et al., 1997; Tomita et al., 1999). ICCA is also inherited in an autosomal dominant fashion and is characterized by benign afebrile infantile convulsions that start within the first year of life and usually stop by 3 years of age, variably associated with paroxysmal dyskinesia (Table 1). Benign familial infantile convulsions, ICCA and PKD have thus been proposed to be different expressions of the same disorder or allelic disorders (Caraballo et al., 2001). Linkage of families with PKD, ICCA and benign familial infantile convulsions to the same region on chromosome 16 has been confirmed by many groups, but despite the sequencing of the 157 genes contained in the region, the causative one has remained a mystery for more than a decade (Kikuchi et al., 2007).

The recent development of next-generation sequencing (massive parallel sequencing) has revolutionized genetic analyses by drastically reducing the cost of DNA sequencing compared with the classical Sanger method and allowing fast and efficient sequencing of complete genomes. Combined with specific DNA sequence capture, next-generation sequencing in particular permits all coding variations present in an individual to be determined, a process known as exome sequencing. This method has rapidly become the tool for identifying genes underlying Mendelian diseases, especially when candidate gene approaches have failed (Bamshad et al., 2011). Exome sequencing usually detects >20,000 variants (single nucleotide substitutions and indels) in every individual, 95% of which are present in databases and, for the most part, constitute known polymorphisms. The identification of the causative mutation among the thousands of novel variants still remains a challenge. The combination of exome sequencing with other genetic approaches, such as linkage study, considerably decreases the number of variants potentially implicated and facilitates the quest for the causative gene.

In this issue of Brain, a strategy combining classical genome-wide linkage study and exome sequencing has been used by Wang and collaborators (2011) to identify the first gene involved in PKD. The authors determined all the coding variants present in the candidate region on chromosome 16 in three affected members from two Chinese Han families with PKD (Wang et al., 2011). Two different mutations at the heterozygous state were identified in a single common gene, PRRT2 (proline-rich transmembrane protein 2). Both mutations (c.487C>T/p.Glu163X and c.649dupC/p.Arg217ProfsX8) led to premature termination codons, predicting either a truncating protein or degradation of the mutated messenger RNA by nonsense-mediated decay. The analysis of three additional unrelated Chinese families by Sanger sequencing detected the c.649dupC mutation in two families and the c.796C>T/p.Arg266Trp missense mutation in the remaining one, confirming that PRRT2 was the gene responsible for PKD. This finding now allows genetic confirmation of the clinical diagnosis as well as genetic testing and adapted genetic counselling to family members.

PRRT2 was responsible for PKD in all of the five Chinese families studied by Wang and colleagues (2011) indicating that this is a major gene accounting for this disorder, at least in China. However, several lines of evidence indicate that genes other than PRRT2 could also cause PKD: a second locus on chromosome 16q12.1-16q21 (EKD2) has been identified in an Indian family and the existence of at least a third locus has been suggested by the exclusion of both loci in a British family (Fig. 1; Valente et al., 2000; Spacey et al., 2002).

Most patients with a PRRT2 mutation exhibit the clinical criteria established for pure forms of PKD (Bruno et al., 2004). However,
four patients from two unrelated families also presented with afebrile infantile convulsions, therefore extending their phenotype to the definition of ICCA. These results suggest that PRRT2 could also be the gene involved in ICCA families, although this remains to be demonstrated. Additionally, benign familial infantile convulsions without PKD were also linked to the same locus as ICCA on chromosome 16p12-q12 (BFIC2 locus) (Caraballo et al., 2001). It is, therefore, tempting to hypothesize that mutations in PRRT2 cause multiple clinical phenotypes including pure forms of PKD, pure forms of benign familial infantile convulsions or the variable association of both (ICCA). Interestingly, ICCA presents striking clinical similarities with rolandic epilepsy with paroxysmal exercise-induced dystonia and writer’s cramp, an autosomal recessive disorder also associating dystonia and seizures, and their loci overlap on chromosome 16 (Guerrini et al., 1999). However, PRRT2 is outside the rolandic epilepsy with paroxysmal exercise-induced dystonia and writer’s cramp locus; if PRRT2 mutations are also found in ICCA, rolandic epilepsy with paroxysmal exercise-induced dystonia and writer’s cramp and ICCA will be caused by mutations in different genes.

Two of the three PRRT2 mutations found in patients with PKD introduce premature termination codons that are situated 455 nt before the last exon–exon junction on the spliced messenger RNA. The expected effect of these mutations is therefore the degradation of the mutated messenger RNA by the nonsense-mediated messenger RNA decay surveillance system of the cells (Cartegni et al., 2002) and PRRT2 haploinsufficiency. Yet, the pericentromeric region on chromosome 16 is prone to deletions and...
L-DOPA-responsive parkinsonism (Lipton and Rivkin, 2009), PKD abnormalities are found in of highly homologous segmental duplications (Fig. 1). Both duplications that are recurrent and reciprocal due to the presence of highly homologous segmental duplications (Fig. 1). Both abnormalities are found in ~1% of patients with variable phenotypes including autistic spectrum disorder, schizophrenia, developmental delay, mental retardation, epilepsy, obesity and multiple congenital abnormalities (Kumar et al., 2008; Weiss et al., 2008; Shinawi et al., 2010; Walters et al., 2010). These micro-rearrangements span ~600 Mb, contain 25–30 genes, including PRRT2, and can occur de novo or be inherited from an affected or asymptomatic parent. Surprisingly, with the exception of a single patient diagnosed with PKD and L-DOPA-responsive parkinsonism (Lipton and Rivkin, 2009), PKD is not reported in the patients carrying the 16p11.2 deletion. This suggests that PKD has been overlooked in patients with complex phenotypes, that the molecular mechanism involved in PKD could be more complex than simply PRRT2 haploinsufficiency, or that the deletion of nearby genes could have an epistatic effect or compensate for the PKD phenotype.

PKD shares many features with epilepsy, including paroxysmal, brief and stereotyped manifestations, wide expression variability and an excellent response to anticonvulsants. In addition, infantile convulsions and epilepsy can be symptomatic of PKD or ICCA. Motor manifestations of paroxysmal dyskinesia are sometimes difficult to differentiate clinically from epilepsy although, in PKD, EEGs are typically normal and a subcortical origin related to basal ganglia is probable, based on neurophysiological and imaging studies. It has been proposed that PKD and epilepsy could therefore share common physiological mechanisms and genetic factors, and that PKD, as with most genetic epilepsies (Mulley et al., 2003) and other paroxysmal disorders such as episodic ataxia and familial migraine, could be an ion channel disorder or channelopathy (Guerini, 2001). PRRT2 encodes a transmembrane protein of unknown function and very few data exist to decipher its potential role. The sole clue comes from the human two-hybrid interaction initiative, which revealed a potential interaction between the PRRT2 protein and SNAP25, a constituent of SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complexes (Stelzl et al., 2005), which regulates synaptic vesicle membrane docking and fusion, a key process in neuronal exocytosis and neurotransmitter release. Both PRRT2 and SNAP25 are expressed in the basal ganglia, making this interaction potentially very relevant to PKD. However, further studies are necessary to assess the biological and cellular processes in which PRRT2 is involved and to unravel the mechanisms by which mutations in this gene leads to PKD.

### Table 1 Clinical characteristics and inheritance of PKD and other familial neurological disorders linked to chromosome 16p12.1-q12

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Primary clinical features</th>
<th>Inheritance</th>
<th>References</th>
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<tr>
<td>PKD (or paroxysmal kinesigenic choreoathetosis)</td>
<td>Attacks of dystonic, choreic, athetotic or ballic involuntary movements of short duration (&lt;1 min), precipitated by sudden voluntary movements and responsive to anti-epileptic drugs, occurring without loss of consciousness or pain; age at onset between 1 and 20 years; exclusion of other organic diseases.</td>
<td>Autosomal dominant (~70%); sporadic (~30%)</td>
<td>Bruno et al. (2004)</td>
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<tr>
<td>ICCA</td>
<td>Benign infantile convulsions starting from 4 months and usually stopping before the age of 3 years variably associated later on with paroxysmal dystonic movements triggered by anxiety, sudden movements or exercise (age at onset between 5 and 20 years)</td>
<td>Autosomal dominant</td>
<td>Szepetowski et al. (1997)</td>
</tr>
<tr>
<td>Benign familial infantile convulsions</td>
<td>Afebrile convulsions starting between 3 and 12 months of age, responsive to anti-convulsants with a favourable outcome.</td>
<td>Autosomal dominant</td>
<td>Vigevano et al. (1992); Caraballo et al. (2001)</td>
</tr>
<tr>
<td>Syndrome of rolandic epilepsy with paroxysmal exercise-induced dystonia and writer’s cramp</td>
<td>Rolandic epilepsy and paroxysmal exercise-induced dystonia culminating in childhood and stable writer’s cramp</td>
<td>Autosomal recessive</td>
<td>Guerrini et al. (1999)</td>
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