Nature Reviews Neurology **8**, 657 (2012); published online 20 November 2012; doi:10.1038/nrneurol.2012.240

GENETICS

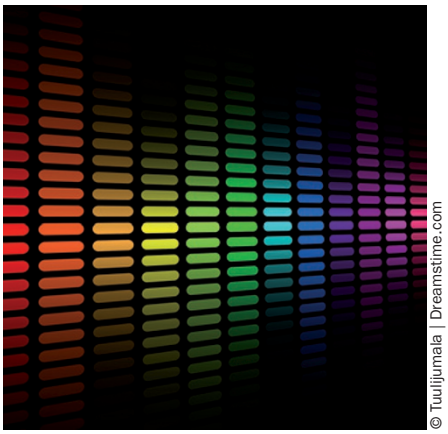
Expanding the spectrum of neurological disorders associated with *PRRT2* mutations

Mutations in the proline-rich transmembrane protein 2 (*PRRT2*) gene have been implicated in a number of childhood-onset paroxysmal disorders, including paroxysmal kinesigenic dyskinesia (PKD), infantile convulsions with PKD (PKD/IC; formerly known as infantile convulsions and choreoathetosis), and benign familial infantile epilepsy (BFIE). Five papers recently published in *Neurology* further expand the phenotypic spectrum of *PRRT2* mutations, to encompass conditions such as hemiplegic migraine, episodic ataxia and febrile seizures.

PRRT2 is a transmembrane protein that is capable of binding to synaptosomal-associated protein 25 (SNAP25). The function of PRRT2 is poorly understood, although its interaction with SNAP25 suggests a role in synaptic vesicle docking and exocytosis. Most of the pathological mutations in the *PRRT2* gene that have been discovered to date cause truncation of the protein, leading to loss of function.

Hemiplegic migraine is a variant of migraine with aura, in which the attacks are accompanied by temporary weakness down one side of the body. This disorder has previously been linked to dominantly inherited mutations in three different genes—*ATP1A2*, *CACNA1A* and *SCN1A*—but these genes do not account for all cases. The paroxysmal nature of hemiplegic migraine prompted several groups to investigate a possible role for *PRRT2* mutations in the aetiology of this condition.

In one of the new studies, Florence Riant and colleagues sequenced the coding region of *PRRT2* in 101 patients with hemiplegic migraine, none of whom had mutations in the three genes typically associated with this condition. Four of the patients were found to have mutations in *PRRT2*: two had the c.649dupC mutation, which is frequently observed in patients with PKD, and two had a novel mutation known as c.649delC. "Our study emphasizes the role of non-ion channel genes in the pathogenesis of genetically determined hemiplegic migraine," the authors conclude.



© Tuuljumala | Dreamstime.com

Further support for a role for *PRRT2* mutations in hemiplegic migraine was provided by a second study, which also linked mutations in this gene to episodic ataxia. Alice Gardiner and co-workers detected *PRRT2* mutations in one sporadic case each of hemiplegic migraine and episodic ataxia alone. The researchers also found that mutations in this gene occurred at a high frequency in families who exhibited hemiplegic migraine in association with PKD.

In a third study, Robin Cloarec and co-workers sequenced the coding exons of *PRRT2* in 18 families with PKD/IC, some of whom also had migraine. In addition to providing further confirmation for a link between *PRRT2* mutations and hemiplegic migraine, the findings extended the phenotypic spectrum to other types of migraine. According to the paper, the data "argue in favour of a nonspurious association of typical migraine in the context of familial PKD/IC with *PRRT2* mutations; indeed, the proportion of migraineurs among *PRRT2* mutation carriers was significantly increased as compared with the overall migraine prevalence."

The results of two further studies indicate that *PRRT2* mutations could underlie a broader range of seizure subtypes than was previously suspected. Carla Marini and colleagues confirmed the previously described role of *PRRT2* mutations in BFIE, and also provided evidence of associations with febrile seizures and childhood absence seizures, as well as further confirming the link with migraine. Ingrid Scheffer and colleagues identified eight individuals with *PRRT2* mutations who exhibited febrile seizures or febrile seizures plus (a condition in which the seizures continue beyond 6 years of age, or occur in conjunction with afebrile seizures).

Taken together, these new findings suggest that *PRRT2* mutations could account for a wide range of different paroxysmal disorders. However, the underlying mechanisms remain to be elucidated. As Scheffer *et al.* point out in their paper, "it is difficult to hypothesize how the same mutation in this gene can cause both epilepsy and a movement disorder either in the same individual or family, or in separate families." Possible topics for future research include the effects of *PRRT2* mutations on the interaction between PRRT2 and SNAP25, and the consequences for neurotransmitter release and ion channel activity.

Heather Wood

Original articles Marini, C. *et al. PRRT2* mutations in familial infantile seizures, paroxysmal dyskinesia, and hemiplegic migraine. *Neurology* doi:10.1212/WNL.0b013e3182752ca2 | Gardiner, A. R. *et al. PRRT2* gene mutations: from paroxysmal dyskinesias to episodic ataxia and hemiplegic migraine. *Neurology* doi:10.1212/WNL.0b013e3182752c5a | Cloarec, R. *et al. PRRT2* links infantile convulsions and paroxysmal dyskinesia with migraine. *Neurology* doi:10.1212/WNL.0b013e3182752c46 | Scheffer, I. E. *et al. PRRT2* phenotypic spectrum includes sporadic and fever-related infantile seizures. *Neurology* doi:10.1212/WNL.0b013e3182752c6c | Riant, F. *et al. PRRT2* mutations cause hemiplegic migraine. *Neurology* doi:10.1212/WNL.0b013e3182752cb8