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Review

PRRT2: from Paroxysmal Disorders to Regulation of Synaptic Function

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In the past few years, proline-rich transmembrane protein (PRRT)2 has been identified as the causative gene for several paroxysmal neurological disorders. Recently, an important role of PRRT2 in synapse development and function has emerged. Knock down of the protein strongly impairs the formation of synaptic contacts and neurotransmitter release. At the nerve terminal, PRRT2 endows synaptic vesicle exocytosis with Ca^{2+} sensitivity by interacting with proteins of the fusion complex and with the Ca^{2+} sensors synaptotagmins (Syts). In the postsynaptic compartment, PRRT2 interacts with glutamate receptors. The study of PRRT2 and of its mutations may help in refining our knowledge of the process of synaptic transmission and elucidating the pathogenetic mechanisms leading to derangement of network function in paroxysmal disorders.

Neurogenetic Research Puts PRRT2 under the Spotlight

In the past 5 years a deluge of scientific articles has been published concerning the *PRRT2* gene. Knowledge about the role of *PRRT2* (also referred to as LOC112476) [1], was very limited until 2011 (Figure 1). Interest about this gene suddenly increased when next-generation sequencing, combined with classic linkage analysis, allowed the identification of an array of *PRRT2* mutations as the leading cause of the most common type of familial paroxysmal movement disorder, **paroxysmal kinesigenic dyskinesia** (**PKD**) (see Glossary) (Figure 2; [2,3]).

PKD was first described in 1892 in a young Japanese patient presenting with short attacks of purposeless involuntary movements triggered by rapid voluntary motion, with no loss of consciousness. The disease was initially misdiagnosed as a form of reflex epilepsy, and later shown to occur in families with an autosomal dominant pattern of inheritance, exhibiting few sporadic cases (for review, see [4]).

The causative role of *PRRT2* mutations in the pathogenesis of PKD and of a variety of additional paroxysmal disorders with a similar pattern of inheritance is now documented by extensive studies and summarized by recent comprehensive reviews [5–7]. Until recently, however, knowledge concerning the molecular mechanisms by which *PRRT2* mutations cause the disease and manifest with different phenotypes remained scarce. In a spate of recent studies, this topic has been thoroughly investigated by several laboratories [8–13]. The emerging picture leads us to hypothesize that the PRRT2 protein is an important component of the neurotransmitter release machinery, involved in brain development and synapse formation.

Trends

Mutations in *PRRT2* are the main cause of paroxysmal kinesigenic dyskinesia, benign infantile familial seizures and infantile seizures with choreoathetosis.

Mutations in the gene are responsible also for a minor fraction of cases of other neurological disorders, such as hemiplegic migraine and episodic ataxia, which share the feature of being paroxysmal disorders.

PRRT2 is a neuronal protein localized at synaptic contacts.

During development, PRRT2 plays a role in neuronal migration, spinogenesis, and synapse formation and maintenance.

PRRT2 is required for synchronous neurotransmitter release.

PRRT2 is a key component of the Ca^{2+}-sensing machinery of synchronous release.

PRRT2 endows the SNARE complex with Ca^{2+}-sensitivity through its interaction with the fast Ca^{2+} sensors Syts 1 and 2.

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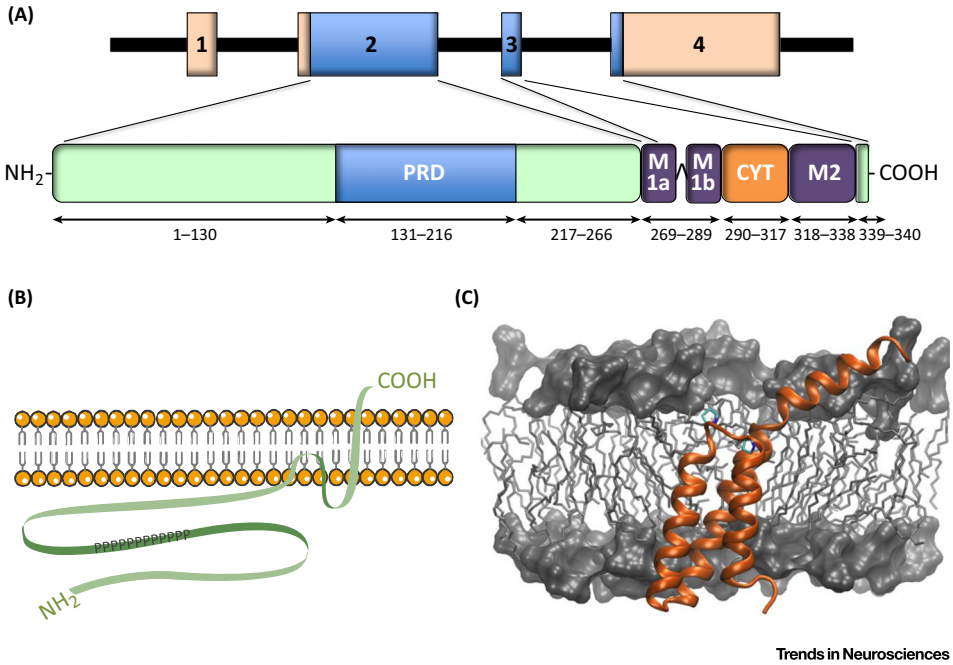

Figure 1. Gene and Protein Structure and Membrane Topology of Proline-Rich Transmembrane Protein (PRRT2). (A) The PRRT2 gene contains four exons, with exons 2–4 encoding a multidomain protein of 340 amino acids formed by a long N-terminal domain (1–268) containing a proline-rich region (PRD); two putative transmembrane helices, M1 (269–289) and M2 (318–338), separated by an intracellular loop (CYT, 290–317), and a C-terminal dipeptide (339–340). Despite the similarity with the proteins of the dispanin family, only M2 is a true transmembrane helix, while M1 is folded into two halves (M1a and M1b) by a hinge formed by two proline residues. As a consequence, M1 does not cross the membrane. (B) Membrane topology of PRRT2. Due to its single transmembrane domain, PRRT2 exposes the long N-terminal domain and the short M1–M2 loop to the cytoplasm and maintains a C-terminal anchor, conforming the model of a type II transmembrane protein. (C) Snapshot of the membrane system model, with the PRRT2 region encompassing the M1 and M2 helices (residues 261–340) predicted by molecular dynamics simulations. While M2 is a true transmembrane domain, all-atom structural models of the N-terminal M1 helix identified the best-scoring model in a helix–loop–helix motif (M1a/M1b) in which the hinge occurs in the proximity of two proline residues ($Pro^{279,282}$). The protein backbone (excluding the N-terminal region) is shown as schematic, with the two proline residues represented in green. Modified from [10].

PRRT2-Related Diseases: A Spectrum of Diverse Neurological Disorders

It has now become clear that, in addition to patients with PKD, heterozygous PRRT2 mutations are also found in the majority of patients with **benign familial infantile seizures** (**BFISs**) and **infantile convulsions with choreoathetosis** (**ICCA**, also known as **infantile convulsions with PKD**, **PKD/IC**). Indeed, these three disorders had long been hypothesized to be allelic disorders. This hypothesis had been raised because of the common linkage of the diseases to the pericentromeric region of chromosome 16, some shared clinical features, and the comorbidity within the same family or even within the same individual, occasionally at different ages. *PRRT2* mutations have also been described in a minor fraction of patients affected by other paroxysmal disorders, such as childhood epilepsies, **paroxysmal hypnogenic dyskinesia** (**PHD**), paroxysmal torticollis, migraine, **hemiplegic migraine** (**HM**) and **episodic ataxia** (**EA**) (e.g., [6,14–21]). Interestingly, all *PRRT2*-associated disorders appear paroxysmal in nature, suggesting the presence of shared pathophysiological mechanisms. In contrast, other common nonparoxysmal movement disorders, such as Parkinson's disease, are not associated with *PRRT2* mutations [22].

In spite of the numerous missense, nonsense and frameshift mutations described so far (Figure 2), no specific genotype–phenotype correlations have emerged. A common c.649dupC frameshift mutation segregates in about 80% of the *PRRT2* mutant families, resulting in diverse