

What is proline-rich transmembrane protein 2 (PRRT2)?

PRRT2 is a gene that encodes the proline-rich transmembrane protein 2, which is highly expressed in the central nervous system. While its function is not fully understood, it is believed to play a major role in the regulation of signaling between neurons at the level of synapses (the site of transmission of the electric activity between neurons). DNA variants in the PRRT2 gene may be associated with seizures, movement disorders, hemiplegic migraines, and other neurological symptoms. Variants in the PRRT2 gene may be inherited from a symptomatic or asymptomatic parent or occur for the first time in an individual (*de novo*). The mode of inheritance is autosomal dominant, although there have been rare cases in which individuals were found to have two variants in the PRRT2 gene, which has been associated with more severe neurological symptoms including developmental delay and intellectual disability.

Other names for proline-rich transmembrane protein 2 (PRRT2) include: PRRT2 gene or PRRT2 associated neurological syndromes.

It may be associated with one -or a combination- of the following neurological conditions:

- [Self-limited \(Familial\) Infantile Epilepsy \(SeLIE\)](#)
- Paroxysmal Kinesigenic Dyskinesia (PKD)
- Hemiplegic migraines
- Episodic ataxia

What are seizure and non-seizure symptoms associated with variants in PRRT2?

Variants in the PRRT2 gene may be associated with several neurological symptoms including seizures, movement disorders, and migraines. Individuals may have one or a combination of two or more syndromes or manifestations. Some individuals are carriers and never develop any clinical signs or symptoms, and the clinical presentation may not be predicted based on the type of variant in the PRRT2 gene.

The syndromes and symptoms associated with PRRT2 variants variably affect individuals and include:

Self-limited (Familial) Infantile Epilepsy [SeLIE]

This syndrome is characterized by seizure onset in the first year of life, most commonly at 4-6 months of age, with focal seizures commonly occurring in [clusters \(several seizures per day\)](#), and frequently associated with a [trigger such as illness](#), fever, or vaccination. Seizures tend to resolve by the age of 2 years.

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Contact your local Epilepsy Foundation: epilepsy.com/local

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Paroxysmal Kinesigenic Dyskinesia (PKD)

This movement disorder is characterized by sudden attacks of involuntary movements on one or both sides of the body, typically triggered by sudden voluntary movements or a startle. The age of onset is variable and ranges from 1 to 20 years, with most presenting by late childhood to mid-adolescence. While these attacks are brief (under 1 minute), they may frequently occur throughout the day.

Hemiplegic migraine

This is a type of migraine that occurs with an aura, characterized by motor weakness on one side of the body which may be accompanied by other auras including impairment in sensation, speech, or vision. The weakness typically starts in the hand and gradually involves the arm and the face. Either side may be affected during each attack. The symptoms may mimic a stroke. The symptoms typically last for a few hours and resolve completely. Headache might be present during the aura, although it might occur after resolution of the weakness, or not occur at all.

Episodic ataxia

These episodes consist of attacks of clumsiness and unsteadiness that may last for hours to days and then resolve completely.

How are PRRT2 variants diagnosed?

Clinical suspicion should be raised if any of the above clinical symptoms are encountered, especially with a positive family history. PRRT2 variants can only be identified by [genetic testing](#). Targeted testing of the PRRT2 gene specifically is the most direct method of testing an individual when there is a high degree of confidence that a variant in the PRRT2 gene is likely to be the underlying cause. Epilepsy gene panels, which involve testing of multiple epilepsy-associated genes, and exome sequencing (ES) will also detect PRRT2 variants.

Genetic counseling before genetic testing is an important step in making sure that the best testing strategy is selected, and that patients and families understand the risks, benefits, limitations, and outcomes of testing.

EEGs often do not show abnormalities unless it is recorded during a seizure. Occasionally, however, they might show “focal or multifocal spikes” (i.e., abnormal epileptic activity in one or different regions). The organization of the EEG, however, remains overall normal. Brain MRIs are typically normal.

How are PRRT2-related conditions treated?

Infantile seizures associated with PRRT2 variants often respond well to standard anti-seizure medications. Carbamazepine or oxcarbazepine may be more effective and/or better tolerated than phenobarbital or levetiracetam. Treatment is usually maintained until the patient is 2 years old if there has been complete remission. Treatment of seizure clusters is more complicated. Typically, benzodiazepines are used as a first line treatment, but some patients do not respond. A bolus of phenobarbital or levetiracetam may be considered, as well as fosphenytoin.

It is of clinical importance to differentiate the presentation of PRRT2-related infantile epilepsy (typically clusters of short seizures) from the presentation of [SCN1A-related infantile epilepsy](#) including [Dravet syndrome](#) (typically prolonged, continuous seizure or [status epilepticus](#)) as they may occur at similar ages and might have similar triggers. Oxcarbazepine or other sodium channel blockers should be avoided if Dravet Syndrome is suspected.

Paroxysmal dyskinesia typically responds to low doses of carbamazepine or oxcarbazepine. These may theoretically be used for hemiplegic migraine prevention although the existing evidence for this is limited.

How common are PRRT2-related conditions?

The prevalence of PRRT2-associated neurological conditions is not well understood, as there have been no large population studies, and the symptoms may be mild and might not prompt genetic testing. PRRT2-associated neurological conditions are rare.

What is the outlook for PRRT2-related conditions?

The prognosis is generally favorable. Seizures tend to resolve before the age of 2 years, generally with no subsequent increased risk for seizures later in life or recurrence of epilepsy. Some children with infantile seizures develop PKD later in childhood or early adulthood, but there are no clinical or molecular factors that predict who is at risk for this. Many individuals with PRRT2 variants will never have seizures and will only develop PKD. PKD may be a life-long condition but typically responds well to medications. In large cohort studies, there have been no reports of developmental delay or regression associated with heterozygous PRRT2 variants. Systematic analyses, however, remain limited so the possibility of mild cognitive or learning difficulties or behavioral problems may not be ruled out.



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