PRRT2 gene

proline rich transmembrane protein 2

Normal Function

The *PRRT2* gene provides instructions for making the proline-rich transmembrane protein 2 (PRRT2). This protein is found in nerve cells (neurons) in the brain, and it helps regulate signaling from neuron to neuron. Communication between neurons depends on chemicals called neurotransmitters. Neurotransmitters are contained in compartments (vesicles) inside the nerve cell and are released from one neuron and taken up by neighboring neurons. The release of neurotransmitters is controlled by many processes. The flow of charged atoms (ions) into the neuron through ion channels generates and transmits electrical signals that stimulate and coordinate neurotransmitter release. In addition, the vesicles carrying neurotransmitters join (fuse) with the cell membrane to release the chemicals into the junction between neurons (the synapse).

The PRRT2 protein interacts with several proteins inside neurons that take part in the process of neurotransmitter release. PRRT2 is thought to affect the function of several types of ion channels. In addition, the PRRT2 protein impedes the formation of a group of proteins called the SNARE complex that helps vesicles fuse with the cell membrane. Through these roles, the PRRT2 protein helps regulate signaling in the brain.

Health Conditions Related to Genetic Changes

Familial hemiplegic migraine

Variants (also known as mutations) in the *PRRT2* gene have been identified in people with familial hemiplegic migraine. This condition is characterized by migraine headaches with a pattern of neurological symptoms known as aura. In familial hemiplegic migraine, the aura includes temporary numbness or weakness on one side of the body (hemiparesis).

One *PRRT2* gene variant that is found in multiple people with familial hemiplegic migraine inserts an extra DNA building block (nucleotide) in the gene. (This change is written as 649dupC.) This change alters the blueprint used for making the protein and

leads to production of an abnormally short PRRT2 protein that is quickly broken down. As a result, affected individuals have a shortage of PRRT2 protein. Other variants likely reduce the amount or impair the function of the PRRT2 protein. Researchers speculate that a shortage of functioning PRRT2 affects the activity of ion channels and the SNARE complex, leading to abnormal signaling between neurons. It is thought that the changes in signaling in the brain lead to development of the severe headaches characteristic of the disorder.

Familial paroxysmal kinesigenic dyskinesia

Variants in the *PRRT2* gene have been found to cause another neurological disorder called familial paroxysmal kinesigenic dyskinesia. This condition is characterized by episodes of involuntary jerking or shaking of the body that are triggered by sudden motion, such as standing up quickly or being startled. The 649dupC variant (described above) is the most common genetic change in familial paroxysmal kinesigenic dyskinesia. Most *PRRT2* gene variants involved in this condition, including 649dupC, lead to an abnormally short protein that is quickly broken down. As a result, affected individuals have less PRRT2 protein than normal. Researchers speculate that a shortage of PRRT2 dysregulates neurotransmitter release by altering ion channel activity and SNARE complex formation. This abnormal neuronal activity is thought to underlie the movement problems characteristic of familial paroxysmal kinesigenic dyskinesia.

Other disorders

PRRT2 gene variants have been found to cause other neurological conditions, including benign familial infantile seizures (BFIS) and infantile convulsions and choreoathetosis (ICCA). BFIS is characterized by recurrent seizures that begin in infancy and usually disappear by age 2. ICCA is characterized by both benign infantile seizures like those that occur in BFIS and episodes of involuntary movements like those that occur in familial paroxysmal kinesigenic dyskinesia (described above). The 649dupC variant that causes both familial paroxysmal kinesigenic dyskinesia and familial hemiplegic migraine (described above) can also cause BFIS and ICCA. It is unclear how this variant can cause one condition in some people and a different condition in others.

Although they have been described as separate disorders, researchers speculate that paroxysmal kinesigenic dyskinesia, BFIS, ICCA, and familial hemiplegic migraine may represent a spectrum of related disorders. In some families with a *PRRT2* gene variant, affected individuals have different conditions; for example, one may have paroxysmal kinesigenic dyskinesia and another may have familial hemiplegic migraine. Rarely, *PRRT2* gene variants are associated with paroxysmal dyskinesia during sleep (called paroxysmal hypnogenic dyskinesia) or recurrent episodes of poor coordination and balance (which is known as episodic ataxia). Sometimes, an affected individual has the features of more than one of these related conditions. In addition, the same genetic change can be involved in all of these conditions. A combination of environmental and genetic factors may influence the pattern of signs and symptoms an affected individual develops.

Other Names for This Gene

- dispanin subfamily B member 3
- DKFZp547J199
- DSPB3
- EKD1
- FLJ25513
- IFITMD1
- interferon induced transmembrane protein domain containing 1
- PKC
- proline-rich transmembrane protein 2
- PRRT2_HUMAN

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PRRT2 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=112476[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28PRRT2%5BTIAB%5D%29+OR+%28proline-rich+transmembrane+protein+2%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- CONVULSIONS, FAMILIAL INFANTILE, WITH PAROXYSMAL CHOREOATHETOSIS; ICCA (https://omim.org/entry/602066)
- SEIZURES, BENIGN FAMILIAL INFANTILE, 2; BFIS2 (https://omim.org/entry/605751)
- PROLINE-RICH TRANSMEMBRANE PROTEIN 2; PRRT2 (https://omim.org/entry/614386)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/112476)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PRRT2[gene])

References

- Chen WJ, Lin Y, Xiong ZQ, Wei W, Ni W, Tan GH, Guo SL, He J, Chen YF, ZhangQJ, Li HF, Lin Y, Murong SX, Xu J, Wang N, Wu ZY. Exome sequencing identifiestruncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. NatGenet. 2011 Nov 20;43(12):1252-5. doi: 10.1038/ng.1008. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22101681)
- Coleman J, Jouannot O, Ramakrishnan SK, Zanetti MN, Wang J, Salpietro V, Houlden H, Rothman JE, Krishnakumar SS. PRRT2 Regulates Synaptic Fusion byDirectly Modulating SNARE Complex Assembly. Cell Rep. 2018 Jan 16;22(3):820-831.doi: 10.1016/j.celrep.2017.12.056. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/29346777)
- Dale RC, Gardiner A, Antony J, Houlden H. Familial PRRT2 mutation withheterogeneous paroxysmal disorders including paroxysmal torticollis andhemiplegic migraine. Dev Med Child Neurol. 2012 Oct;54(10):958-60. doi:10.1111/j.1469-8749.2012.04394.x. Epub 2012 Jul 31. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22845787)
- Ferrante D, Sterlini B, Prestigio C, Marte A, Corradi A, Onofri F, TortaroloG, Vicidomini G, Petretto A, Muia J, Thalhammer A, Valente P, Cingolani LA,Benfenati F, Baldelli P. PRRT2 modulates presynaptic Ca2+ influx byinteracting with P/Q-type channels. Cell Rep. 2021 Jun 15;35(11):109248. doi:10.1016/j.celrep.2021.109248. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/34133925)
- Fruscione F, Valente P, Sterlini B, Romei A, Baldassari S, Fadda M, PrestigioC, Giansante G, Sartorelli J, Rossi P, Rubio A, Gambardella A, Nieus T, BroccoliV, Fassio A, Baldelli P, Corradi A, Zara F, Benfenati F. PRRT2 controls neuronalexcitability by negatively modulating Na+ channel 1.2/1.6 activity. Brain. 2018Apr 1;141(4):1000-1016. doi: 10.1093/brain/awy051. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/29554219)
- Gardiner AR, Bhatia KP, Stamelou M, Dale RC, Kurian MA, Schneider SA, Wali GM, Counihan T, Schapira AH, Spacey SD, Valente EM, Silveira-Moriyama L, Teive HA, Raskin S, Sander JW, Lees A, Warner T, Kullmann DM, Wood NW, Hanna M, Houlden H.PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia andhemiplegic migraine. Neurology. 2012 Nov 20;79(21):2115-21. doi:10.1212/WNL.0b013e3182752c5a. Epub 2012 Oct 17. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23077024) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3511930/)
- Landolfi A, Barone P, Erro R. The Spectrum of PRRT2-AssociatedDisorders: Update on Clinical Features and Pathophysiology. Front Neurol. 2021Mar 4;12:629747. doi: 10.3389/fneur.2021.629747. eCollection 2021. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/33746883)
- Liu XR, Huang D, Wang J, Wang YF, Sun H, Tang B, Li W, Lai JX, He N, Wu M, SuT, Meng H, Shi YW, Li BM, Tang BS, Liao WP. Paroxysmal hypnogenic dyskinesia isassociated with mutations in the PRRT2 gene. Neurol Genet. 2016 Mar 22;2(2):e66.doi: 10.1212/NXG.0000000000000066. eCollection 2016 Apr. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/27123484)

- Meneret A, Gaudebout C, Riant F, Vidailhet M, Depienne C, Roze E. PRRT2mutations and paroxysmal disorders. Eur J Neurol. 2013 Jun;20(6):872-8. doi: 10.1111/ene.12104. Epub 2013 Feb 9. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23398397)
- Riant F, Roze E, Barbance C, Meneret A, Guyant-Marechal L, Lucas C, SabouraudP, Trebuchon A, Depienne C, Tournier-Lasserve E. PRRT2 mutations cause hemiplegicmigraine. Neurology. 2012 Nov 20;79(21):2122-4. doi:10.1212/WNL.0b013e3182752cb8. Epub 2012 Oct 17. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23077016)
- Schubert J, Paravidino R, Becker F, Berger A, Bebek N, Bianchi A, Brockmann K, Capovilla G, Dalla Bernardina B, Fukuyama Y, Hoffmann GF, Jurkat-Rott K, AnttonenAK, Kurlemann G, Lehesjoki AE, Lehmann-Horn F, Mastrangelo M, Mause U, Muller S,Neubauer B, Pust B, Rating D, Robbiano A, Ruf S, Schroeder C, Seidel A, SpecchioN, Stephani U, Striano P, Teichler J, Turkdogan D, Vigevano F, Viri M, Bauer P,Zara F, Lerche H, Weber YG. PRRT2 mutations are the major cause of benignfamilial infantile seizures. Hum Mutat. 2012 Oct;33(10):1439-43. doi:10.1002/humu.22126. Epub 2012 Jun 11. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22623405)

Genomic Location

The *PRRT2* gene is found on chromosome 16 (https://medlineplus.gov/genetics/chromosome/16/).

Last updated February 11, 2022