



PNKP gene

polynucleotide kinase 3'-phosphatase

Normal Function

The *PNKP* gene provides instructions for making the polynucleotide kinase-phosphatase (PNKP) enzyme. This enzyme is critical for repairing broken strands of DNA molecules. It can help fix damage that affects one DNA strand (single-strand breaks) or both strands (double-strand breaks). At the site of the damage, the PNKP enzyme modifies the broken ends of the DNA strands so that they can be joined back together.

Health Conditions Related to Genetic Changes

Ataxia with oculomotor apraxia

At least nine *PNKP* gene mutations have been found to cause ataxia with oculomotor apraxia type 4. This condition is characterized by poor coordination and balance (ataxia) and problems with side-to-side movement of the eyes (oculomotor apraxia). These problems are due to the breakdown (degeneration) of nerve cells in the part of the brain that coordinates movement (the cerebellum).

PNKP gene mutations that cause ataxia with oculomotor apraxia type 4 lead to production of an unstable enzyme that is quickly broken down in the cell. Shortage of the PNKP enzyme prevents efficient repair of damaged DNA. Researchers suggest that the repair of single-strand breaks is particularly impaired in ataxia with oculomotor apraxia type 4. It is thought that single-strand DNA damage increases after birth as the brain grows. Without repair, the accumulating damage leads to a loss of nerve cell in the brain, resulting in the movement problems characteristic of ataxia with oculomotor apraxia type 4.

Microcephaly, seizures, and developmental delay

At least six mutations in the *PNKP* gene have been found to cause microcephaly, seizures, and developmental delay (MCSZ). This condition is characterized by problems with brain development before birth that result in an unusually small head size (microcephaly), recurrent seizures (epilepsy), and delayed development of speech and motor skills. Rarely, affected individuals also have difficulty coordinating movements (ataxia) due to degeneration of nerve cells in the cerebellum.

PNKP gene mutations that cause MCSZ lead to production of an unstable enzyme that is quickly broken down in the cell. Shortage of the PNKP enzyme prevents efficient repair of damaged DNA. Researchers suggest that, in contrast to ataxia with oculomotor apraxia type 4 (described above), the repair of double-strand breaks

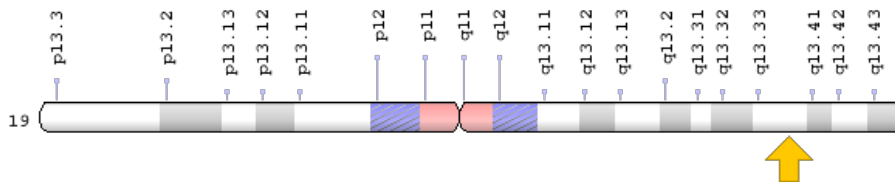
is particularly impaired in MCSZ. The accumulating damage is especially harmful to nerve cells. It is thought that excessive DNA damage before birth leads to the death of nerve cell precursors, impairing normal brain development and causing microcephaly and the other neurological features of MCSZ.

It is unclear why mutations in the same gene, even the same mutation in some cases, can have different effects on single-strand or double-strand DNA damage repair and cause either ataxia with oculomotor apraxia type 4 or MCSZ.

Chromosomal Location

Cytogenetic Location: 19q13.33, which is the long (q) arm of chromosome 19 at position 13.33

Molecular Location: base pairs 49,861,204 to 49,867,576 on chromosome 19 (Homo sapiens Updated Annotation Release 109.20190607, GRCh38.p13) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- AOA4
- bifunctional polynucleotide phosphatase/kinase
- DNA 5'-kinase/3'-phosphatase
- EIEE10
- Homo sapiens polynucleotide kinase 3'-phosphatase (PNKP)
- MCSZ
- PNK

Additional Information & Resources

Educational Resources

- The Cell: A Molecular Approach (second edition, 2000): DNA Repair
<https://www.ncbi.nlm.nih.gov/books/NBK9900/>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28PNKP%5BTIAB%5D%29+OR+%28polynucleotide+kinase+3'-phosphatase%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

- POLYNUCLEOTIDE KINASE 3-PRIME PHOSPHATASE
<http://omim.org/entry/605610>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Genes/GC_PNKP.html
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=PNKP%5Bgene%5D>
- HGNC Gene Symbol Report
https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:9154
- Monarch Initiative
<https://monarchinitiative.org/gene/NCBIGene:11284>
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/11284>
- UniProt
<https://www.uniprot.org/uniprot/Q96T60>

Sources for This Summary

- Aceytuno RD, Piett CG, Havali-Shahriari Z, Edwards RA, Rey M, Ye R, Javed F, Fang S, Mani R, Weinfeld M, Hammel M, Tainer JA, Schriemer DC, Lees-Miller SP, Glover JNM. Structural and functional characterization of the PNKP-XRCC4-LigIV DNA repair complex. *Nucleic Acids Res.* 2017 Jun 2;45(10):6238-6251. doi: 10.1093/nar/gkx275.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/28453785>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5449630/>
- Bras J, Alonso I, Barbot C, Costa MM, Darwent L, Orme T, Sequeiros J, Hardy J, Coutinho P, Guerreiro R. Mutations in PNKP cause recessive ataxia with oculomotor apraxia type 4. *Am J Hum Genet.* 2015 Mar 5;96(3):474-9. doi: 10.1016/j.ajhg.2015.01.005. Epub 2015 Feb 26.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/25728773>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4375449/>

- Breslin C, Mani RS, Fanta M, Hoch N, Weinfeld M, Caldecott KW. The Rev1 interacting region (RIR) motif in the scaffold protein XRCC1 mediates a low-affinity interaction with polynucleotide kinase/phosphatase (PNKP) during DNA single-strand break repair. *J Biol Chem.* 2017 Sep 29; 292(39):16024-16031. doi: 10.1074/jbc.M117.806638. Epub 2017 Aug 16.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/28821613>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5625035/>
- Dumitrache LC, McKinnon PJ. Polynucleotide kinase-phosphatase (PNKP) mutations and neurologic disease. *Mech Ageing Dev.* 2017 Jan;161(Pt A):121-129. doi: 10.1016/j.mad.2016.04.009. Epub 2016 Apr 26. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/27125728>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5161711/>
- OMIM: POLYNUCLEOTIDE KINASE 3-PRIME PHOSPHATASE
<http://omim.org/entry/605610>
- Poulton C, Oegema R, Heijnsman D, Hoogeboom J, Schot R, Stroink H, Willemsen MA, Verheijen FW, van de Spek P, Kremer A, Mancini GM. Progressive cerebellar atrophy and polyneuropathy: expanding the spectrum of PNKP mutations. *Neurogenetics.* 2013 Feb;14(1):43-51. doi: 10.1007/s10048-012-0351-8. Epub 2012 Dec 9.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23224214>
- Reynolds JJ, Walker AK, Gilmore EC, Walsh CA, Caldecott KW. Impact of PNKP mutations associated with microcephaly, seizures and developmental delay on enzyme activity and DNA strand break repair. *Nucleic Acids Res.* 2012 Aug;40(14):6608-19. doi: 10.1093/nar/gks318. Epub 2012 Apr 15.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/22508754>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413127/>
- Shen J, Gilmore EC, Marshall CA, Haddadin M, Reynolds JJ, Eyaid W, Bodell A, Barry B, Gleason D, Allen K, Ganesh VS, Chang BS, Grix A, Hill RS, Topcu M, Caldecott KW, Barkovich AJ, Walsh CA. Mutations in PNKP cause microcephaly, seizures and defects in DNA repair. *Nat Genet.* 2010 Mar;42(3):245-9. doi: 10.1038/ng.526. Epub 2010 Jan 31.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20118933>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835984/>
- Shimada M, Dumitrache LC, Russell HR, McKinnon PJ. Polynucleotide kinase-phosphatase enables neurogenesis via multiple DNA repair pathways to maintain genome stability. *EMBO J.* 2015 Oct 1;34(19):2465-80. doi: 10.15252/embj.201591363. Epub 2015 Aug 19.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/26290337>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4601665/>
- Weinfeld M, Mani RS, Abdou I, Aceytuno RD, Glover JN. Tidying up loose ends: the role of polynucleotide kinase/phosphatase in DNA strand break repair. *Trends Biochem Sci.* 2011 May; 36(5):262-71. doi: 10.1016/j.tibs.2011.01.006. Epub 2011 Feb 25. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21353781>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3134258/>

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