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.

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

Tests Listed in the Genetic Testing Registry

- Tests of PNKP (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=11284[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?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; PNKP (https://omim.org/entry/605610)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/11284)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PNKP[gene])

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Genomic Location

The *PNKP* gene is found on chromosome 19 (https://medlineplus.gov/genetics/chromosome/19/).

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