

EXT2 gene

exostosin glycosyltransferase 2

Normal Function

The *EXT2* gene provides instructions for producing a protein called exostosin-2. This protein is found in a cell structure called the Golgi apparatus, which modifies newly produced enzymes and other proteins. In the Golgi apparatus, exostosin-2 attaches (binds) to another protein, exostosin-1, to form a complex that modifies a protein called heparan sulfate so it can be used in the body. Heparan sulfate is involved in regulating a variety of body processes including the formation of blood vessels (angiogenesis) and blood clotting. It also has a role in the spread (metastasis) of cancer cells.

Health Conditions Related to Genetic Changes

Hereditary multiple osteochondromas

About 220 mutations in the *EXT2* gene have been identified in people with hereditary multiple osteochondromas type 2, a condition in which people develop multiple benign (noncancerous) bone tumors called osteochondromas. Most of these mutations prevent any functional exostosin-2 protein from being made, and are called "loss-of-function" mutations. The loss of exostosin-2 protein function prevents it from forming a complex with the exostosin-1 protein and modifying heparan sulfate. It is unclear how this impairment leads to the development of multiple osteochondromas.

Potocki-Shaffer syndrome

A genetic change resulting in the deletion of the *EXT2* gene causes a condition called Potocki-Shaffer syndrome. People with this condition have multiple osteochondromas (described above) and enlarged openings in two bones that make up much of the top and sides of the skull (enlarged parietal foramina). Other signs and symptoms seen in some people with Potocki-Shaffer syndrome include intellectual disability, developmental delay, distinctive facial features, vision problems, and defects in the heart, kidneys, and urinary tract.

Potocki-Shaffer syndrome (sometimes referred to as proximal 11p deletion syndrome) is caused by a deletion of genetic material from the short (p) arm of chromosome 11. In people with this condition, a loss of the *EXT2* gene within this region is responsible for multiple osteochondromas. The deletion likely leads to a reduction of exostosin-2

protein and the inability to process heparan sulfate correctly. Although heparan sulfate is involved in many body processes, it is unclear how the lack of this protein causes multiple osteochondromas. The loss of additional genes in the deleted region likely contributes to the other features of Potocki-Shaffer syndrome. Specifically, loss of the *ALX4* gene results in enlarged parietal foramina, and deletion of the *PHF21A* gene causes intellectual disability and distinctive facial features.

Other disorders

At least two mutations in the *EXT2* gene have been found in a family with seizures-scoliosis-macrocephaly syndrome. In individuals with this condition, seizures typically begin in early childhood. Affected individuals also have an abnormal curvature of the spine (scoliosis), an unusually large head (macrocephaly), intellectual disability, and weak muscle tone (hypotonia). The *EXT2* gene mutations associated with seizures-scoliosis-macrocephaly syndrome change single protein building blocks (amino acids) in the exostosin-2 protein. These changes reduce the amount of functional exostosin-2 protein, which likely disrupts normal modification of heparan sulfate. It is unclear how this disruption leads to the varied signs and symptoms of the condition. Individuals with seizures-scoliosis-macrocephaly syndrome do not appear to develop osteochondromas (described above).

Other Names for This Gene

- exostoses (multiple) 2
- exostosin 2
- EXT2_HUMAN
- Glucuronosyl-N-acetylglucosaminyl-proteoglycan 4-alpha-N-acetylglucosaminyltransferase
- N-acetylglucosaminyl-proteoglycan 4-beta-glucuronosyltransferase
- SOTV

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of EXT2 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2132\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2132[geneid]))

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28EXT2%5BTIAB%5D%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

- EXOSTOSIN GLYCOSYLTRANSFERASE 2; EXT2 (<https://omim.org/entry/608210>)

Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/2132>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=EXT2\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=EXT2[gene]))

References

- Clement ND, Porter DE. Hereditary multiple exostoses: anatomical distribution and burden of exostoses is dependent upon genotype and gender. *Scott Med J*. 2014Feb;59(1):35-44. doi: 10.1177/0036933013518150. Epub 2014 Jan 10. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/24413927>)
- Farhan SM, Wang J, Robinson JF, Prasad AN, Rupar CA, Siu VM; FORGE Canada Consortium; Hegele RA. Old gene, new phenotype: mutations in heparan sulfatesynthesis enzyme, EXT2 leads to seizure and developmental disorder, no exostoses. *J Med Genet*. 2015 Oct;52(10):666-75. doi: 10.1136/jmedgenet-2015-103279. Epub 2015 Aug 5. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/26246518>)
- Jochmann K, Bachvarova V, Vortkamp A. Heparan sulfate as a regulator of endochondral ossification and osteochondroma development. *Matrix Biol*. 2014Feb;34:55-63. doi: 10.1016/j.matbio.2013.11.003. Epub 2013 Dec 24. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/24370655>)
- Labonne JD, Vogt J, Reali L, Kong IK, Layman LC, Kim HG. A microdeletion encompassing PHF21A in an individual with global developmental delay and craniofacial anomalies. *Am J Med Genet A*. 2015 Dec;167A(12):3011-8. doi:10.1002/ajmg.a.37344. Epub 2015 Sep 3. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/26333423>)
- Lonie L, Porter DE, Fraser M, Cole T, Wise C, Yates L, Wakeling E, Blair E, Morava E, Monaco AP, Ragoussis J. Determination of the mutation spectrum of the EXT1/EXT2 genes in British Caucasian patients with multiple osteochondromas, and exclusion of six candidate genes in EXT negative cases. *Hum Mutat*. 2006Nov;27(11):1160. doi: 10.1002/humu.9467. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/17041877>)
- McCormick C, Duncan G, Goutsos KT, Tufaro F. The putative tumor suppressors EXT1 and EXT2 form a stable complex that accumulates in the Golgi apparatus and catalyzes the synthesis of heparan sulfate. *Proc Natl Acad Sci U S A*. 2000 Jan 18;97(2):668-73. doi: 10.1073/pnas.97.2.668. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/10639137>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC15388/>)
- Musso N, Caronia FP, Castorina S, Lo Monte AI, Barresi V, Condorelli DF. Somatic

loss of an EXT2 gene mutation during malignant progression in a patient with hereditary multiple osteochondromas. *Cancer Genet.* 2015 Mar;208(3):62-7. doi: 10.1016/j.cancergen.2015.01.002. Epub 2015 Jan 16. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/25744876>)

- Romeike BF, Wuyts W. Proximal chromosome 11p contiguous gene deletion syndrome phenotype: case report and review of the literature. *Clin Neuropathol.* 2007 Jan-Feb;26(1):1-11. doi: 10.5414/npp26001. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/17290930>)
- Tian C, Yan R, Wen S, Li X, Li T, Cai Z, Li X, Du H, Chen H. A splice mutation and mRNA decay of EXT2 provoke hereditary multiple exostoses. *PLoS One.* 2014 Apr 11;9(4):e94848. doi: 10.1371/journal.pone.0094848. eCollection 2014. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/24728384>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3984245/>)
- Wakui K, Gregato G, Ballif BC, Glotzbach CD, Bailey KA, Kuo PL, Sue WC, Sheffield LJ, Irons M, Gomez EG, Hecht JT, Potocki L, Shaffer LG. Construction of a natural panel of 11p11.2 deletions and further delineation of the critical region involved in Potocki-Shaffer syndrome. *Eur J Hum Genet.* 2005 May;13(5):528-40. doi: 10.1038/sj.ejhg.5201366. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15852040>)
- Wuyts W, Waeber G, Meinecke P, Schuler H, Goecke TO, Van Hul W, Bartsch O. Proximal 11p deletion syndrome (P11pDS): additional evaluation of the clinical and molecular aspects. *Eur J Hum Genet.* 2004 May;12(5):400-6. doi:10.1038/sj.ejhg.5201163. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/14872200>)

Genomic Location

The *EXT2* gene is found on chromosome 11 (<https://medlineplus.gov/genetics/chromosome/11/>).

Last updated May 1, 2016