

## **NOG gene**

noggin

### **Normal Function**

The *NOG* gene provides instructions for making a protein called noggin. This protein is involved in the development of many body tissues, including nerve tissue, muscles, and bones. Noggin's role in bone development makes it important for proper joint formation.

Noggin interacts with members of a group of proteins called bone morphogenetic proteins (BMPs). These proteins help control the development of bone and other tissues.

In order to begin these developmental processes, BMPs attach (bind) to other proteins called receptors, and this binding stimulates specific cellular processes. The noggin protein regulates the activity of certain BMPs by attaching to them and blocking them from binding to the receptor, which leads to a decrease in BMP signaling.

### **Health Conditions Related to Genetic Changes**

#### Tarsal-carpal coalition syndrome

Several mutations in the *NOG* gene have been identified in people with a condition called tarsal-carpal coalition syndrome. This condition is characterized by fusion of the individual bones in the wrists (the carpal bones) and in the ankles (the tarsal bones) as well as fusion at the joints between the bones that make up each finger and toe (sympylangism). Sympylangism makes the fingers and toes stiff and difficult to bend.

This condition is caused by mutations in the *NOG* gene that change single protein building blocks (amino acids) in the noggin protein. These mutations alter the structure or stability of noggin, impair the transport of noggin out of the cell, or reduce the protein's ability to bind to BMPs, resulting in a reduction of functional noggin protein. With decreased noggin function, BMPs abnormally stimulate bone formation in joint areas, where there should be no bone, causing the bone fusions seen in people with tarsal-carpal coalition syndrome.

#### Other disorders

Several other bone-related disorders are caused by mutations in the *NOG* gene. These gene mutations change single protein building blocks (amino acids) in the noggin protein.

Proximal symphalangism is characterized by fusion at the joints between the bones in the fingers and toes, particularly at the joint at the base of the digit. Other signs and symptoms include abnormally short middle fingers, webbed toes, and hearing loss that is due to fusion of the bones in the ears (stapes fixation).

Multiple synostoses syndrome 1 is characterized by symphalangism and characteristic facial features, such as a broad nose and thin lips. In addition, affected individuals can have fusion of the bones in the hands, feet, hips, and upper part of the spine (cervical vertebrae). People with this condition can have hearing loss due to stapes fixation.

People with stapes ankylosis with broad thumb and toes (also known as Teunissen-Cremers syndrome) have hearing loss due to stapes fixation, farsightedness, and broad thumbs and big toes. Some affected individuals may have fusion of the cervical vertebrae and characteristic facial features like those seen in multiple synostoses syndrome 1.

Brachydactyly type B2 is characterized by short fingers and toes, which occurs because the middle bone of the digit or the bone that forms the tip of the digit is abnormally small or absent. In addition, people with this condition can have symphalangism, fusion of the carpal bones, and connection of the skin between two or more fingers or toes (syndactyly).

As in tarsal-carpal coalition syndrome, the *NOG* gene mutations that cause these conditions reduce the amount of functional noggin protein. For reasons that are unknown, the same mutations can cause different disorders in different people. Because of a shared genetic cause and overlapping features, researchers have suggested that these conditions, including tarsal-carpal coalition syndrome, represent a spectrum of related conditions referred to as *NOG*-related-symphalangism spectrum disorder (*NOG*-SSD).

## Other Names for This Gene

- NOGG\_HUMAN
- noggin precursor
- SYM1
- symphalangism 1 (proximal)
- SYNS1

## Additional Information & Resources

### Tests Listed in the Genetic Testing Registry

- Tests of *NOG* ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=9241\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=9241[geneid]))

### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28%28NOG%5BTIAB%5D%29+OR+%28noggin%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+720+days%22%5Bdp%5D>)

### Catalog of Genes and Diseases from OMIM

- STAPES ANKYLOSIS WITH BROAD THUMBS AND TOES (<https://omim.org/entry/184460>)
- SYMPHALANGISM, PROXIMAL, 1A; SYM1A (<https://omim.org/entry/185800>)
- MULTIPLE SYNOSTOSES SYNDROME 1; SYNS1 (<https://omim.org/entry/186500>)
- NOGGIN; NOG (<https://omim.org/entry/602991>)
- BRACHYDACTYLY, TYPE B2; BDB2 (<https://omim.org/entry/611377>)

### Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/9241>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=NOG\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=NOG[gene]))

### **References**

- Brown DJ, Kim TB, Petty EM, Downs CA, Martin DM, Strouse PJ, Moroi SE, Milunsky JM, Lesperance MM. Autosomal dominant stapes ankylosis with broad thumbs and toes, hyperopia, and skeletal anomalies is caused by heterozygous nonsense and frameshift mutations in NOG, the gene encoding noggin. *Am J Hum Genet.* 2002 Sep;71(3):618-24. doi: 10.1086/342067. Epub 2002 Jun 27. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/12089654>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC379196/>)
- Dixon ME, Armstrong P, Stevens DB, Bamshad M. Identical mutations in NOG can cause either tarsal/carpal coalition syndrome or proximal symphalangism. *Genet Med.* 2001 Sep-Oct;3(5):349-53. doi: 10.1097/00125817-200109000-00004. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/11545688>)
- Drawbert JP, Stevens DB, Cadle RG, Hall BD. Tarsal and carpal coalition and symphalangism of the Fuhrmann type. Report of a family. *J Bone Joint Surg Am.* 1985 Jul;67(6):884-9. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/4019538>)
- Gong Y, Krakow D, Marcelino J, Wilkin D, Chitayat D, Babul-Hirji R, Hudgins L, Cremers CW, Cremers FP, Brunner HG, Reinker K, Rimo DL, Cohn DH, Goodman FR, Reardon W, Patton M, Francomano CA, Warman ML. Heterozygous mutations in the gene encoding noggin affect human joint morphogenesis. *Nat Genet.* 1999 Mar;21(3):302-4. doi: 10.1038/6821. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/10386821>)

v/10080184)

- Groppe J, Greenwald J, Wiater E, Rodriguez-Leon J, Economides AN, Kwiatkowski W, Affolter M, Vale WW, Izpisua Belmonte JC, Choe S. Structural basis of BMP signalling inhibition by the cystine knot protein Noggin. *Nature*. 2002 Dec 12; 420(6916):636-42. doi: 10.1038/nature01245. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/12478285>)
- Hogan BL. Bone morphogenetic proteins: multifunctional regulators of vertebrate development. *Genes Dev*. 1996 Jul 1;10(13):1580-94. doi:10.1101/gad.10.13.1580. No abstract available. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/8682290>)
- Krause C, Guzman A, Knaus P. Noggin. *Int J Biochem Cell Biol*. 2011 Apr;43(4):478-81. doi: 10.1016/j.biocel.2011.01.007. Epub 2011 Jan 21. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/21256973>)
- Lehmann K, Seemann P, Silan F, Goecke TO, Irgang S, Kjaer KW, Kjaergaard S, Mahoney MJ, Morlot S, Reissner C, Kerr B, Wilkie AO, Mundlos S. A new subtype of brachydactyly type B caused by point mutations in the bone morphogenetic protein antagonist NOGGIN. *Am J Hum Genet*. 2007 Aug;81(2):388-96. doi: 10.1086/519697. Epub 2007 Jun 8. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/17668388>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1950796/>)
- Marcelino J, Sciortino CM, Romero MF, Ulatowski LM, Ballock RT, Economides AN, Eimon PM, Harland RM, Warman ML. Human disease-causing NOG missense mutations: effects on noggin secretion, dimer formation, and bone morphogenetic protein binding. *Proc Natl Acad Sci U S A*. 2001 Sep 25;98(20):11353-8. doi:10.1073/pnas.201367598. Epub 2001 Sep 18. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/11562478>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC58733/>)
- Potti TA, Petty EM, Lesperance MM. A comprehensive review of reported heritable noggin-associated syndromes and proposed clinical utility of one broadly inclusive diagnostic term: NOG-related-symphalangism spectrum disorder (NOG-SSD). *Hum Mutat*. 2011 Aug;32(8):877-86. doi: 10.1002/humu.21515. Epub 2011 Jun 21. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/21538686>)
- Usami S, Abe S, Nishio S, Sakurai Y, Kojima H, Tono T, Suzuki N. Mutations in the NOG gene are commonly found in congenital stapes ankylosis with symphalangism, but not in otosclerosis. *Clin Genet*. 2012 Dec;82(6):514-20. doi:10.1111/j.1399-0004.2011.01831.x. Epub 2012 Jan 30. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22288654>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3532604/>)

## Genomic Location

The *NOG* gene is found on chromosome 17 (<https://medlineplus.gov/genetics/chromosome/17/>).

**Last updated April 1, 2012**