

TNFRSF11A Gene

Subjects: **Genetics & Heredity**

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TNF receptor superfamily member 11a: The TNFRSF11A gene provides instructions for making a protein called receptor activator of NF- κ B (RANK).

genes

1. Normal Function

The *TNFRSF11A* gene provides instructions for making a protein called receptor activator of NF- κ B (RANK). This protein plays an important role in bone remodeling, a normal process in which old bone is broken down and new bone is created to replace it. During bone remodeling, RANK helps direct the formation and function of specialized cells called osteoclasts, which break down bone tissue. RANK is located on the surface of immature osteoclasts, where it receives signals that trigger these cells to mature and become fully functional.

2. Health Conditions Related to Genetic Changes

2.1. Paget disease of bone

At least two very similar mutations in the *TNFRSF11A* gene have been found to cause the rare, early-onset form of Paget disease of bone. Both mutations are duplications, which means that they abnormally copy a segment of genetic material within the gene. Each of these mutations results in the production of a RANK protein that contains several extra protein building blocks (amino acids).

Through a mechanism that is not well understood, duplication mutations in the *TNFRSF11A* gene appear to overactivate the chemical signaling pathway that promotes osteoclast formation. The increased signaling stimulates the production of too many osteoclasts and triggers these cells to break down bone abnormally. In people with early-onset Paget disease of bone, affected bone is broken down and replaced much faster than usual. When the new bone tissue grows, it is weaker and less organized than normal bone. These problems with bone remodeling cause certain bones to become unusually large, misshapen, and easily broken (fractured).

2.2. Other disorders

Mutations in the *TNFRSF11A* gene are responsible for several other rare bone diseases, including two very similar disorders called familial expansile osteolysis (FEO) and expansile skeletal hyperphosphatasia (ESH). These disorders have signs and symptoms that overlap with those of early-onset Paget disease of bone. In fact, some

researchers believe that FEO, ESH, and early-onset Paget disease of bone actually may be slightly different forms of a single condition. FEO and ESH both appear early in life and are characterized by skeletal abnormalities, tooth loss, and progressive hearing loss.

Like early-onset Paget disease of bone, FEO and ESH result from duplication mutations in the *TNFRSF11A* gene. Studies suggest that these mutations overactivate RANK, leading it to stimulate the production of too many osteoclasts and trigger these cells to break down bone abnormally. The resulting imbalance in bone remodeling causes the major features of these disorders. It is unclear why duplication mutations in the *TNFRSF11A* gene can cause several different bone diseases.

TNFRSF11A gene mutations also cause a bone disease called autosomal recessive osteopetrosis (ARO). This disorder appears in infancy and is characterized by abnormally dense bones. The increased bone density leads to a variety of complications, including an increased risk of fractures, vision impairment, hearing loss, and problems with the immune system related to defective bone marrow. Mutations in the *TNFRSF11A* gene appear to be a very rare cause of ARO; fewer than 10 mutations have been found in affected individuals. Most of these mutations change single amino acids in the RANK protein, which prevents it from receiving signals on the surface of immature osteoclasts. As a result, people with this condition have a total absence of mature, functional osteoclasts. Without these specialized cells to break down bone tissue, excess bone is formed throughout the skeleton.

Osteopetrosis

3. Other Names for This Gene

- CD265
- FEO
- ODFR
- OFE
- OPTB7
- osteoclast differentiation factor receptor
- OSTS
- PDB2
- RANK
- receptor activator of NF-kappa-B
- receptor activator of nuclear factor-kappa B
- TNFR11_HUMAN
- TRANCER
- tumor necrosis factor receptor superfamily member 11a
- tumor necrosis factor receptor superfamily member 11a, NFkB activator
- tumor necrosis factor receptor superfamily, member 11a
- tumor necrosis factor receptor superfamily, member 11a, activator of NFkB

- tumor necrosis factor receptor superfamily, member 11a, NFkB activator

References

1. Elahi E, Shafaghathi Y, Asadi S, Absalan F, Goodarzi H, Gharaii N, Karimi-NejadMH, Shahram F, Hughes AE. Intragenic SNP haplotypes associated with 84dup18mutation in TNFRSF11A in four FEO pedigrees suggest three independent origins forthis mutation. *J Bone Miner Metab.* 2007;25(3):159-64.
2. Guerrini MM, Sobacchi C, Cassani B, Abinun M, Kilic SS, Pangrazio A, MorattoD, Mazzolari E, Clayton-Smith J, Orchard P, Coxon FP, Helfrich MH, Crockett JC,Mellis D, Vellodi A, Tezcan I, Notarangelo LD, Rogers MJ, Vezzoni P, Villa A,Frattini A. Human osteoclast-poor osteopetrosis with hypogammaglobulinemia due toTNFRSF11A (RANK) mutations. *Am J Hum Genet.* 2008 Jul;83(1):64-76. doi:10.1016/j.ajhg.2008.06.015.
3. Hughes AE, Ralston SH, Marken J, Bell C, MacPherson H, Wallace RG, van Hul W, Whyte MP, Nakatsuka K, Hovy L, Anderson DM. Mutations in TNFRSF11A, affecting thesignal peptide of RANK, cause familial expansile osteolysis. *Nat Genet.* 2000Jan;24(1):45-8.
4. Johnson-Pais TL, Singer FR, Bone HG, McMurray CT, Hansen MF, Leach RJ.Identification of a novel tandem duplication in exon 1 of the TNFRSF11A gene into two unrelated patients with familial expansile osteolysis. *J Bone Miner Res.* 2003Feb;18(2):376-80.
5. Ke YH, Yue H, He JW, Liu YJ, Zhang ZL. Early onset Paget's disease of bonecaused by a novel mutation (78dup27) of the TNFRSF11A gene in a Chinese family.*Acta Pharmacol Sin.* 2009 Aug;30(8):1204-10. doi: 10.1038/aps.2009.90.
6. Li J, Sarosi I, Yan XQ, Morony S, Capparelli C, Tan HL, McCabe S, Elliott R,Scully S, Van G, Kaufman S, Juan SC, Sun Y, Tarpley J, Martin L, Christensen K,McCabe J, Kostenuik P, Hsu H, Fletcher F, Dunstan CR, Lacey DL, Boyle WJ. RANK isthe intrinsic hematopoietic cell surface receptor that controlsosteoclastogenesis and regulation of bone mass and calcium metabolism. *Proc Natl Acad Sci U S A.* 2000 Feb 15;97(4):1566-71.
7. Nakatsuka K, Nishizawa Y, Ralston SH. Phenotypic characterization of earlyonset Paget's disease of bone caused by a 27-bp duplication in the TNFRSF11A gene. *J Bone Miner Res.* 2003 Aug;18(8):1381-5.
8. Palenzuela L, Vives-Bauza C, Fernández-Cadenas I, Meseguer A, Font N, SarretE, Schwartz S, Andreu AL. Familial expansile osteolysis in a large Spanishkindred resulting from an insertion mutation in the TNFRSF11A gene. *J Med Genet.* 2002 Oct;39(10):E67.
9. Whyte MP, Hughes AE. Expansile skeletal hyperphosphatasia is caused by a15-base pair tandem duplication in TNFRSF11A encoding RANK and is allelic tofamilial expansile osteolysis. *J Bone Miner Res.* 2002 Jan;17(1):26-9.

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