Frontometaphyseal dysplasia

Description

Frontometaphyseal dysplasia is a disorder involving abnormalities in skeletal development and other health problems. It is a member of a group of related conditions called otopalatodigital spectrum disorders, which also includes otopalatodigital syndrome type 1, otopalatodigital syndrome type 2, Melnick-Needles syndrome, and terminal osseous dysplasia. In general, these disorders involve hearing loss caused by malformations in the tiny bones in the ears (ossicles), problems in the development of the roof of the mouth (palate), and bony abnormalities involving various areas of the skeleton.

Frontometaphyseal dysplasia is distinguished from the other otopalatodigital spectrum disorders by the presence of joint deformities called contractures that restrict the movement of certain joints. People with frontometaphyseal dysplasia may also have bowed limbs, an abnormal curvature of the spine (scoliosis), and abnormalities of the fingers and hands.

Characteristic facial features may include prominent brow ridges; wide-set and downward-slanting eyes; a very small lower jaw and chin (micrognathia); and small, missing, or misaligned teeth. Some affected individuals have hearing loss.

In addition to skeletal abnormalities, individuals with frontometaphyseal dysplasia may have obstruction of the ducts between the kidneys and bladder (ureters), heart defects, or constrictions in the passages leading from the windpipe to the lungs (the bronchi) that can cause problems with breathing.

There are three types of frontometaphyseal dysplasia, known as type 1, type 2, and type 3. The three types differ in their genetic cause and the way they are inherited.

Frequency

Frontometaphyseal dysplasia is a rare disorder; over a hundred cases have been reported worldwide.

Causes

Variants (also called mutations) in the *FLNA* gene cause frontometaphyseal dysplasia type 1. Variants in the *MAP3K7* gene cause frontometaphyseal dysplasia type 2, and

TAB2 gene variants cause type 3.

The *FLNA* gene provides instructions for producing the protein filamin A, which helps build the network of protein filaments (cytoskeleton) that gives structure to cells and allows them to change shape and move. Filamin A binds to another protein called actin, and helps the actin form the branching network of filaments that make up the cytoskeleton. Filamin A also links actin to many other proteins to perform various functions within the cell.

Variants in the *FLNA* gene have been identified in people with frontometaphyseal dysplasia. These mutations are described as "gain-of-function" because they appear to enhance the activity of the filamin A protein or give the protein a new, atypical function. Researchers think that the mutations may change the way the filamin A protein helps regulate processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of frontometaphyseal dysplasia.

Learn more about the gene associated with Frontometaphyseal dysplasia

- FLNA

Additional Information from NCBI Gene:

- MAP3K7
- TAB2

Inheritance

When frontometaphyseal dysplasia is caused by variants in the *FLNA* gene, it is inherited in an X-linked dominant pattern. The *FLNA* gene is located on the X chromosome, which is one of the two sex chromosomes. In females (who have two X chromosomes), a variant in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a variant in the only copy of the gene in each cell causes the disorder. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons. Males with frontometaphyseal dysplasia type 1 generally have more severe signs and symptoms of the disorder than do females, who may show only the characteristic facial features.

When frontometaphyseal dysplasia is caused by variants in the *MAP3K7* or *TAB2* gene, it is inherited in an autosomal dominant pattern. Autosomal dominant inheritance means one copy of the altered gene in each cell is sufficient to cause the disorder.

Other Names for This Condition

- FMD

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Frontometaphyseal dysplasia 1 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4281559/)
- Genetic Testing Registry: Frontometaphyseal dysplasia 2 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4310697/)

Genetic and Rare Diseases Information Center

- Frontometaphyseal dysplasia (https://rarediseases.info.nih.gov/diseases/826/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- FRONTOMETAPHYSEAL DYSPLASIA 1; FMD1 (https://omim.org/entry/305620)
- FRONTOMETAPHYSEAL DYSPLASIA 2; FMD2 (https://omim.org/entry/617137)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28frontometaphyseal+dysplasia%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

References

- Giuliano F, Collignon P, Paquis-Flucklinger V, Bardot J, Philip N. A newthree-generational family with frontometaphyseal dysplasia, male-to-femaletransmission, and a previously reported FLNA mutation. Am J Med Genet A. 2005 Jan15;132A(2):222. doi: 10.1002/ajmg.a.30396. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15523633)
- Morava E, Illes T, Weisenbach J, Karteszi J, Kosztolanyi G. Clinical andgenetic heterogeneity in frontometaphyseal dysplasia: severe progressivescoliosis in two families. Am J Med Genet A. 2003 Jan 30;116A(3):272-7. doi:10.1002/ajmg.a.10831. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12503106)
- Robertson S. X-Linked Otopalatodigital Spectrum Disorders. 2005 Nov 30[updated 2019 Oct 3]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE,Amemiya A, editors. GeneReviews(R) [Internet]. Seattle (WA): Universityof Washington,

Seattle; 1993-2025. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1393/ Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20301567)

- Robertson SP, Jenkins ZA, Morgan T, Ades L, Aftimos S, Boute O, FiskerstrandT, Garcia-Minaur S, Grix A, Green A, Der Kaloustian V, Lewkonia R, McInnes B, vanHaelst MM, Mancini G, Illes T, Mortier G, Newbury-Ecob R, Nicholson L, Scott CI, Ochman K, Brozek I, Shears DJ, Superti-Furga A, Suri M, Whiteford M, Wilkie AO, Krakow D. Frontometaphyseal dysplasia: mutations in FLNA and phenotypicdiversity. Am J Med Genet A. 2006 Aug 15;140(16):1726-36. doi:10.1002/ajmg.a.31322. Erratum In: Am J Med Genet A. 2006 Dec 15;140(24):2840.Macini, Grazia [corrected to Mancini, Grazia]. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16835913)
- Robertson SP, Twigg SR, Sutherland-Smith AJ, Biancalana V, Gorlin RJ, Horn D, Kenwrick SJ, Kim CA, Morava E, Newbury-Ecob R, Orstavik KH, Quarrell OW, SchwartzCE, Shears DJ, Suri M, Kendrick-Jones J, Wilkie AO; OPD-spectrum DisordersClinical Collaborative Group. Localized mutations in the gene encoding thecytoskeletal protein filamin A cause diverse malformations in humans. Nat Genet. 2003 Apr;33(4):487-91. doi: 10.1038/ng1119. Epub 2003 Mar 3. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12612583)
- Robertson SP. Otopalatodigital syndrome spectrum disorders: otopalatodigitalsyndrome types 1 and 2, frontometaphyseal dysplasia and Melnick-Needles syndrome.Eur J Hum Genet. 2007 Jan;15(1):3-9. doi: 10.1038/sj.ejhg.5201654. Epub 2006 Aug23. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16926860)
- Wade EM, Daniel PB, Jenkins ZA, McInerney-Leo A, Leo P, Morgan T, Addor MC, Ades LC, Bertola D, Bohring A, Carter E, Cho TJ, Duba HC, Fletcher E, Kim CA, Krakow D, Morava E, Neuhann T, Superti-Furga A, Veenstra-Knol I, Wieczorek D, Wilson LC, Hennekam RC, Sutherland-Smith AJ, Strom TM, Wilkie AO, Brown MA, Duncan EL, Markie DM, Robertson SP. Mutations in MAP3K7 that Alter the Activityof the TAK1 Signaling Complex Cause Frontometaphyseal Dysplasia. Am J Hum Genet.2016 Aug 4;99(2):392-406. doi: 10.1016/j.ajhg.2016.05.024. Epub 2016 Jul 15. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/27426733)
- Wade EM, Halliday BJ, Jenkins ZA, O'Neill AC, Robertson SP. The X-linkedfilaminopathies: Synergistic insights from clinical and molecular analysis. HumMutat. 2020 May;41(5):865-883. doi: 10.1002/humu.24002. Epub 2020 Mar 11. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32108395)
- Wade EM, Jenkins ZA, Daniel PB, Morgan T, Addor MC, Ades LC, Bertola D, Bohring A, Carter E, Cho TJ, de Geus CM, Duba HC, Fletcher E, Hadzsiev K, Hennekam RCM, Kim CA, Krakow D, Morava E, Neuhann T, Sillence D, Superti-Furga A,Veenstra-Knol HE, Wieczorek D, Wilson LC, Markie DM, Robertson SP. Autosomaldominant frontometaphyseal dysplasia: Delineation of the clinical phenotype. Am JMed Genet A. 2017 Jul;173(7):1739-1746. doi: 10.1002/ajmg.a.38267. Epub 2017 May12. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/28498505)
- Zenker M, Nahrlich L, Sticht H, Reis A, Horn D. Genotype-epigenotype-phenotypecorrelations in females with frontometaphyseal dysplasia. Am J Med

Genet A. 2006May 15;140(10):1069-73. doi: 10.1002/ajmg.a.31213. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16596676)

Last updated June 16, 2022