FLNA gene

filamin A

Normal Function

The *FLNA* gene provides instructions for producing the protein filamin A, which helps build cells' extensive internal network of protein filaments called the cytoskeleton. The cytoskeleton gives structure to cells and allows them the flexibility to change shape. The cytoskeleton is also important for certain processes inside the cells, such as the movement of proteins within the cell and the breakdown of unneeded proteins. Filamin A primarily attaches (binds) to another protein called actin and helps it form the branching network of filaments that make up the cytoskeleton.

Filamin A can also bind to many other proteins in the cell to carry out various functions, including the attachment of cells to one another (cell adhesion), cell movement (migration), determination of cell shape, the relay of signals within cells, and cell survival. These numerous functions involving filamin A have been found to play roles in regulating skeletal and brain development, the formation of heart tissue and blood vessels, blood clotting, skin elasticity, the maintenance of lung tissue, and the function of the digestive system.

Filamin A is also involved in the organization of the extracellular matrix, which is the lattice of proteins and other molecules outside the cell. Filamin A binds to proteins called integrins, which span the cell membrane and anchor cells to the extracellular matrix. Through this binding, cells are correctly positioned and signals can be exchanged between the cell and the extracellular matrix.

Health Conditions Related to Genetic Changes

Frontometaphyseal dysplasia

Variants (also known as mutations) in the *FLNA* gene have been identified in people with frontometaphyseal dysplasia. This condition is a member of a group of related conditions called otopalatodigital spectrum disorders, which also includes otopalatodigital syndrome type 1, otopalatodigital syndrome type 2, frontometaphyseal dysplasia, and Melnick-Needles syndrome(described below). Frontometaphyseal dysplasia involves abnormalities in skeletal development, particularly involving the joints, and other health problems, including kidney, heart, and airway defects.

FLNA gene variants that cause frontometaphyseal dysplasia 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. Different variants in the *FLNA* gene appear to produce specific changes in the protein, resulting in particular signs and symptoms that are classified as individual *FLNA*-related disorders. Researchers suspect that the variants involved in frontometaphyseal dysplasia 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 the condition.

Intestinal pseudo-obstruction

Several variants in the *FLNA* gene have been identified in people with intestinal pseudo-obstruction, a condition characterized by impairment of the muscle contractions that move food through the digestive tract (peristalsis).

The *FLNA* gene variants that cause intestinal pseudo-obstruction include deletions or duplications of genetic material. The variants are thought to reduce levels of the filamin A protein or impair its function; this type of variant is called "loss of function." Research suggests that decreased filamin A function may affect the shape of cells in the smooth muscles of the gastrointestinal tract during development before birth, causing abnormalities in the layering of these muscles. Smooth muscles line the internal organs; they contract and relax without being consciously controlled. Abnormal layering of these muscles may interfere with these musclar movements that move food through the digestive tract.

Deletions or duplications of genetic material can affect all or part of the *FLNA* gene, and may also include nearby genes on the X chromosome. Changes in these additional genes may account for some of the other signs and symptoms, such as neurological abnormalities and unusual facial features, that occur in some affected individuals.

Melnick-Needles syndrome

Several variants in a region of the *FLNA* gene called exon 22 have been identified in people with Melnick-Needles syndrome. This condition is typically the most severe of the otopalatodigital spectrum disorders (described above). It involves abnormalities in skeletal development, causing short stature, abnormal curvature of the spine, partial dislocation of joints, and other health problems. The *FLNA* gene variants associated with Melnick-Needles syndrome 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 believe that the variants involved in Melnick-Needles syndrome 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 the condition.

Otopalatodigital syndrome type 1

Several variants in the *FLNA* gene have been found to cause otopalatodigital syndrome type 1. This condition is typically the mildest of the otopalatodigital spectrum disorders (

described above). It is characterized by hearing loss caused by malformations in tiny bones in the ears (ossicles), an opening in the roof of the mouth (cleft palate), and skeletal abnormalities involving the fingers or toes (digits).

The *FLNA* gene variants that cause otopalatodigital syndrome type 1 all result in changes to the filamin A protein in a region that binds to actin (known as the CH2 domain). Many of these variants change single amino acids in the filamin A protein. These variants are described as "gain-of-function" because they appear to lead to a protein with an increased ability to bind to actin. Researchers believe that the *FLNA* gene variants impair the stability of the cytoskeleton and disrupt cellular processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of otopalatodigital syndrome type 1.

Otopalatodigital syndrome type 2

Several variants in the *FLNA* gene have been found to cause otopalatodigital syndrome type 2, which is part of the otopalatodigital spectrum (described above). This condition is similar to otopalatodigital syndrome type 1 (described above) and is characterized by hearing loss caused by malformations in the ossicles, a cleft palate, and skeletal abnormalities involving the digits. These abnormalities in skeletal development are typically more severe than in otopalatodigital syndrome type 1.

The *FLNA* gene variants that cause otopalatodigital syndrome type 2 all result in changes to the filamin A protein in a region that binds to actin (known as the CH2 domain). Most of these variants change single amino acids in the filamin A protein. These variants are described as "gain-of-function" because they appear to lead to a protein with an increased ability to bind to actin. Researchers believe that the *FLNA* gene variants impair the stability of the cytoskeleton and disrupt cellular processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of otopalatodigital syndrome type 2.

Periventricular heterotopia

Hundreds of *FLNA* gene variants have been identified in individuals with periventricular heterotopia, a condition in which nerve cells (neurons) do not move (migrate) properly during the early development of the fetal brain leading to seizures and other neurological problems. Most of these variants result in a lack of filamin A protein, which makes the cytoskeleton disorganized and impairs the attachment (adhesion) of cells to one another. Impaired adhesion alters cells that line the fluid-filled cavities near the center of the brain (the ventricles), which is where neurons develop. Disruption of this lining prevents the movement of neurons to the surface of the brain. Neurons that do not migrate properly during development form clumps (nodules) around the ventricles, resulting in the signs and symptoms of periventricular heterotopia.

In some cases, variants result in the substitution of one protein building block (amino acid) for another amino acid in the protein sequence. These variants may result in the production of a partially functional protein, sometimes causing a milder form of the disorder.

Terminal osseous dysplasia

At least one variant in the *FLNA* gene has been found to cause terminal osseous dysplasia, which is part of the otopalatodigital spectrum of disorders (described above). Terminal osseous dysplasia is characterized by skeletal abnormalities in the hands and feet, noncancerous (benign) tumors on the fingers and toes (digits), and dark patches of skin on the face.

The *FLNA* gene variant that causes terminal osseous dysplasia changes a single DNA building block (nucleotide) in the gene, substituting adenine for guanine at DNA position 5217 (written as 5217G>A). This DNA change alters the way the blueprint for making the filamin A protein is put together. The version of the protein made using this blueprint is abnormally short. Researchers suspect the altered protein may not be able to interact with other molecules normally. It is thought that the inability to bind to other proteins disrupts important processes involved in skeletal development and cell growth, leading to the bone and skin abnormalities characteristic of terminal osseous dysplasia.

X-linked cardiac valvular dysplasia

Variants in the *FLNA* gene have been found to cause X-linked cardiac valvular dysplasia, a condition characterized by abnormally thick heart valves. Most of these variants change single amino acids in the filamin A protein. These variants likely alter the shape of the protein, impairing its ability to bind to actin and other proteins. As a result, the cell cytoskeleton is weakened and valve cells and the extracellular matrix are disorganized. The cells are not positioned properly within the valve, so the valve becomes malformed. In addition, the cells' decreased ability to change shape impairs the valves' ability to open and close when the heart pumps blood. It appears that excess proteins are produced in the abnormal extracellular matrix, causing the valves to become thickened and further impairing their ability to open and close normally.

It is unclear why the heart valves are the only tissue affected by these *FLNA* gene variants. The variants that cause X-linked cardiac valvular dysplasia occur in a different part of the gene than those that cause other disorders (described above). It has been suggested that the region of the filamin A protein affected by these variants is necessary for binding to other proteins that play a significant role in heart development.

FG syndrome

MedlinePlus Genetics provides information about FG syndrome

Other Names for This Gene

- ABP-280
- ABPX
- actin-binding protein 280
- DKFZp434P031
- filamin 1

- filamin A, alpha
- filamin A, alpha (actin binding protein 280)
- FLN
- FLN1
- FLNA_HUMAN

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of FLNA (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2316[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28FLNA%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

- FILAMIN A; FLNA (https://omim.org/entry/300017)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/2316)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=FLNA[gene])

References

- Brunetti-Pierri N, Torrado M, Fernandez Mdel C, Tello AM, Arberas CL,Cardinale A, Piccolo P, Bacino CA. Terminal osseous dysplasia with pigmentarydefects (TODPD) due to a recurrent filamin A (FLNA) mutation. Mol Genet GenomicMed. 2014 Nov;2(6):467-71. doi: 10.1002/mgg3.90. Epub 2014 Aug 8. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/25614868)
- Duval D, Lardeux A, Le Tourneau T, Norris RA, Markwald RR, Sauzeau V, ProbstV, Le Marec H, Levine R, Schott JJ, Merot J. Valvular dystrophy associatedfilamin A mutations reveal a new role of its first repeats in small-GTPaseregulation. Biochim Biophys Acta. 2014 Feb;1843(2):234-44. doi:10.1016/j.bbamcr.2013.10.022. Epub 2013 Nov 4. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/24200678) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3928473/)

- Gargiulo A, Auricchio R, Barone MV, Cotugno G, Reardon W, Milla PJ, BallabioA, Ciccodicola A, Auricchio A. Filamin A is mutated in X-linked chronicidiopathic intestinal pseudo-obstruction with central nervous system involvement.Am J Hum Genet. 2007 Apr;80(4):751-8. doi: 10.1086/513321. Epub 2007 Feb 26. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17357080) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1852717/)
- Jenkins ZA, Macharg A, Chang CY, van Kogelenberg M, Morgan T, Frentz S, Wei W,Pilch J, Hannibal M, Foulds N, McGillivray G, Leventer RJ, Garcia-Minaur S, Sugito S, Nightingale S, Markie DM, Dudding T, Kapur RP, Robertson SP. Differential regulation of two FLNA transcripts explains some of the phenotypicheterogeneity in the loss-of-function filaminopathies. Hum Mutat. 2018Jan; 39(1):103-113. doi: 10.1002/humu.23355. Epub 2017 Nov 2. Citation on PubMed (ht tps://pubmed.ncbi.nlm.nih.gov/29024177)
- Kapur RP, Robertson SP, Hannibal MC, Finn LS, Morgan T, van Kogelenberg M, Loren DJ. Diffuse abnormal layering of small intestinal smooth muscle is presentin patients with FLNA mutations and x-linked intestinal pseudo-obstruction. Am JSurg Pathol. 2010 Oct;34(10):1528-43. doi: 10.1097/PAS.0b013e3181f0ae47. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20871226)
- Kyndt F, Gueffet JP, Probst V, Jaafar P, Legendre A, Le Bouffant F, Toquet C,Roy E, McGregor L, Lynch SA, Newbury-Ecob R, Tran V, Young I, Trochu JN, Le MarecH, Schott JJ. Mutations in the gene encoding filamin A as a cause for familialcardiac valvular dystrophy. Circulation. 2007 Jan 2;115(1):40-9. doi:10.1161/ CIRCULATIONAHA.106.622621. Epub 2006 Dec 26. Citation on PubMed (https://pu bmed.ncbi.nlm.nih.gov/17190868)
- Lange M, Kasper B, Bohring A, Rutsch F, Kluger G, Hoffjan S, Spranger S, Behnecke A, Ferbert A, Hahn A, Oehl-Jaschkowitz B, Graul-Neumann L, Diepold K, Schreyer I, Bernhard MK, Mueller F, Siebers-Renelt U, Beleza-Meireles A, UyanikG, Janssens S, Boltshauser E, Winkler J, Schuierer G, Hehr U. 47 patients withFLNA associated periventricular nodular heterotopia. Orphanet J Rare Dis. 2015Oct 15;10: 134. doi: 10.1186/s13023-015-0331-9. Citation on PubMed (https://pubmed.ncbi.nlm .nih.gov/26471271) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC4608144/)
- Lu J, Tiao G, Folkerth R, Hecht J, Walsh C, Sheen V. Overlapping expression ofARFGEF2 and Filamin A in the neuroependymal lining of the lateral ventricles: insights into the cause of periventricular heterotopia. J Comp Neurol. 2006 Jan20; 494(3):476-84. doi: 10.1002/cne.20806. Citation on PubMed (https://pubmed.ncbi.nl m.nih.gov/16320251)
- Moro F, Carrozzo R, Veggiotti P, Tortorella G, Toniolo D, Volzone A, GuerriniR. Familial periventricular heterotopia: missense and distal truncating mutationsof the FLN1 gene. Neurology. 2002 Mar 26;58(6):916-21. doi: 10.1212/wnl.58.6.916. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11914408)
- Moutton S, Fergelot P, Naudion S, Cordier MP, Sole G, Guerineau E, Hubert C, Rooryck C, Vuillaume ML, Houcinat N, Deforges J, Bouron J, Deves S, Le Merrer M, David A, Genevieve D, Giuliano F, Journel H, Megarbane A, Faivre L, Chassaing N, Francannet C, Sarrazin E, Stattin EL, Vigneron J, Leclair D, Abadie C, Sarda P,

Baumann C, Delrue MA, Arveiler B, Lacombe D, Goizet C, Coupry I. Otopalatodigitalspectrum disorders: refinement of the phenotypic and mutational spectrum. J HumGenet. 2016 Aug;61(8):693-9. doi: 10.1038/jhg.2016.37. Epub 2016 May 19. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/27193221)

- Parrini E, Ramazzotti A, Dobyns WB, Mei D, Moro F, Veggiotti P, Marini C,Brilstra EH, Dalla Bernardina B, Goodwin L, Bodell A, Jones MC, Nangeroni M,Palmeri S, Said E, Sander JW, Striano P, Takahashi Y, Van Maldergem L, LeonardiG, Wright M, Walsh CA, Guerrini R. Periventricular heterotopia: phenotypicheterogeneity and correlation with Filamin A mutations. Brain. 2006 Jul;129(Pt7):1892-906. doi: 10.1093/brain/awl125. Epub 2006 May 9. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16684786)
- Robertson SP, Thompson S, Morgan T, Holder-Espinasse M, Martinot-Duquenoy V, Wilkie AO, Manouvrier-Hanu S. Postzygotic mutation and germline mosaicism in theotopalatodigital syndrome spectrum disorders. Eur J Hum Genet. 2006May;14(5):549-54. doi: 10.1038/sj.ejhg.5201586. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16538226)
- 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)
- Sasaki E, Byrne AT, Phelan E, Cox DW, Reardon W. A review of filamin Amutations and associated interstitial lung disease. Eur J Pediatr. 2019Feb;178(2):121-129. doi: 10.1007/s00431-018-3301-0. Epub 2018 Dec 13. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/30547349)
- Sheen VL, Dixon PH, Fox JW, Hong SE, Kinton L, Sisodiya SM, Duncan JS, DubeauF, Scheffer IE, Schachter SC, Wilner A, Henchy R, Crino P, Kamuro K, DiMario F,Berg M, Kuzniecky R, Cole AJ, Bromfield E, Biber M, Schomer D, Wheless J, SilverK, Mochida GH, Berkovic SF, Andermann F, Andermann E, Dobyns WB, Wood NW, WalshCA. Mutations in the X-linked filamin 1 gene cause periventricular nodularheterotopia in males as well as in females. Hum Mol Genet. 2001 Aug15;10(17):1775-83. doi: 10.1093/hmg/10.17.1775. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11532987)
- Sheen VL, Jansen A, Chen MH, Parrini E, Morgan T, Ravenscroft R, Ganesh V, Underwood T, Wiley J, Leventer R, Vaid RR, Ruiz DE, Hutchins GM, Menasha J, Willner J, Geng Y, Gripp KW, Nicholson L, Berry-Kravis E, Bodell A, Apse K, HillRS, Dubeau F, Andermann F, Barkovich J, Andermann E, Shugart YY, Thomas P, ViriM, Veggiotti P, Robertson S, Guerrini R, Walsh CA. Filamin A mutations

causeperiventricular heterotopia with Ehlers-Danlos syndrome. Neurology. 2005 Jan25;64(2):254 doi: 10.1212/01.WNL.0000149512.79621.DF. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15668422)

- Shelmerdine SC, Semple T, Wallis C, Aurora P, Moledina S, Ashworth MT, OwensCM. Filamin A (FLNA) mutation-A newcomer to the childhood interstitial lungdisease (ChILD) classification. Pediatr Pulmonol. 2017 Oct;52(10):1306-1315. doi:10.1002/ppul.23695. Epub 2017 Sep 12. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/28898549)
- Sun Y, Almomani R, Aten E, Celli J, van der Heijden J, Venselaar H, RobertsonSP, Baroncini A, Franco B, Basel-Vanagaite L, Horii E, Drut R, Ariyurek Y, denDunnen JT, Breuning MH. Terminal osseous dysplasia is caused by a singlerecurrent mutation in the FLNA gene. Am J Hum Genet. 2010 Jul 9;87(1):146-53.doi: 10.1016/j.ajhg.2010.06.008. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20598277)
- 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)

Genomic Location

The *FLNA* gene is found on the X chromosome (https://medlineplus.gov/genetics/chromosome/x/).

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