FGF23 Gene

Subjects: Genetics & Heredity
Contributor: Peter Tang

Fibroblast growth factor 23

genes

1. Normal Function

The *FGF23* gene provides instructions for making a protein called fibroblast growth factor 23, which is produced in bone cells. This protein is necessary in regulating the phosphate levels within the body (phosphate homeostasis). Among its many functions, phosphate plays a critical role in the formation and growth of bones in childhood and helps maintain bone strength in adults. Phosphate levels are controlled in large part by the kidneys. The kidneys normally rid the body of excess phosphate by excreting it in urine, and they reabsorb this mineral into the bloodstream when more is needed. Fibroblast growth factor 23 signals the kidneys to stop reabsorbing phosphate into the bloodstream.

In order to function, fibroblast growth factor 23 must be released (secreted) from the cell and it must attach (bind) to a receptor protein. To be secreted from the cell, sugar molecules are attached to fibroblast growth factor 23 by another protein called ppGalNacT3 in a process called glycosylation. Glycosylation allows fibroblast growth factor 23 to move out of the cell and protects the protein from being broken down. Once outside the bone cell, the protein must bind to a receptor protein called FGF receptor 1 that spans the membrane of kidney cells. Binding of fibroblast growth factor 23 to its receptor stimulates signaling that stops phosphate reabsorption into the bloodstream.

Studies suggest that fibroblast growth factor 23 has additional functions. It helps determine how much phosphate from the diet is absorbed by the intestines and plays a role in regulating vitamin D.

Fibroblast growth factor 23 is normally cut (cleaved) at a certain site, which turns off (inactivates) the protein. The cleavage site is located at positions 179 to 180 in the string of building blocks (amino acids) that make up the protein. This cleavage helps regulate the amount of active fibroblast growth factor 23 circulating in the bloodstream.

2. Health Conditions Related to Genetic Changes

2.1. Hereditary hypophosphatemic rickets

At least three mutations in the *FGF23* gene have been found to cause a rare form of hereditary hypophosphatemic rickets known as autosomal dominant hypophosphatemic rickets. These mutations change single protein building blocks (amino acids) in fibroblast growth factor 23, which prevents the protein from being cleaved. As a result, the protein is not inactivated, and an increased amount of the full-length, active protein circulates in the bloodstream. Overactivity of fibroblast growth factor 23 reduces phosphate reabsorption by the kidneys, leading to low levels of phosphate in the blood (hypophosphatemia) and related problems with bone growth in people with autosomal dominant hypophosphatemic rickets.

2.2. Hyperphosphatemic familial tumoral calcinosis

At least seven mutations in the *FGF23* gene have been found to cause hyperphosphatemic familial tumoral calcinosis (HFTC), a condition characterized by an increase in the levels of phosphate in the blood (hyperphosphatemia) and abnormal deposits of phosphate and calcium (calcinosis) in the body's tissues. Mutations in the *FGF23* gene lead to the production of a protein with decreased function. This nonfunctional protein is quickly broken down in cells, leading to a shortage of available fibroblast growth factor 23. This protein shortage decreases signaling and increases the amount of phosphate that is reabsorbed back into the bloodstream by the kidneys, leading to hyperphosphatemia. Calcinosis results when the excess phosphate combines with calcium to form deposits that build up in soft tissues.

2.3. Kidney stones

3. Other Names for This Gene

- ADHR
- FGF-23
- FGF23_HUMAN
- HPDR2
- HYPF
- phosphatonin
- PHPTC
- tumor-derived hypophosphatemia-inducing factor

References

1. ADHR Consortium. Autosomal dominant hypophosphataemic rickets is associatedwith mutations in FGF23. Nat Genet. 2000 Nov;26(3):345-8. Citation on PubMed
2. Bergwitz C, Jüppner H. Regulation of phosphate homeostasis by PTH, vitamin D, and FGF23. Annu Rev Med. 2010;61:91-104. doi: 10.1146/annurev.med.051308.111339. Review. Citation on PubMed or Free article on PubMed Central

3. Farrow EG, Imel EA, White KE. Miscellaneous non-inflammatory musculoskeletalconditions. Hyperphosphatemic familial tumoral calcinosis (FGF23, GALNT3 andαKlotho). Best Pract Res Clin Rheumatol. 2011 Oct;25(5):735-47. doi:10.1016/j.berh.2011.10.020. Review. Citation on PubMed or Free article on PubMed Central
4. Fukumoto S. Physiological regulation and disorders of phosphatemetabolism--pivotal role of fibroblast growth factor 23. Intern Med.2008;47(5):337-43. Epub 2008 Mar 3. Review. Citation on PubMed
5. Garringer HJ, Malekpour M, Esteghamat F, Mortazavi SM, Davis SI, Farrow EG, YuX, Arking DE, Dietz HC, White KE. Molecular genetic and biochemical analyses ofFGF23 mutations in familial tumoral calcinosis. Am J Physiol Endocrinol Metab.2008 Oct;295(4):E929-37. doi: 10.1152/ajpendo.90456.2008. Epub 2008 Aug 5. Citation on PubMed or Free article on PubMed Central
6. Imel EA, Econs MJ. Fibroblast growth factor 23: roles in health and disease. JAm Soc Nephrol. 2005 Sep;16(9):2565-75. Epub 2005 Jul 20. Review. Citation on PubMed
7. Quarles LD. FGF23, PHEX, and MEPE regulation of phosphate homeostasis andskeletal mineralization. Am J Physiol Endocrinol Metab. 2003 Jul;285(1):E1-9.Review. Citation on PubMed
8. Ramon I, Kleynen P, Body JJ, Karmali R. Fibroblast growth factor 23 and itsrole in phosphate homeostasis. Eur J Endocrinol. 2010 Jan;162(1):1-10. doi:10.1530/EJE-09-0597. Epub 2009 Sep 23. Review. Citation on PubMed
9. Razzaque MS. The FGF23-Klotho axis: endocrine regulation of phosphatehomeostasis. Nat Rev Endocrinol. 2009 Nov;5(11):611-9. doi:10.1038/nrendo.2009.196. Review. Citation on PubMed or Free article on PubMed Central
10. Saito T, Fukumoto S. Fibroblast Growth Factor 23 (FGF23) and Disorders ofPhosphate Metabolism. Int J Pediatr Endocrinol. 2009;2009:496514. doi:10.1155/2009/496514. Epub 2009 Oct 7. Citation on PubMed or Free article on PubMed Central
11. Sprecher E. Familial tumoral calcinosis: from characterization of a rarephenotype to the pathogenesis of ectopic calcification. J Invest Dermatol. 2010Mar;130(3):652-60. doi: 10.1038/jid.2009.337. Epub 2009 Oct 29. Citation on PubMed or Free article on PubMed Central