FH gene

fumarate hydratase

Normal Function

The *FH* gene provides instructions for making an enzyme called fumarase (also known as fumarate hydratase). Fumarase participates in an important series of reactions known as the citric acid cycle or Krebs cycle, which allows cells to use oxygen and generate energy. Specifically, fumarase helps convert a molecule called fumarate to a molecule called malate.

Health Conditions Related to Genetic Changes

Fumarase deficiency

More than 20 *FH* gene mutations have been identified in people with fumarase deficiency, a condition that primarily affects the brain and is often fatal in infancy. Fumarase deficiency occurs in individuals who inherit two mutated copies of the *FH* gene in each cell. Most of these mutations replace one protein building block (amino acid) with another amino acid in the fumarase enzyme. These changes disrupt the ability of the enzyme to help convert fumarate to malate, interfering with the function of this reaction in the citric acid cycle. Impairment of the process that generates energy for cells is particularly harmful to cells in the developing brain, and this impairment results in the signs and symptoms of fumarase deficiency.

Hereditary leiomyomatosis and renal cell cancer

More than 70 mutations in the *FH* gene that cause hereditary leiomyomatosis and renal cell cancer (HLRCC) have been reported. Most of these mutations replace one amino acid with another amino acid in the fumarase enzyme.

HLRCC is a disorder in which affected individuals tend to develop benign tumors containing smooth muscle tissue (leiomyomas) in the skin and, in females, the uterus. This condition also increases the risk of kidney cancer. People with HLRCC are born with one mutated copy of the *FH* gene in each cell. The second copy of the *FH* gene in certain cells may also acquire mutations as a result of environmental factors such as ultraviolet radiation from the sun or an error that occurs as DNA copies itself during cell division. These changes are called somatic mutations and are not inherited.

FH gene mutations may interfere with the enzyme's role in the citric acid cycle, resulting in a buildup of fumarate. Researchers believe that the excess fumarate may interfere with the regulation of oxygen levels in the cell. Chronic oxygen deficiency (hypoxia) in cells with two mutated copies of the *FH* gene may encourage tumor formation and result in the tendency to develop leiomyomas and renal cell cancer.

Primary macronodular adrenal hyperplasia

MedlinePlus Genetics provides information about Primary macronodular adrenal hyperplasia

Other Names for This Gene

- fumarase
- fumarase hydratase
- FUMH_HUMAN
- HLRCC
- LRCC
- MCL
- MCUL1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of FH (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2271[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28FH%5BTIAB%5D%29+OR+%28fumarate+hydratase%5BTIAB%5D%29%29+AND+%28%28fumarase%5BMAJR%5D%29+OR+%28fumarate+hydratase%5BMAJR%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+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- FUMARATE HYDRATASE; FH (https://omim.org/entry/136850)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/2271)

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

References

- Alam NA, Rowan AJ, Wortham NC, Pollard PJ, Mitchell M, Tyrer JP, Barclay E, Calonje E, Manek S, Adams SJ, Bowers PW, Burrows NP, Charles-Holmes R, Cook LJ,Daly BM, Ford GP, Fuller LC, Hadfield-Jones SE, Hardwick N, Highet AS, Keefe M,MacDonald-Hull SP, Potts ED, Crone M, Wilkinson S, Camacho-Martinez F, JablonskaS, Ratnavel R, MacDonald A, Mann RJ, Grice K, Guillet G, Lewis-Jones MS, McGrathH, Seukeran DC, Morrison PJ, Fleming S, Rahman S, Kelsell D, Leigh I, Olpin S,Tomlinson IP. Genetic and functional analyses of FH mutations in multiplecutaneous and uterine leiomyomatosis, hereditary leiomyomatosis and renal cancer,and fumarate hydratase deficiency. Hum Mol Genet. 2003 Jun 1;12(11):1241-52. doi:10.1093/hmg/ddg148. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12761039)
- Badeloe S, van Geel M, van Steensel MA, Bastida J, Ferrando J, Steijlen PM,Frank J, Poblete-Gutierrez P. Diffuse and segmental variants of cutaneousleiomyomatosis: novel mutations in the fumarate hydratase gene and review of theliterature. Exp Dermatol. 2006 Sep;15(9):735-41. doi:10.1111/j.1600-0625.2006.00470.x. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16881969)
- Bayley JP, Launonen V, Tomlinson IP. The FH mutation database: an onlinedatabase of fumarate hydratase mutations involved in the MCUL (HLRCC) tumorsyndrome and congenital fumarase deficiency. BMC Med Genet. 2008 Mar 25; 9:20.doi: 10.1186/1471-2350-9-20. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18366737) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2322961/)
- Deschauer M, Gizatullina Z, Schulze A, Pritsch M, Knoppel C, Knape M, Zierz S, Gellerich FN. Molecular and biochemical investigations in fumarase deficiency.Mol Genet Metab. 2006 Jun;88(2):146-52. doi: 10.1016/j.ymgme.2006.01.007. Epub2006 Feb 28. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16510303)
- King A, Selak MA, Gottlieb E. Succinate dehydrogenase and fumarate hydratase: linking mitochondrial dysfunction and cancer. Oncogene. 2006 Aug7;25(34):4675-82. doi: 10.1038/sj.onc.1209594. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16892081)
- Lehtonen HJ, Kiuru M, Ylisaukko-Oja SK, Salovaara R, Herva R, Koivisto PA, Vierimaa O, Aittomaki K, Pukkala E, Launonen V, Aaltonen LA. Increased risk ofcancer in patients with fumarate hydratase germline mutation. J Med Genet. 2006Jun;43(6):523-6. doi: 10.1136/jmg.2005.036400. Epub 2005 Sep 9. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16155190) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564537/)
- Lorenzato A, Olivero M, Perro M, Briere JJ, Rustin P, Di Renzo MF. Acancer-predisposing "hot spot" mutation of the fumarase gene creates a dominantnegative protein. Int J Cancer. 2008 Feb 15;122(4):947-51. doi:10.1002/ijc.23209. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17960613)

- Ottolenghi C, Hubert L, Allanore Y, Brassier A, Altuzarra C, Mellot-DraznieksC, Bekri S, Goldenberg A, Veyrieres S, Boddaert N, Barbier V, Valayannopoulos V, Slama A, Chretien D, Ricquier D, Marret S, Frebourg T, Rabier D, Munnich A, deKeyzer Y, Toulhoat H, de Lonlay P. Clinical and biochemical heterogeneityassociated with fumarase deficiency. Hum Mutat. 2011 Sep;32(9):1046-52. doi:10.1002/humu.21534. Epub 2011 Jul 12. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21560188)
- Picaud S, Kavanagh KL, Yue WW, Lee WH, Muller-Knapp S, Gileadi O, SacchettiniJ, Oppermann U. Structural basis of fumarate hydratase deficiency. J InheritMetab Dis. 2011 Jun;34(3):671-6. doi: 10.1007/s10545-011-9294-8. Epub 2011 Mar29. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21445611) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109261/)
- Raimundo N, Ahtinen J, Fumic K, Baric I, Remes AM, Renkonen R, Lapatto R, Suomalainen A. Differential metabolic consequences of fumarate hydratase andrespiratory chain defects. Biochim Biophys Acta. 2008 May;1782(5):287-94. doi: 10.1016/j.bbadis.2008.01.008. Epub 2008 Feb 14. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18313410)
- Ratcliffe PJ. Fumarate hydratase deficiency and cancer: activation of hypoxiasignaling? Cancer Cell. 2007 Apr;11(4):303-5. doi: 10.1016/j.ccr.2007.03.015. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17418405)
- Sudarshan S, Linehan WM, Neckers L. HIF and fumarate hydratase in renalcancer. Br J Cancer. 2007 Feb 12;96(3):403-7. doi: 10.1038/sj.bjc.6603547. Epub2007 Jan 9. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17211469) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2360036/)
- Sudarshan S, Pinto PA, Neckers L, Linehan WM. Mechanisms of disease: hereditary leiomyomatosis and renal cell cancer--a distinct form of hereditarykidney cancer. Nat Clin Pract Urol. 2007 Feb;4(2):104-10. doi:10.1038/ncpuro0711. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17287871)
- Zeman J, Krijt J, Stratilova L, Hansikova H, Wenchich L, Kmoch S, Chrastina P, Houstek J. Abnormalities in succinylpurines in fumarase deficiency: possible rolein pathogenesis of CNS impairment. J Inherit Metab Dis. 2000 Jun;23(4):371-4.doi: 10.1023/a:1005639516342. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/10896297)

Genomic Location

The *FH* gene is found on chromosome 1 (https://medlineplus.gov/genetics/chromosome/1/).

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