Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Mini Review

FH (fumarate hydratase)

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Identity

Hugo: FH
Location: 1q42.1
Local order: Telomeric to RGS7, centromeric to KMO

DNA/RNA

Description

10 exons; 22,152 base pairs.

Transcription

1,1790 bp. Multiple RNA transcripts encode two FH gene products- one with a mitochondrial signal protein and the other lacking the signal sequence.

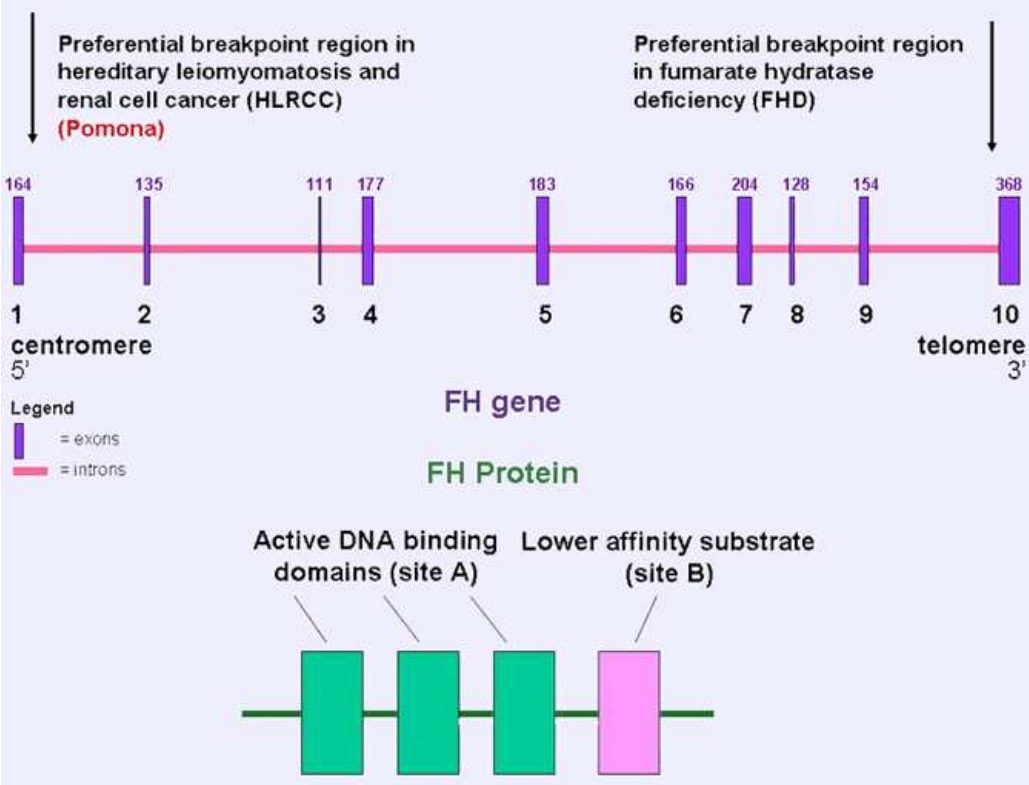


Fig1. Genomic structure of FH. Exons are represented by purple boxes with base pair number above and exon number below. Image is not drawn to scale.

Protein

Description

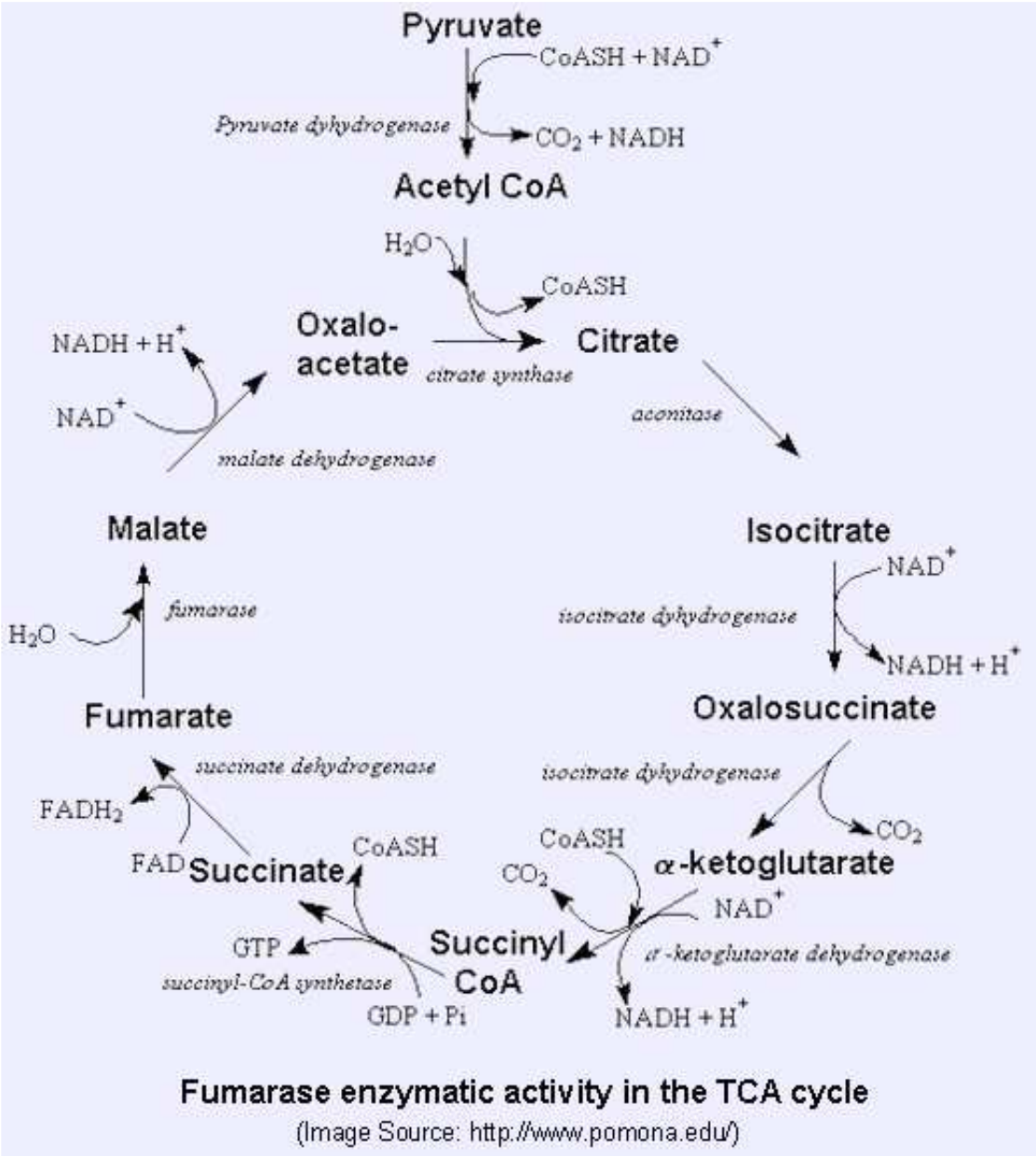
FH encodes the homotetrameric enzyme, fumarase, composed of 510 amino acids (molecular weight 54,637 Da); four identical subunits (50 kDa each); three active DNA binding sites (site A) and one lower affinity substrate (site B). Isoenzyme products have nearly identical amino acid sequences, but vary at the amino terminus.

Expression

Widespread in both fetal and adult tissues; most abundantly expressed in the skin, parathyroid, lymph and colon (four highest NCBI expression profiles). Tumors: expression in benign mesenchymal tissue (e.g., uterine, cutaneous); malignant tumors: leiomyosarcoma and papillary (type II) renal cell carcinoma.

Localisation

Mitochondrial and cytosolic. Subcellular localization is determined by presence or absence of a signal sequence at the amino terminus. Presence of the signal generates the mitochondrial-targeted form while absence of the signal results in the cytosolic form.



Fumarase enzymatic activity in the TCA cycle

(Image Source: http://www.pomona.edu/)

Function

Fumarase plays a key enzymatic role in fundamental metabolic pathways. The mitochondrial isoenzyme catalyzes conversion of fumarate to malate in the Krebs, or tricarboxylic acid (TCA) cycle, in which acetyl-CoA produces CO2, reduced electron carriers (FADH2 and NADH) and ATP. The cytosolic isoenzyme is involved with amino acid metabolism.

Mutations

Germinal

Germline mutations in FH are associated with two distinct conditions:
Homozygous and compound heterozygous mutations (e.g., missense and in-frame deletions) of the 3' end result in fumarate hydratase deficiency (FHD).
Heterozygous 5' mutations (e.g., nonsense, missense and deletions ranging from one base pair to whole gene) predispose individuals to somatic mutations in the normal allele leading to Hereditary leiomyomatosis and renal cell carcinoma/multiple cutaneous and uterine leiomyomatosis (HLRCC/MCUL1).

Somatic

Loss-of-heterozygosity of the wild type allele results in functional nullizygosity for fumarate hydratase. Malignant uterine and kidney tumors characteristic of HLRCC can subsequently develop.

Implicated in

Uterine Leiomyomata (UL)

Note: Synonyms include uterine fibroids, fibromas, myofibromas and myomas.

Disease

Benign mesenchymal tumors of the uterus.

Prognosis

Excellent, but may require surgical intervention as one-third of hysterectomies performed in the United States have a primary indication of UL.

Cytogenetics

UL rarely associated with cytologically visible 1q42 deletions.

Hybrid/Mutated Gene

Deletions of FH from structural rearrangements of 1q42.1.

Abnormal Protein

Presumed haploinsufficiency or functional null if mutation in other FH allele occurs.

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) / multiple cutaneous and uterine leiomyomatosis (MCUL1)

Note: Also known as Reed's syndrome.

Disease

HLRCC is an autosomal dominant disorder, characterized by smooth muscle tumors of the skin and uterus and/or kidney.

Prognosis

Good, if early diagnosis.

Abnormal Protein

Inherited mutations can predispose to somatic deletions resulting in truncated, non-functional or absent proteins.

Oncogenesis

FH acts as classic tumor suppressor gene in HLRCC/MCUL1. Genetic or epigenetic alterations in FH resulting from substitution, deletion or methylation follow the Knudson 'two hit' mechanism. The resulting functionally null state for fumarase can lead to subsequent oxidative tissue damage and tumorigenesis.

Fumarate hydratase deficiency (FHD)

Note: Synonymous with fumarase deficiency and fumaric aciduria.

Disease

Autosomal recessive condition characterized by delayed development, diminished muscle tone, and encephalopathy likely due to limited energy generation during development.

Prognosis

Poor. FHD is a rare condition, but reported cases indicate most affected individuals survive only several months while very few survive into their third decade.

Hybrid/Mutated Gene

The most common allelic abnormality is a 3 base pair-AAA insertion.

Abnormal Protein

Mutations near fumarase active site result in absent or truncated protein.

References

Wu M, Tzagoloff A. Mitochondrial and cytoplasmic fumarases in Saccharomyces cerevisiae are encoded by a single nuclear gene FUM1. J Biol Chem 1987;262:12275-12282.

Weaver T, Banaszak L. Crystallographic studies of the catalytic a second site in fumarase C from Escherichia coli. Biochemistry 1996;35:13955-13965.

Kiuru M, Launonen V, Hietala M, Aittomäki K, Vierimaa O, Salovaara R, Arola J, Pukkala E, Sistonen P, Herva R, Aaltonen LA. Familial cutaneous leiomyomatosis is a two-hit condition associated with renal cell cancer of characteristic histopathology. Am J Path 2001;159:825-829.

Launonen V, Vierimaa O, Kiuru M, Isola J, Roth S, Pukkala E, Sistonen P, Herva R, Aaltonen LA. Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc Natl Acad Sci USA 2001;98:3387-3392.

Barker KT, Bevan S, Wang R, Lu Y-J, Flanagan AM, Bridge JA, Fisher C, Finlayson CJ, Shipley J, Houlston RS. Low frequency of somatic mutations in FH/ multiple cutaneous leiomyomatosis gene in sporadic leiomyosarcomas and uterine leiomyomas. Brit J Cancer 2002;87:446-448.

Kiuru M, Lehtonen R, Arola J, Salovaara R, Järvinen H, Aittomäki K, Sjöberg J, Visakorpi T, Knuutila S, Isola J, Delahunt B, Herva R, Launonen V, Karhu A, Aaltonen LA. Few FH mutations in sporadic counterparts of tumor types observed in hereditary leiomyomatosis and renal cell cancer families. Cancer Res 2002;62:4554-4557.

Tomlinson IPM, Alam NA, Rowan AJ, Barclay E, Jaeger EEM, Kelsell D, Leigh I, Gorman P, Lamlum H, Rahman S, Bevan S, Barker K, Kiuru M, Lehtonen R, Karhu A, Vilkki S, Laiho P, Eklund C, Vierimaa O, Aittomaki K, Hietala M, Sistonen P, Paetau A, Salovaara R, Herva R, Launonen V, Aaltonen LA. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nature Genet 2002;30:406-410.

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 EDA, Crone M, Wilkinson S, Camacho-Martinez F, Jablonska S, Ratnavel R, MacDonald A, Mann RJ, Grice K, Guillet G, Lewis-Jones MS, McGrath H, Seukeran DC, Morrison PJ, Fleming S, Rahman S, Kelsell D, Leigh I, Olpin S, Tomlinson IPM. Genetic and functional analyses of FH mutations in multiple cutaneous and uterine leiomyomatosis, hereditary leiomyomatosis and renal cancer, and fumarate hydratase deficiency. Hum Molec Genet 2003;12:1241-1252.

Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, Stewart L, Duray P, Tourre O, Sharma N, Choyoke P, Stratton P, Merino M, Walther MM, Linehan WM, Schmidt LS, Zbar B. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet 2003;73:95-106.

Gross KL, Panhuysen CIM, Kleinman MS, Goldhammer H, Jones ES, Nassery N, Stewart EA, Morton CC. Involvement of fumarate hydratase in nonsyndromic uterine leiomyomas: genetic linkage analysis and FISH studies. Genes Chromosomes Cancer 2004;41:183-190.

Stewart EA and Morton CC. The genetics of uterine leiomyomata. Obstet Gynecol 2006;107:917-921. (Review).

Vanharanta S, Pollard PJ, Lehtonen HJ, Laiho P, Sjöberg J, Leminen A, Aittomaki K, Arola J, Kruhoffer M, Orntoft TF, Tomlinson IP, Kiuru M, Arango D, Aaltonen LA. Distinct expression profile in fumarate-hydratase-deficient uterine fibroids. Hum Mol Genet 2006;15:97-103.

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