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

<table>
<thead>
<tr>
<th>Description</th>
<th>10 exons; 22,152 base pairs.</th>
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<tr>
<td>Transcription</td>
<td>1,1790 bp. Multiple RNA transcripts encode two FH gene products- one with a mitochondrial signal protein and the other lacking the signal sequence.</td>
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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.
**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.

- **Cyto genetics**
  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 tumorigensis.

**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**


This article should be referenced as such: