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Gene Section
Mini Review

FHIT (fragile histidine triad)

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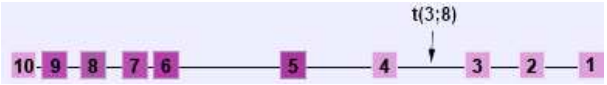
Identity

Hugo: FHIT
Location: 3p14.2

DNA/RNA



Depiction of the more than 1.67 Mb FHIT gene genomic locus with coding exons 5 through 9 (dark purple) and untranslated exons 1-4 and 10 (light purple). The position of the familial kidney cancer associated chromosome translocation is also shown.

Description

The FHIT gene spans more than 1.6 Mb of genomic DNA and is composed of 10 exons.

Transcription

The FHIT gene encodes a 1.1 kb mRNA which is expressed at low levels in most tissue types. FHIT encompasses the common fragile site FRA3B, where carcinogen-induced damage can lead to deletions, translocations and subsequent aberrant transcripts. Aberrant transcripts from this gene have been found in about half of all esophageal carcinomas, stomach carcinomas, and other carcinomas.

Pseudogene

A pseudogene, with sequences nearly identical to the 5¹UTR of FHIT, is located on chromosome 1.

Protein

Description

FHIT encodes a 147 amino acid (16.8 kDa) protein that can be phosphorylated at tyrosine 114 by Src family proteins.

Expression

Fhit is expressed at low to moderate levels in most tissue types, with kidney and liver expressing the highest steady state levels.

Localisation

Fhit is primarily located in the cytosol, but is also found in the mitochondria.

Function

Fhit protein is a tumor suppressor with reduced or no expression in many types of cancer. Fhit expression is more frequently lost in cancers of individuals with familial mutations causing deficiency in DNA repair genes such as BRCA1 and BRCA2 and MSH2. In vitro Fhit acts as a hydrolase that cleaves diadenosine triphosphate (Ap3A) to ADP and AMP. The Fhit-Ap3A enzyme-substrate complex appears to be the tumor suppressor signal. Restoration of Fhit expression in Fhit-deficient cancer cells causes death by apoptosis, involving the intrinsic caspase pathway, in cancer-derived cells and in tumor xenografts.

Homology

Fhit is similar to a yeast enzyme, diadenosine tetraphosphate (Ap4A) hydrolase and is a member of the large HIT family of proteins characterized by the histidine triad motif, HxHxHxx (where x is a hydrophobic residue).

Mutations

Note: The following FHIT polymorphisms have been described:
524 A/G (exon 6) silent
545 G/A (exon 6) silent
626 C/T (exon 7) silent
651 G/T (exon 8) valine to phenylalanine
656 T/C (exon 8) silent

Several intronic splice regions

Somatic

No bona fide somatic point mutations thus far confirmed.

Implicated in

Various types of cancer

Disease

Loss of expression occurs in more than 60% of human cancers; loss is very early in some cancers such as lung cancer. In a large, 4 generation family, a balanced translocation between FHIT (in intron 3) at 3p14.2 and TRC8, a patched related gene, at chromosome 8q24 is associated with bilateral, multifocal clear cell kidney carcinoma. Also, microsatellite loci within the FHIT gene were shown to be closely linked to a gene that contributes to susceptibility to familial prostate cancer.

Prognosis

There are numerous reports of association of Fhit loss with specific prognostic or other clinical features of specific types of cancer.

Cytogenetics

The FHIT locus is involved in translocations and deletions in some fraction of many types of cancer, likely due to the recombinogenicity of the fragile region within FHIT and subsequent selective growth or survival advantage of cells with reduced Fhit protein expression.

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