Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Mini Review

GGH (gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)

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Identity

Other names: Conjugase; GH; FPGH

HGNC (Hugo): GGH

Location: 8q12.3

DNA/RNA

Description

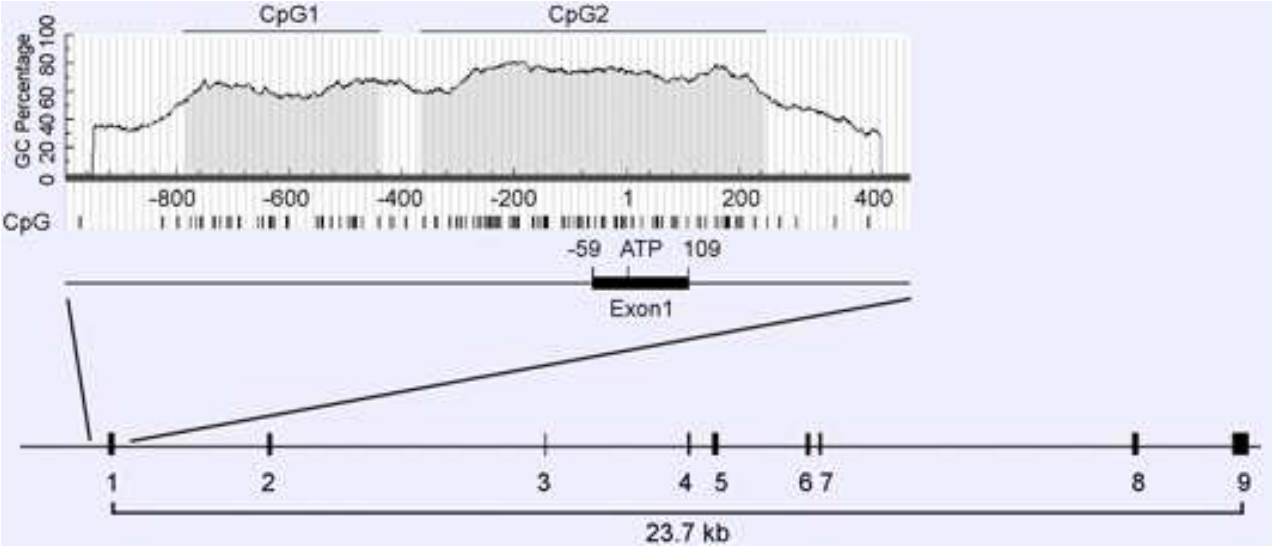
The GGH gene is 23,749 bp in length, consisting of 9 exons.

Transcription

The sequence upstream of exon 1 consists of a promoter-like GC-rich region and a number of putative cis active elements; there is no TATA sequence. There are 2 CpG islands in the region extending from the GGH promoter through the first exon and into intron 1. Methylation of both CpG is associated with significantly reduced GGH mRNA expression.

Pseudogene

None identified.



Genomic structure of GGH and CpG islands in the GGH promoter region. Two CpG islands in the GGH 5' promoter region extend into intron 1. The CpG1 and CpG2 regions (shaded areas) are indicated relative to the A of the translation start codon defined as nucleotide +1.

Protein

Description

The cDNA encodes a 318-amino acid protein. Catalytically essential residues, Cys-110 and His-220, are located in the center of a large l-shaped cleft that is closed at one end and open at the other. The N-terminal 24 residues are likely a leader sequence that mediates translocation of GGH into the endoplasmic reticulum for secretion.

Expression

Wide. Expressions are high in tissues such as liver, kidney, and placenta, and are relatively low in spleen, lung, small intestine, and peripheral blood leukocytes, as determined by Northern blot and RT-PCR analyses.

Localisation

Lysosome (primarily intracellular location), secreted, extracellular space, melanosome.

Function

GGH catalyzes the removal of gamma-linked polyglutamates, including folylpoly-gamma-glutamates and antifolylpoly-gamma-glutamates, including MTX polyglutamates.

Homology

Human GGH encodes a deduced amino acid sequence 67% identical to that of the rat enzyme. While human GGH primarily functioned as an exopeptidase, rat Ggh showed exclusively endopeptidase activity, cleaving the innermost gamma-glutamyl linkage.

Mutations

Germinal

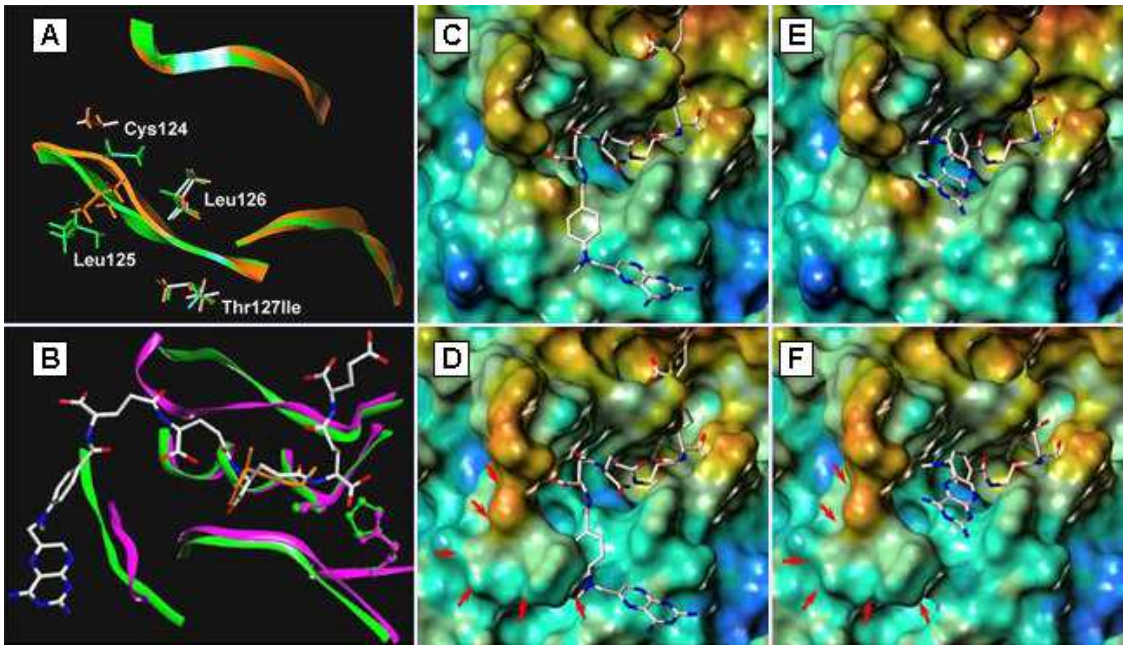
GGH SNP 452C -->T (rs11545078) alters the molecular surface conformation at the catalytic cleft-tail, and reduces binding affinity with long-chain MTXPG, but not short-chain MTXPG, in acute lymphoblastic leukemia (ALL) cells. However, the side effects of MTX in inflammatory bowel disease were not associated with GGH SNP 452C -->T, indicating a different genetic regulation between cancer and normal cells in response to MTX treatment. Caucasians (10%) were found to have a significantly higher frequency of 452C -->T variant allele than African-Americans (4.4%) and Japanese (5.6%).

Rheumatoid arthritis patients with homozygous variant allele of GGH -401C -->T had stronger GGH activity.

GGH promoter SNP -124T G (rs11545076) is associated with a stepwise increase in DNA uracil content, might modulate the risk of carcinogenesis.

Somatic

GGH promoter SNP -401C -->T (rs3758149) is associated with higher GGH expression and better response to platinum-based neoadjuvant chemotherapy in patients with cervical cancer.



Structure modeling of wild-type and T127I variant GGH. (A) Comparison of local structure of wild-type GGH (green) versus the T127I variant (orange). The structure of T127I GGH model is superimposed onto that of wild-type GGH. The local backbone structures of open tail end, loop 123-128, 74-79 and beta 9 168-173, are depicted as green (GGH) or orange (T127I) ribbons. The side chain overlapping four residues from Cys124 to Thr127 is also represented in green (GGH) and orange (T127I). (B) The crystal structure of carbamoyl-phosphate synthetase (eCPS) variant H353N (magenta) and glutamine thioester (orange) complex was used to superimpose onto the complex of GGH (green) and $MTXPG_5$ substrate by least-squares fitting of a-carbons of 20 residues around the active site. Docking models: (C) wild-type GGH with $MTXPG_5$; (D) T127I variant with $MTXPPG_5$; (E) wild-type GGH with $MTXPG_2$; (F) T127I variant with $MTXPG_2$. Docking models are shown at the end of the cleft-tail. The arrows indicate protrusions of the region at the surface of residues Cys124 and Leu125.

Implicated in

Childhood acute lymphoblastic leukemia (ALL)

Note

GGH activity is directly related to GGH mRNA expression in acute lymphoblastic leukemia (ALL) cells in patients with a wildtype germline GGH genotype, and methylation of entire GGH promoter region (seen in leukemia cells from approximately 15% of patients with nonhyperdiploid B-lineage ALL) is associated with significantly reduced GGH mRNA expression and catalytic activity and with significantly higher accumulation of MTX polyglutamates in ALL cells.

Cytogenetics

Chromosomal gain can alter the concordance of germline genotype and cancer cell phenotypes. GGH activities in somatic cells were concordant with germline genotypes, whereas activities in leukemia cells were determined by chromosomal number and whether the acquired chromosomes contained a wildtype or variant allele. Leukemia cells that had acquired an additional chromosome containing a wildtype GGH allele had significantly lower accumulation of methotrexate polyglutamates.

Colorectal cancer

Note

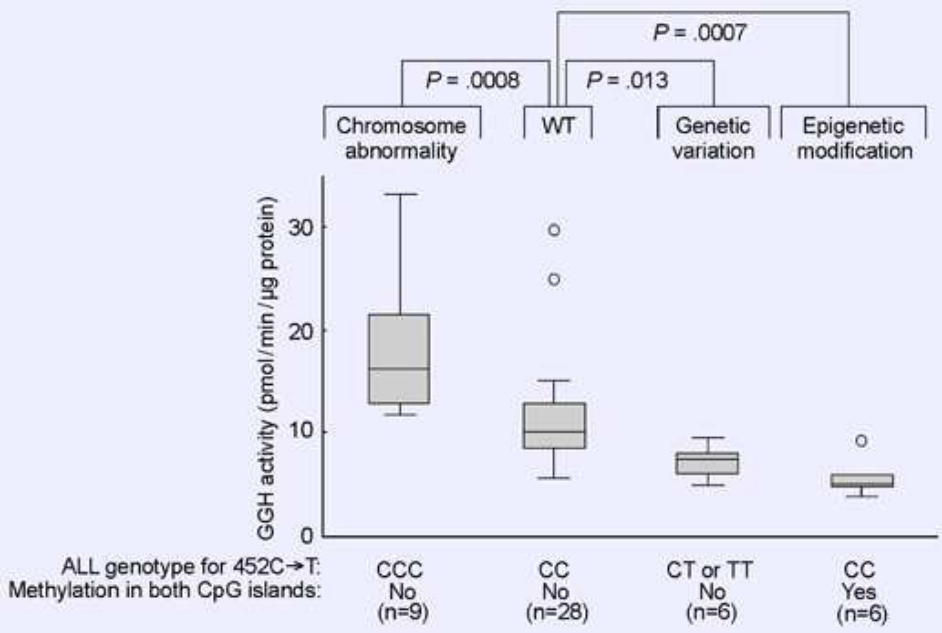
Low expression of gamma-glutamyl hydrolase (GGH) is strongly associated with CpG island methylator phenotype ($CIMP^+$) in colorectal cancer (CRC), and $CIMP^+$-related clinicopathological and molecular features. Trends for inverse association between GGH expression and the concentration of folate intermediates were also observed. $CIMP^+$ CRC is associated with low expression of GGH, suggesting involvement of the folate pathway in the development and/or progression of this phenotype.

5-fluorouracil (5-FU) plus leucovorin (LV) is a standard chemotherapy regimen for colorectal cancer. Downregulation of GGH by siRNA increased cellular sensitivity to 5-fluoro-2'-deoxyuridine (FdUrd)-combined with leucovorin (LV). These results suggest that FPGS and GGH expression levels in tumors are determinants of the efficacy of LV in enhancing the antitumor activity of 5-fluorouracil (5-FU).

Pulmonary neuroendocrine tumors

Note

Undetectable GGH protein expression is correlated with good prognosis in patients with pulmonary neuroendocrine tumors.



GGH activity in human leukemia cells is regulated by epigenetic modification, genetic polymorphisms and karyotypic abnormalities, which collectively determine interindividual differences in GGH activity and influence MTXPG accumulation in leukemia cells.

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