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Gene Section
Review

GSTA1 (glutathione S-transferase alpha 1)

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Abstract

Review on GSTA1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: GST2, GSTA1-1, GTH1

HGNC (Hugo): GSTA1

Location: 6p12.2

Local order

Between the LOC647169 (similar to glutathione transferase) and GSTA6P (glutathione S-transferase alpha 6 pseudogene) (according to PubMed).

Note

The GSTA1 gene is composed of 7 exons spanning a region of 12487 bases.

DNA/RNA

Note

The human alpha class genes are located in a cluster on chromosome 6p12 and comprise five functional genes (GSTA1, GSTA2, GSTA3, GSTA4, GSTA5) and seven pseudogenes (Morel et al., 2002).

Description

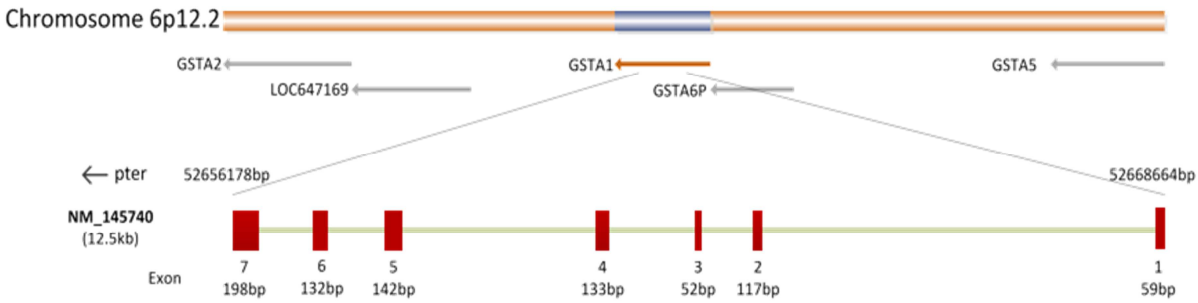
The GSTA1 gene is approximately 12 kb in length and is closely flanked by other alpha class gene sequences. The complete sequence of the 1,7-kb intergenic region between exon 7 of an upstream pseudogene and exon 1 of the GSTA1 gene has been determined (Suzuki et al., 1993).

Transcription

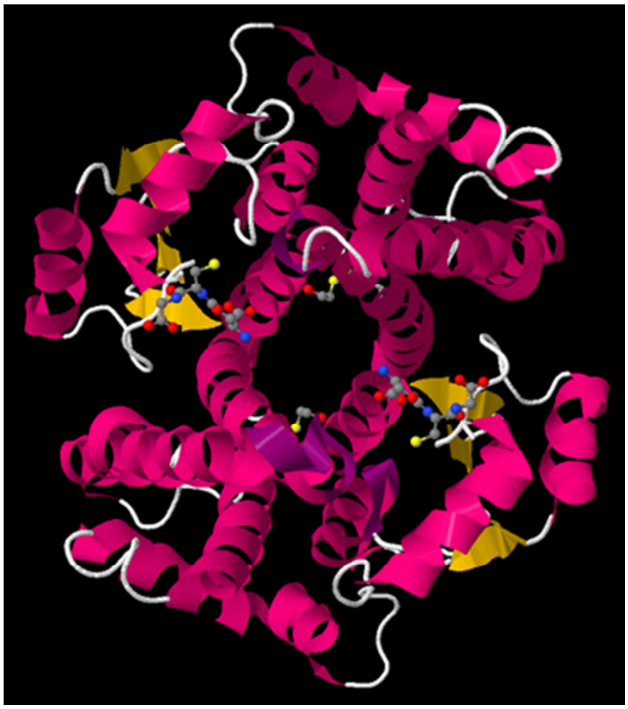
The 1276-nucleotide transcript encodes a protein of 222 amino acid residues.

Pseudogene

An additional gene that encodes an uncharacterized Alpha class GST has been identified. The protein derived from this gene would have 19 amino acid substitutions compared with the GSTA1 isoenzyme. Several pseudogenes with single-base and/or complete exon deletions have been identified, but no reverse-transcribed pseudogenes have been detected (Suzuki et al., 1993).



GSTA1 gene. The GSTA1 gene spans a region of 12,5 kb composed of the seven exons (red) and six introns (green). Exons 1, 2, 3, 4, 5, 6 and 7 are 59 bp, 117 bp, 52 bp, 133 bp, 142 bp, 132 bp and 198 bp in length, respectively.



Crystal structure of human glutathione transferase (GST) A1-1 in complex with glutathione. Adapted from PDB (Grahn et al., 2006).

Polymorphisms: GSTA1 has a functional three apparently linked single nucleotide polymorphisms (SNPs) in an SP1-responsive element within the proximal promoter (G-52A, C-69T and T-567G), plus at least four SNPs further upstream and a silent SNP A-375G. Two variants, GSTA1*A (-567T, -69C,-52G) and GSTA1*B (-67G, -69T, -52A), have been named according to the linked functional SNPs. Specifically, these substitutions result in differential expression with lower transcriptional activation of variant GSTA1*B than common GSTA1*A allele. It has been suggested that this genetic variation can change an individual's susceptibility to carcinogens and toxins, as well as, affect the efficacy of some drugs (Coles and Kadlubar, 2003). In addition, the linkage disequilibrium between GSTA1*A/GSTA1*B and GSTA2G335C (Ser112Thr) has been shown in Caucasians: specifically, GSTA1*A/GSTA2C335 (Thr112) and GSTA1*B/GSTA2G335 (Ser112) (Ning et al., 2004). It seems that the higher hepatic expression of GSTA1 enzyme in homozygous GSTA1 individuals is associated with the lower hepatic expression of GSTA2 in GSTA2C335 (Thr112) individuals (Coles et al., 2001a; Ning et al., 2004). Other haplotypes within this nomenclature but including SNPs C-115T, T-631G, and C-1142G also have been proposed (Bredschneider et al., 2002; Guy et al., 2004). Polymorphisms upstream of G-52C seem to have little effect on GSTA1 expression (Morel et al., 2002).

Protein

Note

Glutathione S-transferase A1 is N-terminally processed.

Amino acids: 222.

Calculated molecular mass: 25,63 kDa.

Description

The active GSTA1-1 enzyme is a homodimer, with each subunit containing a GSH-binding site (G-site) and a second adjacent hydrophobic binding site for the electrophilic substrate (H-site) (Wilce and Parker, 1994).

The C-terminal region of GSTA1-1 contributes to the catalytic and noncatalytic ligand-binding functions of the enzyme, while the conserved G-site is located in the N-terminal domain (Balogh et al., 2009).

Protein flexibility and dynamics in a molten globule-active site including the C-terminal α9 helix and the protruding ends of the α4-α5 helices result in achieving remarkable catalytic promiscuity of GSTA1-1 (Wu and Dong, 2012; Honaker et al., 2013). It has been proposed that the α9 helix may function as a mobile gate to the active-site cavity, controlling substrate access and product release.

Structure determination and refinement of human alpha class glutathione transferase A1-1, and a comparison with the MU and PI class enzymes. Adapted from PDB (Sinning et al., 1993).

Expression

GSTA1-1 is highly expressed (as mRNA and protein) in liver, intestine, kidney, adrenal gland, pancreas and testis, while expression in a wide range of tissues is low (Hayes and Pulford, 1995; Coles et al., 2001a). Both positive and negative regulatory regions are present in the 5` noncoding region of GSTA1, including a polymorphic SP1-binding site within the proximal promoter. Binding of the transcription factor AP1 has been suggested as a common mechanism for up-regulation of GSTs (Hayes and Pulford, 1995). The results of recent study also implied the role of a Kelch-like ECH-associated protein 1 (Keap1)-dependent signaling pathway for the induction of the constitutive GSTA1 expression during epithelial cell differentiation (Kusano et al., 2008). Regarding GSH-dependent Δ^5-Δ^4 isomerase activity of this class of enzyme, it has been shown that steroidogenic factor 1 (SF-1) is involved in regulation of expression of GSTA genes (Matsumura et al., 2013). Aberrant overexpression has been observed in various malignancies such as colorectal (Hengstler et al., 1998) and lung cancer (Carmichael et al., 1988), while decrease in alpha class GSTs has been observed in stomach and liver tumors (Howie et al., 1990). A detailed recent review on GSTA1 can be found in Wu and Dong, 2012.

Localisation

Cytosolic.

Function

Human GSTA1-1 enzyme catalyzes the GSH-dependent detoxification of electrophiles showing highly promiscuous substrate selectivity for many structurally unrelated chemicals, including environmental carcinogens (e.g. benzo(a)pyrene diol epoxides), several alkylating chemotherapeutic agents (such as busulfan, chlorambucil, melphalan, phosphoramide mustard, cyclophosphamide, thiotepa), as well as, steroids and products of lipid degradation. GSTA1-1 is the most highly expressed GST of the liver and could therefore, be critical for "systemic" detoxification of electrophilic xenobiotics including carcinogens and drugs (Coles and Kadlubar, 2005).

In addition to enzymatic detoxification, GSTA1 acts as modulator of mitogen-activated protein kinase (MAPK) signal transduction pathway via a mechanism involving protein-protein interactions. Namely, GSTA1 forms complexes with c-Jun N-terminal kinase (JNK), modifying JNK activation during cellular stress (Adnan et al., 2012).

Thus, it is possible that GSTA1 confer drug resistance by two distinct means: by direct inactivation (detoxification) of chemotherapeutic drugs and by acting as inhibitors of MAPK pathway.

Homology

The alpha class GSTs is showing strong intra-class sequence similarity (Balogh et al., 2009).

Mutations

Germinal

None described so far.

Somatic

36 mutations (COSMIC): 26 substitution-missense, 4 substitution-nonsense, 5 substitution-coding silent, 1 unknown type.

Implicated in

Colorectal cancer

Note

Regarding the role of GSTA1 polymorphism in the risk of colorectal cancer, the results of epidemiological studies are still inconclusive. Several studies showed that GSTA1*B genotype (low hepatic expression) is associated with increased susceptibility to colorectal cancer, which imply the possible inefficient hepatic detoxification of food-derived carcinogen metabolite N-acetoxy-PhIP (Coles et al., 2001b; Sweeney et al., 2002). In contrast, meta-analysis of Economopoulos representing the pooled analysis of four studies (1648 cases, 2039 controls) does not confer this association.

Breast cancer

Note

The role of GSTA1 polymorphism in breast cancer risk was mainly based on investigation on response to chemotherapeutic drugs in these patients. In breast cancer patients on cyclophosphamide containing chemotherapy carriers of GSTA1*B/*B genotype showed significantly reduced five years risk of death in comparison to GSTA1*A homozygous carriers. This association was likely caused by decreased detoxification of the therapeutic metabolites of cyclophosphamide in GSTA1*B/*B patients (Sweeney et al., 2003).

Bladder cancer

Note

Recent investigation indicates that the GSTA1-low activity genotype in combination with the GSTM1-null genotype significantly increases the risk of bladder cancer in smokers (Matic et al., 2013). In addition, it seems that GSTA1 polymorphism may influence vulnerability to oxidative DNA damage, thereby contributing to the malignant potential of transitional cell carcinoma (Savic-Radojevic et al., 2013).

Myeloid leukemia

Note

Aberant overexpression of both GSTA1 and GSTA2 proteins was found in blast cells derived from acute myeloid leukemia patients, showing resistance to doxorubicin in vitro (Sargent et al., 1999). In addition, GSTA1 and CYP39A1 (member of cytochrome P450 family) polymorphisms were found to be associated with pharmacokinetics of busulfan, which is used in preparative regimens prior to stem cell transplantation in pediatric patients (ten Brink et al., 2013).

Prostate cancer

Note

Genetic variants of GSTA1 and GSTT1 may modify prostate cancer risk, especially among smokers (Komiya et al., 2005).

Asthma

Note

Genetic alterations in GST enzymes may influence the detoxification of environmental toxic substances in airway and increase the risk of asthma.

Thus, it has been shown that subjects with at least one allele -69T in the GSTA1 genotype have an increased risk of asthma (Polimanti et al., 2010).

References

Carmichael J, Forrester LM, Lewis AD, Hayes JD, Hayes PC, Wolf CR. Glutathione S-transferase isoenzymes and glutathione peroxidase activity in normal and tumour samples from human lung. Carcinogenesis. 1988 Sep;9(9):1617-21

Howie AF, Forrester LM, Glancey MJ, Schlager JJ, Powis G, Beckett GJ, Hayes JD, Wolf CR. Glutathione S-transferase and glutathione peroxidase expression in normal and tumour human tissues. Carcinogenesis. 1990 Mar;11(3):451-8

Sinning I, Kleywegt GJ, Cowan SW, Reinemer P, Dirr HW, Huber R, Gilliland GL, Armstrong RN, Ji X, Board PG. Structure determination and refinement of human alpha class glutathione transferase A1-1, and a comparison with the Mu and Pi class enzymes. J Mol Biol. 1993 Jul 5;232(1):192-212

Suzuki T, Johnston PN, Board PG. Structure and organization of the human alpha class glutathione S-transferase genes and related pseudogenes. Genomics. 1993 Dec;18(3):680-6

Wilce MC, Parker MW. Structure and function of glutathione S-transferases. Biochim Biophys Acta. 1994 Mar 16;1205(1):1-18

Hayes JD, Pulford DJ. The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit Rev Biochem Mol Biol. 1995;30(6):445-600

Hengstler JG, Böttger T, Tanner B, Dietrich B, Henrich M, Knapstein PG, Junginger T, Oesch F. Resistance factors in colon cancer tissue and the adjacent normal colon tissue: glutathione S-transferases alpha and pi, glutathione and aldehyde dehydrogenase. Cancer Lett. 1998 Jun 5;128(1):105-12

Sargent JM, Williamson C, Hall AG, Elgie AW, Taylor CG. Evidence for the involvement of the glutathione pathway in

drug resistance in AML. Adv Exp Med Biol. 1999;457:205-9

Coles BF, Morel F, Rauch C, Huber WW, Yang M, Teitel CH, Green B, Lang NP, Kadlubar FF. Effect of polymorphism in the human glutathione S-transferase A1 promoter on hepatic GSTA1 and GSTA2 expression. Pharmacogenetics. 2001a Nov;11(8):663-9

Coles B, Nowell SA, MacLeod SL, Sweeney C, Lang NP, Kadlubar FF. The role of human glutathione S-transferases (hGSTs) in the detoxification of the food-derived carcinogen metabolite N-acetoxy-PhIP, and the effect of a polymorphism in hGSTA1 on colorectal cancer risk. Mutat Res. 2001b Oct 1;482(1-2):3-10

Bredschneider M, Klein K, Mürdter TE, Marx C, Eichelbaum M, Nüssler AK, Neuhaus P, Zanger UM, Schwab M. Genetic polymorphisms of glutathione S-transferase A1, the major glutathione S-transferase in human liver: consequences for enzyme expression and busulfan conjugation. Clin Pharmacol Ther. 2002 Jun;71(6):479-87

Morel F, Rauch C, Coles B, Le Ferrec E, Guillouzo A. The human glutathione transferase alpha locus: genomic organization of the gene cluster and functional characterization of the genetic polymorphism in the hGSTA1 promoter. Pharmacogenetics. 2002 Jun;12(4):277-86

Sweeney C, Coles BF, Nowell S, Lang NP, Kadlubar FF. Novel markers of susceptibility to carcinogens in diet: associations with colorectal cancer. Toxicology. 2002 Dec 27;181-182:83-7

Coles BF, Kadlubar FF. Detoxification of electrophilic compounds by glutathione S-transferase catalysis: determinants of individual response to chemical carcinogens and chemotherapeutic drugs? Biofactors. 2003;17(1-4):115-30

Sweeney C, Ambrosone CB, Joseph L, Stone A, Hutchins LF, Kadlubar FF, Coles BF. Association between a glutathione S-transferase A1 promoter polymorphism and survival after breast cancer treatment. Int J Cancer. 2003 Mar 1;103(6):810-4

Guy CA, Hoogendoorn B, Smith SK, Coleman S, O'Donovan MC, Buckland PR. Promoter polymorphisms in glutathione-S-transferase genes affect transcription. Pharmacogenetics. 2004 Jan;14(1):45-51

Ning B, Wang C, Morel F, Nowell S, Ratnasinghe DL, Carter W, Kadlubar FF, Coles B. Human glutathione S-transferase A2 polymorphisms: variant expression, distribution in prostate cancer cases/controls and a novel form. Pharmacogenetics. 2004 Jan;14(1):35-44

Coles BF, Kadlubar FF. Human alpha class glutathione S-transferases: genetic polymorphism, expression, and susceptibility to disease. Methods Enzymol. 2005;401:9-42

Komiya Y, Tsukino H, Nakao H, Kuroda Y, Imai H, Katoh T. Human glutathione S-transferase A1, T1, M1, and P1 polymorphisms and susceptibility to prostate cancer in the Japanese population. J Cancer Res Clin Oncol. 2005 Apr;131(4):238-42

Grahn E, Novotny M, Jakobsson E, Gustafsson A, Grehn L, Olin B, Madsen D, Wahlberg M, Mannervik B, Kleywegt GJ. New crystal structures of human glutathione transferase A1-1 shed light on glutathione binding and the conformation of the C-terminal helix. Acta Crystallogr D Biol Crystallogr. 2006 Feb;62(Pt 2):197-207

Kusano Y, Horie S, Shibata T, Satsu H, Shimizu M, Hitomi E, Nishida M, Kurose H, Itoh K, Kobayashi A, Yamamoto M, Uchida K. Keap1 regulates the constitutive expression of GST A1 during differentiation of Caco-2 cells. Biochemistry. 2008 Jun 10;47(23):6169-77

Balogh LM, Le Trong I, Kripps KA, Tars K, Stenkamp RE, Mannervik B, Atkins WM. Structural analysis of a glutathione transferase A1-1 mutant tailored for high catalytic efficiency with toxic alkenals. Biochemistry. 2009 Aug 18;48(32):7698-704

Economopoulos KP, Sergentanis TN. GSTM1, GSTT1, GSTP1, GSTA1 and colorectal cancer risk: a comprehensive meta-analysis. Eur J Cancer. 2010 Jun;46(9):1617-31

Polimanti R, Piacentini S, Moscatelli B, Pellicciotti L, Manfellotto D, Fuciarelli M. GSTA1, GSTO1 and GSTO2 gene polymorphisms in Italian asthma patients. Clin Exp Pharmacol Physiol. 2010 Aug;37(8):870-2

Adnan H, Antenos M, Kirby GM. The effect of menadione on glutathione S-transferase A1 (GSTA1): c-Jun N-terminal kinase (JNK) complex dissociation in human colonic adenocarcinoma Caco-2 cells. Toxicol Lett. 2012 Oct 2;214(1):53-62

Wu B, Dong D. Human cytosolic glutathione transferases: structure, function, and drug discovery. Trends Pharmacol Sci. 2012 Dec;33(12):656-68

Honaker MT, Acchione M, Zhang W, Mannervik B, Atkins WM. Enzymatic detoxication, conformational selection, and the role of molten globule active sites. J Biol Chem. 2013 Jun 21;288(25):18599-611

Matic M, Pekmezovic T, Djukic T, Mimic-Oka J, Dragicevic D, Krivic B, Suvakov S, Savic-Radojevic A, Pljesa-Ercegovac M, Tulic C, Coric V, Simic T. GSTA1, GSTM1, GSTP1, and GSTT1 polymorphisms and susceptibility to smoking-related bladder cancer: a case-control study. Urol Oncol. 2013 Oct;31(7):1184-92

Matsumura T, Imamichi Y, Mizutani T, Ju Y, Yazawa T, Kawabe S, Kanno M, Ayabe T, Katsumata N, Fukami M, Inatani M, Akagi Y, Umezawa A, Ogata T, Miyamoto K. Human glutathione S-transferase A (GSTA) family genes are regulated by steroidogenic factor 1 (SF-1) and are involved in steroidogenesis. FASEB J. 2013 Aug;27(8):3198-208

Savic-Radojevic A, Djukic T, Simic T, Pljesa-Ercegovac M, Dragicevic D, Pekmezovic T, Cekerevac M, Santric V, Matic M. GSTM1-null and GSTA1-low activity genotypes are associated with enhanced oxidative damage in bladder cancer. Redox Rep. 2013;18(1):1-7

ten Brink MH, van Bavel T, Swen JJ, van der Straaten T, Bredius RG, Lankester AC, Zwaveling J, Guchelaar HJ. Effect of genetic variants GSTA1 and CYP39A1 and age on busulfan clearance in pediatric patients undergoing hematopoietic stem cell transplantation. Pharmacogenomics. 2013 Nov;14(14):1683-90

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