Published in final edited form as:
Pharmacogenet Genomics. 2012 August ; 22(8): 646–651. doi:10.1097/FPC.0b013e3283527c02.

PharmGKB summary - very important pharmacogene information for *GSTT1*

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Abstract

This PharmGKB summary briefly discusses the very important pharmacogene *GSTT1* and its variants that can influence drug responses. A fully interactive version of this short review, with links to individual paper annotations and population descriptions can be found at http://www.pharmgkb.org/vip/PA183.

Background

GSTT1 encodes the phase II metabolizing enzyme glutathione s-transferase theta. It is located in a gene cluster with *GSTT2* and *GSTT2B* paralogues on chromosome 22 [1]. Molecular evolution studies suggest that *GSTT* or theta is the oldest of the families of *GST*s since it is present in lower organisms: other *GST* families may have arisen from duplication and diversification of an ancestral *GSTT* gene [1].

The GSTT1 protein catalyzes the conjugation of reduced glutathione to electrophilic moeities of xenobiotics, drugs and endogenous compounds such as peroxidized lipids [2]. The conjugated products – often after further metabolism – are more soluble, allowing them to be more readily eliminated from the body. Important pharmacological substrates include etoposide, busulfan, platinum anticancer drugs, as well as the anti-tuberculosis drugs isoniazid, rifampicin and pyrazinamide [3-7] and several important industrial chemicals including butadiene, dichloromethane and trichloroethylene [8-10].

Human *GSTT1* is constitutively expressed in the liver and can be induced by the consumption of cruciferous vegetables [1, 11]. *GSTT1* is also expressed in the gastrointestinal tract [12], erythroid cells [13], kidney [14] and lung [15]. Most studies of inducers of GSTT1 has been performed in animal models where NSAIDs, phenobarbital, alpha-angelicalactone, alpha-tocopherol, coumarin and oltipraz induced expression of *GSTT1* in the liver or gastrointestinal tract of rodents [1, 16-18]. In rats, some inducers were gender specific, with indole-3-carbinol and phenobarbital significant inducers of *GSTT1* in males and coumarin the most potent inducer in females [18].

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GSTT1 variation

The most studied variant of *GSTT1* is the null variant, also referred to as *GSTT1*0* or *GSTT1* negative, that results from the complete or partial deletion of the gene (see below for more details). A large number of studies have examined the possible role of *GSTT1* null in the etiology of cancer (colorectal [19], oral [20], prostate [21], hepatocellular [22], lung [23] [20729793], ovarian [24], head and neck [25], gastric [16886896] and others). Individuals lacking *GSTT1* may be less able to detoxify environmental xenobiotics and thus be at elevated risk for cellular damage and resultant cancer. However for many cancers, studies have shown conflicting results. For example, a large meta-analysis combining forty-five studies and over twelve thousand cases, suggested that evidence for *GSTT1* involvement in lung cancer was weak [20729793]. In contrast, the *GSTT1* null variant may be protective against certain cancers including bladder cancer, because GSTT1-dependent conjugation of xenobiotics such as the industrial chemical trichloroethylene produces compounds with increased toxicity [26]. Other epidemiological studies suggest a role for *GSTT1* in inflammatory airway diseases such as asthma and emphesema [27, 28]. The pharmacogenomics (PGx) of *GSTT1* null and how it may influence drug response, particularly for anti-neoplastic drug and drug-induced liver injury (DILI) is therefore of great interest (discussed further below).

The related glutathione s-transferase mu gene, *GSTM1* also has a null variant [18056202]. Since *GSTM1* is also involved in drug and xenobiotic detoxification various studies have examined the effects of deletion of *GSTM1* null alone and in combination with *GSTT1* null for both disease risk and drug response [16886896, 18666253, 20214588].

Relatively few studies have reported single nucleotide variants in *GSTT1* [29-32], and only one study has reported a PGx association [33] (see table 1). More variants are listed in dbSNP (103 as of 10/2011). However, most of these variants have not been studied,. The majority of *GSTT1* SNPs are present at very low frequencies, and may be population specific; some population studies have not seen polymorphisms [29, 30, 32, 34, 35]. In a pharmacogenetic study of multiple myeloma patients treated with thalidomide, heterozygotes for the 5'UTR −182C>T variant (rs4630) had lower neurotoxicity [33]. Another study of head and neck cancer patients treated with paclitaxel found no association of this variant with toxicity or survival [36], although patients with two or more variants, including GSTT1 rs4620 as well as variants in CYP2C8, ABCB1, GSTP1 and ERCC1, did have significantly higher overall survival [36].

Important variants

GSTT1 null

The *GSTT1*0* or null variant represents the complete or partial deletion of the *GSTT1* gene. Alignment of the Genbank reference sequence of the GSTT1 deletion/junction region sequence AF240785.1 [37] shows the deletion between chr22:24,343,276 - chr22:24,397,528 on the GRCh37/hg19 build of the human genome. The frequency of *GSTT1* null varies widely in different populations: approximately 50-60% in Asians, 15% in White populations, 15-20% in Blacks or African Americans, and less than 10% in Hispanic populations (reviewed in [1]).

Possible associations with various cancers have been investigated with mixed results. There are several HuGE reviews (colorectal [19], oral [20], prostate [21], hepatocellular [22], lung [23], ovarian [24], head and neck [25] and bladder cancer [26]).

The *GSTT1* null variant is a risk factor for coronary artery disease in Type 2 diabetic patients, especially among smokers [38]. Other epidemiological studies have suggested a role in inflammatory airway diseases such as asthma and emphesema [27, 28].

In a study of samples from White subjects from the Coriell collection, *GSTT1* null was found to be in linkage disequilibrium with a deletion of *GSTT2B* [39]. Cells with the *GSTT2B* deletion also had lower expression of *GSTT2* and a reduced capacity for glutathione conjugation [39]. This linkage may account for some of the discord between studies of cancer risk.

GSTT1 null and drug toxicity

Since *GST*s are expressed in the liver and since glutathione is involved in the detoxification of many drugs, several studies have examined the effect of the *GSTT1* null genotype as well as other *GST* family members, *GSTM1* and *GSTP1*, on adverse drug reactions including DILI and allergic responses in the skin.

The *GSTT1* null variant is associated with an increased risk of allergic skin reactions to a variety of drugs, including NSAIDs and antibiotics [40]. Although not significant for the GSTT1 null variant alone, the double null of *GSTT1* and *GSTM1* is also associated with increased risk for DILI particularly with NSAIDs and cardiovascular drugs [18666253, 20214588]. Neither *GSTT1* null nor *GSTM1* null genotype alone could predict susceptibility to tacrine-induced hepatotoxicity. However, the combination of *GSTT1* null and *GSTM1* null variant is associated with increased hepatotoxicity in patients with Alzheimer disease taking tacrine [41]. The double null mutations of *GSTT1* and *GSTM1* are also associated with troglitazone-induced [42] and alcohol-induced liver injury [43]. However, *GSTT1* null is not associated with DILI after treatment with anti-tuberculosis drugs [44, 45].

GSTT1 null and response to antineoplastic agents in cancer treatment

Several antineoplastic drugs are metabolized by *GST*s, including platinum drugs, anthracyclines, vinca alkaloids, cyclophosphamide and epipodophylotoxins [5, 6, 46-50]. Cytotoxic antineoplastic drugs may contribute to cell death by depleting cellular glutathione, allowing toxic products to build up and damage DNA. A few studies have examined the role of *GSTT1* in antineoplastic drug toxicity. In Hodgkin lymphoma patients treated with anthracyline regimens, the *GSTT1* null variant was associated with increased toxicity [51]. A study of large B-cell lymphoma patients treated with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone showed increased toxicity in individuals with the *GSTT1* null variant [52]. The *GSTT1* null variant is associated with increased likelihood of adverse events, including cognitive impairment in pediatric medulloblastoma patients treated with cisplatin, cyclophosphamide, and vincristine [53]. The null genotype of *GSTT1* is also associated with rate of early death after the initiation of chemotherapy in Japanese AML patients treated with cytarabine, mercaptopurine, prednisone and daunorubicin [54]. However *GSTT1* null is not associated with cardiac damage after anthracycline exposure (pediatric ALL) [55], platinum-based toxicity (mesothelioma) [56], or toxicity with fluorouracil-based regimens (colorectal cancer) [57].

The *GSTT1* and *GSTM1* double null variant has also been associated with decreased event free survival in NHL, adult AML and R-CHOP–treated B-cell lymphoma and increased relapse in pediatric ALL [17454600, 12351375, 20303013, 14607752].

Conclusions

Studies of various cancers and treatments and the *GSTT1* null variant have shown mixed and contradictory results (see Table 2). While the lack of *GSTT1* may increase the efficacy of some cytotoxic drugs towards cancer cells due to a reduction in their elimination from the cell, it could also be hypothesized that *GSTT1* null individuals might have a poorer prognosis. Further studies of focused populations with defined treatments may aid in elucidating any risk or benefit from identifying *GSTT1* variants prior to treatment.

Acknowledgments

This work is supported by the NIH/NIGMS (R24 GM61374).

References

1. Landi S. Mammalian class theta GST and differential susceptibility to carcinogens: a review. Mutat Res. 2000; 463(3):247–83. [PubMed: 11018744]
2. Josephy PD, Kent M, Mannervik B. Single-nucleotide polymorphic variants of human glutathione transferase T1-1 differ in stability and functional properties. Arch Biochem Biophys. 2009; 490(1): 24–9. [PubMed: 19664997]
3. 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. [PubMed: 8770536]
4. Kim SD, Lee JH, Hur EH, Kim DY, Lim SN, Choi Y, et al. Influence of GST gene polymorphisms on the clearance of intravenous busulfan in adult patients undergoing hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011; 17(8):1222–30. [PubMed: 21215809]
5. Wheeler HE, Gamazon ER, Stark AL, O'Donnell PH, Gorsic LK, Huang RS, et al. Genome-wide meta-analysis identifies variants associated with platinating agent susceptibility across populations. Pharmacogenomics J. 2011
6. Moyer AM, Sun Z, Batzler AJ, Li L, Schaid DJ, Yang P, et al. Glutathione pathway genetic polymorphisms and lung cancer survival after platinum-based chemotherapy. Cancer Epidemiol Biomarkers Prev. 2010; 19(3):811–21. [PubMed: 20200426]
7. Teixeira RL, Morato RG, Cabello PH, Muniz LM, Moreira Ada S, Kritski AL, et al. Genetic polymorphisms of NAT2, CYP2E1 and GST enzymes and the occurrence of antituberculosis drug-induced hepatitis in Brazilian TB patients. Mem Inst Oswaldo Cruz. 2011; 106(6):716–24. [PubMed: 22012226]
8. Thier R, Wiebel FA, Hinkel A, Burger A, Bruning T, Morgenroth K, et al. Species differences in the glutathione transferase GSTT1-1 activity towards the model substrates methyl chloride and dichloromethane in liver and kidney. Arch Toxicol. 1998; 72(10):622–9. [PubMed: 9851677]
9. Bruning T, Lammert M, Kempkes M, Thier R, Golka K, Bolt HM. Influence of polymorphisms of GSTM1 and GSTT1 for risk of renal cell cancer in workers with long-term high occupational exposure to trichloroethene. Arch Toxicol. 1997; 71(9):596–9. [PubMed: 9285043]
10. Zhao C, Vodicka P, Sram RJ, Hemminki K. DNA adducts of 1,3-butadiene in humans: relationships to exposure, GST genotypes, single-strand breaks, and cytogenetic end points. Environ Mol Mutagen. 2001; 37(3):226–30. [PubMed: 11317340]
11. Navarro SL, Chang JL, Peterson S, Chen C, King IB, Schwarz Y, et al. Modulation of human serum glutathione S-transferase A1/2 concentration by cruciferous vegetables in a controlled feeding study is influenced by GSTM1 and GSTT1 genotypes. Cancer Epidemiol Biomarkers Prev. 2009; 18(11):2974–8. [PubMed: 19900941]
12. de Bruin WC, Wagenmans MJ, Peters WH. Expression of glutathione Stransferase alpha, P1-1 and T1-1 in the human gastrointestinal tract. Jpn J Cancer Res. 2000; 91(3):310–6. [PubMed: 10760690]
13. Wang L, Groves MJ, Hepburn MD, Bowen DT. Glutathione S-transferase enzyme expression in hematopoietic cell lines implies a differential protective role for T1 and A1 isoenzymes in

erythroid and for M1 in lymphoid lineages. Haematologica. 2000; 85(6):573–9. [PubMed: 10870112]

14. Simic T, Savic-Radojevic A, Pljesa-Ercegovac M, Matic M, Mimic-Oka J. Glutathione S-transferases in kidney and urinary bladder tumors. Nat Rev Urol. 2009; 6(5):281–9. [PubMed: 19424176]
15. Butler MW, Hackett NR, Salit J, Strulovici-Barel Y, Omberg L, Mezey J, et al. Glutathione S-transferase copy number variation alters lung gene expression. Eur Respir J. 2011; 38(1):15–28. [PubMed: 21349909]
16. Van Lieshout EM, Tiemessen DM, Roelofs HM, Peters WH. Nonsteroidal anti-inflammatory drugs enhance glutathione S-transferase theta levels in rat colon. Biochim Biophys Acta. 1998; 1381(3): 305–11. [PubMed: 9729437]
17. Whittington A, Vichai V, Webb G, Baker R, Pearson W, Board P. Gene structure, expression and chromosomal localization of murine theta class glutathione transferase mGSTT1-1. Biochem J. 1999; 337(Pt 1):141–51. [PubMed: 9854036]
18. Sherratt PJ, Manson MM, Thomson AM, Hissink EA, Neal GE, van Bladeren PJ, et al. Increased bioactivation of dihaloalkanes in rat liver due to induction of class theta glutathione S-transferase T1-1. Biochem J. 1998; 335(Pt 3):619–30. [PubMed: 9794803]
19. Cotton SC, Sharp L, Little J, Brockton N. Glutathione S-transferase polymorphisms and colorectal cancer: a HuGE review. Am J Epidemiol. 2000; 151(1):7–32. [PubMed: 10625170]
20. Zhang ZJ, Hao K, Shi R, Zhao G, Jiang GX, Song Y, et al. Glutathione Stransferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1) null polymorphisms, smoking, and their interaction in oral cancer: a HuGE review and meta-analysis. Am J Epidemiol. 2011; 173(8):847–57. [PubMed: 21436184]
21. Mo Z, Gao Y, Cao Y, Gao F, Jian L. An updating meta-analysis of the GSTM1, GSTT1, and GSTP1 polymorphisms and prostate cancer: a HuGE review. Prostate. 2009; 69(6):662–88. [PubMed: 19143011]
22. White DL, Li D, Nurgalieva Z, El-Serag HB. Genetic variants of glutathione S-transferase as possible risk factors for hepatocellular carcinoma: a HuGE systematic review and meta-analysis. Am J Epidemiol. 2008; 167(4):377–89. [PubMed: 18065725]
23. Raimondi S, Paracchini V, Autrup H, Barros-Dios JM, Benhamou S, Boffetta P, et al. Meta- and pooled analysis of GSTT1 and lung cancer: a HuGE-GSEC review. Am J Epidemiol. 2006; 164(11):1027–42. [PubMed: 17000715]
24. Coughlin SS, Hall IJ. Glutathione S-transferase polymorphisms and risk of ovarian cancer: a HuGE review. Genet Med. 2002; 4(4):250–7. [PubMed: 12172391]
25. Geisler SA, Olshan AF. GSTM1, GSTT1, and the risk of squamous cell carcinoma of the head and neck: a mini-HuGE review. Am J Epidemiol. 2001; 154(2):95–105. [PubMed: 11447041]
26. Simic T, Mimic-Oka J, Savic-Radojevic A, Opacic M, Pljesa M, Dragicevic D, et al. Glutathione S-transferase T1-1 activity upregulated in transitional cell carcinoma of urinary bladder. Urology. 2005; 65(5):1035–40. [PubMed: 15882759]
27. Minelli C, Wei I, Sagoo G, Jarvis D, Shaheen S, Burney P. Interactive effects of antioxidant genes and air pollution on respiratory function and airway disease: a HuGE review. Am J Epidemiol. 2011; 173(6):603–20. [PubMed: 21343247]
28. Minelli C, Granell R, Newson R, Rose-Zerilli MJ, Torrent M, Ring SM, et al. Glutathione-S-transferase genes and asthma phenotypes: a Human Genome Epidemiology (HuGE) systematic review and meta-analysis including unpublished data. Int J Epidemiol. 2010; 39(2):539–62. [PubMed: 20032267]
29. Moyer AM, Salavaggione OE, Hebbring SJ, Moon I, Hildebrandt MA, Eckloff BW, et al. Glutathione S-transferase T1 and M1: gene sequence variation and functional genomics. Clin Cancer Res. 2007; 13(23):7207–16. [PubMed: 18056202]
30. Agundez JA, Ladero JM. Glutathione S-transferase GSTT1 and GSTM1 allozymes: beyond null alleles. Pharmacogenomics. 2008; 9(3):359–63. [PubMed: 18303971]
31. Tatewaki N, Maekawa K, Katori N, Kurose K, Kaniwa N, Yamamoto N, et al. Genetic variations and haplotype structures of the glutathione S-transferase genes, GSTT1 and GSTM1, in a Japanese patient population. Drug Metab Pharmacokinet. 2009; 24(1):118–26. [PubMed: 19252342]

32. Piacentini S, Polimanti R, Porreca F, Martinez-Labarga C, De Stefano GF, Fuciarelli M. GSTT1 and GSTM1 gene polymorphisms in European and African populations. Mol Biol Rep. 2011; 38(2):1225–30. [PubMed: 20563854]
33. Cibeira MT, de Larrea CF, Navarro A, Diaz T, Fuster D, Tovar N, et al. Impact on response and survival of DNA repair single nucleotide polymorphisms in relapsed or refractory multiple myeloma patients treated with thalidomide. Leuk Res. 2011; 35(9):1178–83. [PubMed: 21435719]
34. Alexandrie AK, Rannug A, Juronen E, Tasa G, Warholm M. Detection and characterization of a novel functional polymorphism in the GSTT1 gene. Pharmacogenetics. 2002; 12(8):613–9. [PubMed: 12439221]
35. Matsuno K, Kubota T, Matsukura Y, Ishikawa H, Iga T. Genetic analysis of glutathione S-transferase A1 and T1 polymorphisms in a Japanese population. Clin Chem Lab Med. 2004; 42(5): 560–2. [PubMed: 15202795]
36. Grau JJ, Caballero M, Campayo M, Jansa S, Vargas M, Alos L, et al. Gene single nucleotide polymorphism accumulation improves survival in advanced head and neck cancer patients treated with weekly paclitaxel. Laryngoscope. 2009; 119(8):1484–90. [PubMed: 19504558]
37. Sprenger R, Schlagenhaufer R, Kerb R, Bruhn C, Brockmoller J, Roots I, et al. Characterization of the glutathione S-transferase GSTT1 deletion: discrimination of all genotypes by polymerase chain reaction indicates a trimodular genotype-phenotype correlation. Pharmacogenetics. 2000; 10(6): 557–65. [PubMed: 10975610]
38. Manfredi S, Calvi D, del Fiandra M, Botto N, Biagini A, Andreassi MG. Glutathione S-transferase T1- and M1-null genotypes and coronary artery disease risk in patients with Type 2 diabetes mellitus. Pharmacogenomics. 2009; 10(1):29–34. [PubMed: 19102712]
39. Zhao Y, Marotta M, Eichler EE, Eng C, Tanaka H. Linkage disequilibrium between two high-frequency deletion polymorphisms: implications for association studies involving the glutathione-S transferase (GST) genes. PLoS Genet. 2009; 5(5):e1000472. [PubMed: 19424424]
40. Ates NA, Tursen U, Tamer L, Kanik A, Derici E, Ercan B, et al. Glutathione S-transferase polymorphisms in patients with drug eruption. Arch Dermatol Res. 2004; 295(10):429–33. [PubMed: 14740231]
41. Simon T, Becquemont L, Mary-Krause M, de Waziers I, Beaune P, Funck-Brentano C, et al. Combined glutathione-S-transferase M1 and T1 genetic polymorphism and tacrine hepatotoxicity. Clin Pharmacol Ther. 2000; 67(4):432–7. [PubMed: 10801254]
42. Watanabe I, Tomita A, Shimizu M, Sugawara M, Yasumo H, Koishi R, et al. A study to survey susceptible genetic factors responsible for troglitazone-associated hepatotoxicity in Japanese patients with type 2 diabetes mellitus. Clin Pharmacol Ther. 2003; 73(5):435–55. [PubMed: 12732844]
43. Oniki K, Ueda K, Hori M, Mihara S, Marubayashi T, Nakagawa K. Glutathione-S-transferase (GST) M1 null genotype and combined GSTM1 and GSTT1 null genotypes as a risk factor for alcoholic mild liver dysfunction. Clin Pharmacol Ther. 2007; 81(5):634–5. [PubMed: 17438538]
44. Roy B, Chowdhury A, Kundu S, Santra A, Dey B, Chakraborty M, et al. Increased risk of antituberculosis drug-induced hepatotoxicity in individuals with glutathione S-transferase M1 'null' mutation. J Gastroenterol Hepatol. 2001; 16(9):1033–7. [PubMed: 11595069]
45. Huang YS, Su WJ, Huang YH, Chen CY, Chang FY, Lin HC, et al. Genetic polymorphisms of manganese superoxide dismutase, NAD(P)H:quinone oxidoreductase, glutathione S-transferase M1 and T1, and the susceptibility to drug-induced liver injury. J Hepatol. 2007; 47(1):128–34. [PubMed: 17400324]
46. Ramos DL, Gaspar JF, Pingarilho M, Gil OM, Fernandes AS, Rueff J, et al. Genotoxic effects of doxorubicin in cultured human lymphocytes with different glutathione S-transferase genotypes. Mutat Res. 2011; 724(1-2):28–34. [PubMed: 21640195]
47. Rocha JC, Cheng C, Liu W, Kishi S, Das S, Cook EH, et al. Pharmacogenetics of outcome in children with acute lymphoblastic leukemia. Blood. 2005; 105(12):4752–8. [PubMed: 15713801]
48. Dirven HA, van Ommen B, van Bladeren PJ. Involvement of human glutathione S-transferase isoenzymes in the conjugation of cyclophosphamide metabolites with glutathione. Cancer Res. 1994; 54(23):6215–20. [PubMed: 7954469]

49. Yang J, Bogni A, Schuetz EG, Ratain M, Dolan ME, McLeod H, et al. Etoposide pathway. Pharmacogenet Genomics. 2009; 19(7):552–3. [PubMed: 19512958]
50. He Y, Hoskins JM, McLeod HL. Copy number variants in pharmacogenetic genes. Trends Mol Med. 2011; 17(5):244–51. [PubMed: 21388883]
51. Lourenco GJ, Lorand-Metze I, Delamain MT, Miranda EC, Kameo R, Metze K, et al. Polymorphisms of glutathione S-transferase mu 1, theta 1, and pi 1 genes and prognosis in Hodgkin lymphoma. Leuk Lymphoma. 2010; 51(12):2215– 21. [PubMed: 20977336]
52. Cho HJ, Eom HS, Kim HJ, Kim IS, Lee GW, Kong SY. Glutathione-S-transferase genotypes influence the risk of chemotherapy-related toxicities and prognosis in Korean patients with diffuse large B-cell lymphoma. Cancer Genet Cytogenet. 2010; 198(1):40–6. [PubMed: 20303013]
53. Barahmani N, Carpentieri S, Li XN, Wang T, Cao Y, Howe L, et al. Glutathione S-transferase M1 and T1 polymorphisms may predict adverse effects after therapy in children with medulloblastoma. Neuro Oncol. 2009; 11(3):292–300. [PubMed: 18952980]
54. Naoe T, Tagawa Y, Kiyoi H, Kodera Y, Miyawaki S, Asou N, et al. Prognostic significance of the null genotype of glutathione S-transferase-T1 in patients with acute myeloid leukemia: increased early death after chemotherapy. Leukemia. 2002; 16(2):203–8. [PubMed: 11840286]
55. Rajic V, Aplenc R, Debeljak M, Prestor VV, Karas-Kuzelicki N, Mlinaric-Rascan I, et al. Influence of the polymorphism in candidate genes on late cardiac damage in patients treated due to acute leukemia in childhood. Leuk Lymphoma. 2009; 50(10):1693–8. [PubMed: 19863340]
56. Erculj N, Kovac V, Hmeljak J, Dolzan V. The influence of platinum pathway polymorphisms on the outcome in patients with malignant mesothelioma. Ann Oncol. 2011
57. Boige V, Mendiboure J, Pignon JP, Loriot MA, Castaing M, Barrois M, et al. Pharmacogenetic assessment of toxicity and outcome in patients with metastatic colorectal cancer treated with LV5FU2, FOLFOX, and FOLFIRI: FFCD 2000-05. J Clin Oncol. 2010; 28(15):2556–64. [PubMed: 20385995]

Table 1

Single nucleotide variants in *GSTT1* reported in the literature.

Identifier	Common name	Phenotype [PMID]	Frequency [PMID]
	5' FR (-714)C>T		0.01 T Coriell AA (Moyer et al, 2007)[18056202][27] 0.015 T Coriell CA (Moyer et al, 2007)[18056202]
	5' FR (-476)G>A		0.008 A Coriell CA (Moyer et al, 2007)[18056202][27]
	5' FR (-295)C>G		0.01 G Coriell AA (Moyer et al, 2007)[18056202][27]
	5' FR (-56)G>C		0.32 C Coriell AA (Moyer et al, 2007)[18056202][27] 0.008 C Coriell MA (Moyer et al, 2007)[18056202]
rs4630 C>T	5' UTR (−182)C>T	CT had lower neurotoxicity with thalidomide in MM [21435719]. Not assoc with survival in head and neck cancer patients treated with paclitaxel [19504558]	0.03 C (Grau et al) [19504558][36]
rs1130990 C>T	Leu5Leu		0.01 T Coriell AA (Moyer et al, 2007)[18056202][27] 0.023 T Coriell CA (Moyer et al, 2007)[18056202] 0.008 T Coriell MA (Moyer et al, 2007)[18056202] 0/100 Coriell HCA (Moyer et al, 2007) [18056202]
	IVS 1 (-178)C>A		0.01 A Coriell AA (Moyer et al, 2007)[18056202][27]
	IVS 1 (-151)G>A		0.01 A Coriell AA (Moyer et al, 2007)[18056202][27]
	IVS 1 (-24)C>T		0.029 T Coriell AA (Moyer et al, 2007)[18056202][27]
	IVS 1 (-14)T>A		0.008 A Coriell MA (Moyer et al, 2007)[18056202] [27]
rs2266635	Ala21Thr		0/400 (Agundez et al, 2008)[18303971][30]
rs11550606	Leu30Pro		0/400 (Agundez et al, 2008)[18303971][30]
	Asp43Asn	Decreased protein [18303971]	0.01 A Coriell AA (Moyer et al, 2007)[18056202] [27]
rs17856199	Phe45Cys		0/400 (Agundez et al, 2008)[18303971][30]
	Exon 2 (177)C>T		0.008 T Coriell CA (Moyer et al, 2007)[18056202][27]

Identifier	Common name	Phenotype [PMID]	Frequency [PMID]
	Thr65Met	Decreased protein [18303971]	0.008 T Coriell MA (Moyer et al, 2007)[18056202][27] 0/300 Coriell AA, CA, HCA (Moyer et al, 2007)[18056202]
	IVS 2 (-13)C>T		0.136T Coriell AA (Moyer et al, 2007)[18056202][27] 0.008 T Coriell MA (Moyer et al, 2007)[18056202]
	Exon 3(225)G>A		0.01 A Coriell AA (Moyer et al, 2007)[18056202][27] 0.008 A Coriell MA (Moyer et al, 2007)[18056202]
rs11550605 A>C	GSTT1*B, Thr104Pro	Decreased protein [18303971]	0.01 (Alexandrie et al, 2002)[12439221][34] 0/400 (Moyer et al, 2007)[18056202] [27] 0/147 (Matsuno et al, 2004)[15202795][35] 0/317 (Piacentini et al, 2011) [20563854][32] 0/400 (Agundez et al, 2008)[18303971][30]
	Exon 4 G>x	Decreased protein [18303971]	0.008 T Coriell MA (Moyer et al, 2007)[18056202][27]
rs2266633	Asp141Asn		0/400 (Agundez et al, 2008)[18303971][30]
rs2266637 G>A	Val169Ile		0.126 A Coriell AA (Moyer et al, 2007)[18056202][27] 0.008 A Coriell MA (Moyer et al, 2007)[18056202]
rs2234953 G>A	Exon 4 Glu173Lys		0/86 (Piacentini et al, 2011) [20563854][32] 0/400 (Agundez et al, 2008)[18303971][30]
	IVS 4 (-87) del CCT		0.029 del Coriell AA (Moyer et al, 2007)[18056202] [27]
	Exon 5 (573) G>A		0.008 A Coriell MA (Moyer et al, 2007)[18056202] [27]
rs17850155 G>A	Exon 5 Lys228Lys		0/86 (Piacentini et al, 2011) [20563854][32]

numbering from Moyer et al, 2007)[18056202]

Abbreviations: MM, multiple myeloma; AA, African American; CA, Caucasian; HCA, Han Chinese; MA, Mexican American.

Table 2

GSTT1 null and response to antineoplastic agents.

Allele/genotype	Phenotype	Drugs	Population (study size, race/ethnicity)	PMID
GSTT1 null	decreased survival	cytarabine, mercaptopurine, prednisone and daunorubicin	Adult AML (n=193, Asian)	11840286 [54]
GSTT1 null	decreased event free survival	Not specified	NHL/ follicular lymphoma subtype (n=89, unknown race)	17454600
GSTT1 null	decreased event free survival	cyclophosphamide, doxorubicin and fluorouracil	Breast neoplasms (n=152, Multiple)	20459744
GSTT1 null	decreased overall survival	paclitaxel or docetaxel and carboplatin or cisplatin	Ovarian cancer (n=118, Asian)	19203783
GSTT1 null	decreased overall survival, progression free survival	fluorouracil and platinum compounds	Gastric cancer (n=134, unknown race)	19332728
GSTT1 null	increased toxicity	cisplatin, cyclophosphamide, and vincristine	Pediatric Medulloblastoma (n=42, Multiple)	18952980
GSTT1 null	increased toxicity	rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone	de novo diffuse large B-cell lymphoma (n=94, Asian)	20303013
GSTT1 null	increased toxicity, increased overall survival	anthracylines	Hodgkin lymphoma (n=125, unknown)	20977336
GSTT1 null	increased survival	Not specified	NHL/ follicular lymphoma subtype (n=112, multiple)	20029944
GSTT1 null	increased overall survival	platinum compounds, doxorubicin and ifosfamide	Osteosarcoma (n=30, Multiple races)	20577141
GSTT1 null	increased event free survival, increased progression free survival	mitomycin	Bladder cancer (n=282, Asian)	21045267
GSTT1 null	increased overall survival	Not specified	Gastric cancer (n=130, Asian)	21378360
GSTT1 present	increased likelihood of complete response	homoharringtonine, cytarabine, daunorubicin	AML (n=254, Asian)	18035413
GSTT1 present	decreased survival	platinum compounds	Non-small cell lung cancer (n=973, White)	20200426
GSTT1 null	is not associated with toxicity (cardiac damage)	anthracylines	Pediatric ALL (n=76, White)	19863340
GSTT1 null	is not associated with toxicity	fluorouracil-based regimens (FOLFOX/FOLFIRI)	Colorectal neoplasms (n=346, unknown race)	20385995
GSTT1 null	is not associated with toxicity	platinum compounds	Mesothelioma (n=133, White)	21765044
GSTT1 null	is not associated with toxic death *	doxorubicin and cytosine arabinoside	AML (n=98, White)	17671537
GSTT1 null	Is not associated with survival	daunorubicin, cytosine arabinoside, mitoxantrone	AML (n=139, White)	18207572
GSTT1 null	Is not associated with survival	Not specified	Colorectal neoplasms (n=315, Multiple races)	19748847

Allele/genotype	Phenotype	Drugs	Population (study size, race/ethnicity)	PMID
GSTT1 null	Is not associated with survival	oxaliplatin	Colorectal neoplasms (n=65, Multiple races)	20017670
GSTT1 null	Is not associated with survival	paclitaxel/docetaxel, cisplatin	Gastric cancer (n=200, Asian)	20331623
GSTT1 null	Is not associated with survival	cisplatin-based regimens	Gastric cancer (n=138, unknown race)	18443805
GSTT1 null	Is not associated with survival	fluorouracil, oxaliplatin	Colorectal neoplasms (n=107, Multiple races)	12072547
GSTT1 null	Is not associated with survival	cisplatin, paclitaxel	Ovarian Cancer (n=24, unknown race)	12851839
GSTT1 null	Is not associated with treatment associated secondary neoplasms	etoposide/teniposide	treatment-related AML or myelodysplastic syndrome following pediatric ALL (n=302, Multiple races)	10673738
GSTT1 and GSTM1 double null	decreased survival	Not specified	Adult AML (n=106, unknown race)	12351375
GSTT1 and GSTM1 double null	increased likelihood of relapse	doxorubicin, vincristine, prednisone, cyclophosphamide, asparaginase, mercaptopurine, methotrexate, etoposide, cytarabine	Pediatric ALL (n=82, Asian)	14607752
GSTT1 and GSTM1 double null	decreased event free survival	Not specified	NHL/ follicular lymphoma subtype (n=89, unknown race)	17454600
GSTT1 and GSTM1 double null	decreased event free survival	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone	de novo diffuse large B-cell lymphoma (n=60, Asian)	20303013

* the authors suggest that, with larger sample size, this association might be significant

Abbreviations: AML, acute myeloid leukemia; NHL, non-hodgkin lymphoma; ALL, precursor T-Cell lymphoblastic leukemia-lymphoma; FOLFOX, fluorouracil leucovorin and oxaliplatin; FOLFIRI, fluorouracil leucovorin and irinotecan.