Glutathione S-Transferase Theta 1 Gene Deletion and Risk of Acute Myeloid Leukemia[1]

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Abstract

Individuals with a homozygous deletion of the *glutathione S-transferase theta 1* (*GSTT1*) gene lack GSTT1 enzymatic detoxification of environmental carcinogens by conjugation with glutathione. The *GSTT1* gene deletion has been associated with carcinogen-induced chromosomal changes in lymphocytes, and some but not all epidemiological evidence has suggested that the *GSTT1* gene deletion may increase susceptibility to myelodysplasia. We conducted a case-control study to test whether individuals with an inherited homozygous deletion of the *GSTT1* gene are at increased risk of acute myeloid leukemia (AML). The *GSTT1* and GST mu 1 (*GSTM1*) genotypes were determined by PCR using lymphocyte or bone marrow DNA from 297 AML patients and 152 controls. AML patients were selected from Southwest Oncology Group clinical studies, and controls were identified by random digit dialing in Washington state. No association was observed between the *GSTT1* gene deletion and AML [race-adjusted odds ratio (OR), 0.94; 95% confidence interval (CI), 0.55–1.60] or between the *GSTM1* gene deletion and AML (race-adjusted OR, 1.26; 95% CI, 0.85–1.88). Patients with secondary AML had a slightly higher prevalence of the *GSTT1* and *GSTM1* gene deletions compared with *de novo* AML patients or controls, but this was consistent with chance. Exploratory analyses of AML cytogenetics suggested a few associations, *i.e.*, between the *GSTT1* gene deletion and trisomy 8, and between the *GSTM1* gene deletion and non-8 trisomies or inv(16). These results do not support the hypothesis that the *GSTT1* gene deletion is related to the incidence of AML.

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Introduction

Individuals with a homozygous deletion of the *GSTT1*[3] gene lack GSTT1 enzymatic conjugation of foreign compounds with glutathione. This results in diminished ability to detoxify a wide range of environmental carcinogens, including 1,3-butadiene, ethylene oxide, epoxybutanes, and monohalomethanes. For the solvent dichloromethane, on the other hand, functional GSTT1 conjugation can form mutagenic metabolites (1). Absence of GSTT1 activity in blood, corresponding to the *GSTT1* null genotype, has been associated with carcinogen-induced and background chromosomal changes in human lymphocytes (2). Myelodysplasia and AML are associated with exposure to chemicals such as benzene and chemotherapeutic alkylating agents. Because it can lead to a diminished ability to metabolize various environmental carcinogens, the *GSTT1* gene deletion may increase susceptibility to myelodysplasia or AML.

An epidemiological study in the United States observed that individuals with the *GSTT1* null genotype were at a 4-fold increased risk of developing a MDS, a clonal proliferative disorder of bone marrow that often progresses to AML (3). Recently, an epidemiological study in Japan observed that individuals with the *GSTT1* null genotype were at a 2–4-fold increased risk of developing *de novo* MDS, therapy-related AML, or AML with trilineage dysplasia (4). However, four studies in the United Kingdom, France, and Japan have failed to confirm these findings (5–8). The reasons for these discrepancies are unclear but may involve differences in racial or genetic background of the populations studied.

The primary objective of this study was to test the hypothesis that individuals with an inherited homozygous deletion of the *GSTT1* gene are at increased risk of AML. We conducted a study in which we compared the proportion of *GSTT1* null genotypes between a group of AML patients and a control group. As a secondary objective, the *GSTM1* gene deletion was evaluated for its association with AML risk and for possible interactions with the *GSTT1* gene deletion. Heterogeneity of risk according to clinical, morphological, and cytogenetic subtypes of AML was also explored.

Materials and Methods

Subject Selection. Cases were 297 AML patients registered during 1987–1995 in clinical studies conducted by the SWOG, a national clinical research group. Eligibility was restricted to patients from five studies (S8600, S8706, S9031, S9034, and S9129), which had similar eligibility criteria, except for some differences in age criteria (S8600: 15–65 years; S8706: 18–55 years; S9031: ≥56 years; S9034: 16–55 years; and S9129: ≥15

[3] The abbreviations used are: GSTT1, glutathione *S*-transferase theta 1; AML, acute myeloid leukemia; GSTM1, GST mu 1; MDS, myelodysplastic syndrome; SWOG, Southwest Oncology Group; FAB, French-American-British; OR, odds ratio; CI, confidence interval.

years). Bone marrow or peripheral blood samples were obtained at initial diagnosis before therapy for acute leukemia, except for administration of hydroxyurea to control high cell counts. Eligibility required normal hepatic and renal function and absence of any illness that would preclude the possibility of bone marrow transplantation or chemotherapy. Patients who developed AML after a previous diagnosis of MDS or after chemotherapy or radiotherapy for another condition were eligible.

From patients registered in these five studies ($n = 1638$), we excluded 251 patients without confirmation of AML by central histopathological review by the SWOG Leukemia Pathology Committee and 353 patients without an adequate quantity of DNA for analysis. From the remaining 1034 patients, we chose all who were residents of Washington state ($n = 44$) to promote comparability with a Washington-based control group and all remaining patients who had evaluable cytogenetics ($n = 227$). An additional 26 cases were chosen randomly.

Information was obtained from the SWOG database on age at AML diagnosis, sex, race, ethnic origin, place of residence, clinical onset (*de novo* or secondary), FAB morphological classification, and cytogenetics. All FAB classifications were centrally reviewed by the SWOG Leukemia Pathology Committee. All cytogenetic evaluations were made by SWOG-approved cytogenetics laboratories and were centrally reviewed by the SWOG Cytogenetics Committee.

Controls were 152 persons selected from a population-based control group enlisted during 1992–1995 in a large epidemiological study of anogenital cancer in western Washington (9) and for whom peripheral lymphocyte DNA samples were available. These persons were identified using random digit telephone dialing in the three-county area that includes Seattle. To be eligible as a control subject, one had to have a working telephone, be able to communicate, and have no history of anogenital cancer. A household census was successfully conducted for 94% of all residential phone numbers called. Seventy % of eligible controls that were contacted agreed to participate, and peripheral blood samples were obtained for DNA analysis from 84% of participants, in the prior study which enlisted these controls (9). From 507 controls with available DNA samples, 152 were chosen so as to have a similar distribution of race, sex, and age (in 5-year intervals) as the 297 AML cases. Written informed consent was obtained previously from all cases and controls. All research activities were approved by local institutional review.

Laboratory Methods. Genomic DNA was isolated from bone marrow and peripheral WBCs using a standard salt-precipitation method. To distinguish homozygous gene deletion from heterozygous deletion or non-deletion, a multiplex PCR assay was used that simultaneously amplifies the *GSTT1* and *GSTM1* genes (10). The PCR amplification was performed in a 25-μl reaction mixture that contained 100 ng of genomic DNA, 100 ng each of forward and reverse *GSTT1* primers, 100 ng each of forward and reverse *GSTM1* primers, 70 ng each of forward and reverse β-globulin primers, 20 mM Tris-HCl (pH 8.4), 50 mM KCl, 5 mM $MgCl_2$, 0.01% gelatin, 2.5 mM deoxynucleotide triphosphate, and 1 unit of Taq DNA polymerase (Boehringer Mannheim, Indianapolis, IN). After addition of 50 μl of mineral oil to prevent evaporation, a hot-start PCR was performed in a MJ Research PTC-100 thermal cycler. Coamplification of human β-globulin served as a positive control to ensure that a null genotype was attributable to the absence of the respective gene and not because of a PCR failure. Amplification of reaction mixtures without DNA from subjects was used as a negative control to check for potential contamination.

Table 1 Characteristics of cases and controls

	Cases ($n = 297$)				Controls ($n = 152$)			
	Mean	SD	Median	Range	Mean	SD	Median	Range
Age (yr)	53.8	16.8	59	16–88	53.5	16.5	59	18–78
		n		%		*n*		%
Sex								
Male		168		56.6		85		55.9
Female		129		43.4		67		44.1
Race								
White		265		89.2		141		92.8
Black		24		8.1		6		4.0
Native American		1		0.3		1		0.6
Asian		7		2.4		3		2.0
Unknown		0		0.0		1		0.6
Place of residence								
Washington state		44		14.8		152		100.0
Western United States[a]		137		46.1		0		0.0
Eastern United States		113		38.0		0		0.0
Unknown		3		1.0		0		0.0

[a] Excluding Washington state.

Statistical Methods. The principal measure of interest was the relative risk of AML for individuals with the *GSTT1* or *GSTM1* null genotype compared with individuals without the respective null genotype. This was estimated by computing ORs and 95% CIs using the logistic regression model, allowing for efficient control of confounding. AML cases from different geographic areas were compared to assess the extent of geographic heterogeneity of *GSTT1* or *GSTM1* null genotype prevalence. In exploratory analyses, ORs were estimated for the association between the *GSTT1* or *GSTM1* null genotype and specific subtypes of AML defined by clinical, morphological, or cytogenetic characteristics. Sample sizes were planned so as to have 80% power for detecting an OR of 2 for the association between the *GSTT1* gene deletion and AML or an OR of 1.5 for the association between the *GSTM1* gene deletion and AML.

Results

The case and control groups were very similar in race, age, and sex (Table 1). Cases ranged in age from 16 to 88 years, and controls ranged from 18 to 78 years. Eighty-nine % of cases and 93% of controls were white. All 152 controls and 44 (15%) cases were residents of Washington state. The remainder of cases came from 32 other United States states, with most from the West and the Midwest.

Sixteen % of cases had the *GSTT1* null genotype compared with 17% of controls (crude OR for risk of AML, 0.93; 95% CI, 0.55–1.58). The *GSTM1* null genotype was observed in 54% of cases and 49% of controls (crude OR, 1.18; 95% CI, 0.80–1.75). These estimates changed only slightly or not at all after adjusting for race, age, and/or sex. When the estimates did change, the slight amount of confounding was attributable solely to race. The race-adjusted OR for the association between the *GSTT1* null genotype and AML was 0.94 (95% CI, 0.55–1.60), and for the association between the *GSTM1* null genotype and AML, the race-adjusted OR was 1.26 (95% CI, 0.85–1.88; Table 2).

Subjects who had deletions of both *GSTT1* and *GSTM1* genes had a slightly greater risk of AML relative to subjects

Table 2 Race-adjusted ORs for association between *GSTT1* or *GSTM1* null genotype and AML, or subtypes of AML defined by clinical, morphological, or cytogenetic characteristics

Subjects	*GSTT1*			*GSTM1*		
	No. null/Total (%)	OR	95% CI	No. null/Total (%)	OR	95% CI
Controls	26/152 (17.1)	Reference		75/152 (49.3)	Reference	
AML cases	48/297 (16.2)	0.94	0.55–1.60	159/297 (53.5)	1.26	0.85–1.88
Clinical onset						
De novo	16/101 (15.8)	0.95	0.47–1.89	54/101 (53.5)	1.28	0.76–2.16
Secondary	7/35 (20.0)	1.11	0.42–2.89	21/35 (60.0)	1.80	0.82–3.94
Unknown	25/161 (15.5)	0.86	0.47–1.60	84/161 (52.2)	1.15	0.73–1.81
FAB subtype						
M0	4/17 (23.5)	1.18	0.32–4.31	6/17 (35.3)	0.71	0.24–2.16
M1	9/59 (15.3)	0.78	0.33–1.87	25/59 (42.4)	0.80	0.43–1.49
M2	15/101 (14.9)	0.83	0.41–1.68	62/101 (61.4)	1.74	1.03–2.95
M3	6/35 (17.1)	0.94	0.34–2.57	15/35 (42.9)	0.80	0.37–1.69
M4	6/45 (13.3)	0.74	0.28–1.96	30/45 (66.7)	2.34	1.13–4.82
M5	6/28 (21.4)	1.56	0.56–4.30	17/28 (60.7)	1.44	0.63–3.29
M6	0/4 (0.0)	0.00	0.00–4.86	1/4 (25.0)	0.31	0.03–3.06
Cytogenetics						
Normal	17/91 (18.7)	1.13	0.57–2.24	45/91 (49.5)	1.07	0.63–1.81
Abnormal	22/136 (16.2)	0.88	0.46–1.67	74/136 (54.4)	1.32	0.82–2.13
−5/5q-	1/13 (7.7)	0.26	0.03–2.53	6/13 (46.2)	0.95	0.30–3.05
−7/7q-	4/19 (21.1)	1.00	0.27–3.64	9/19 (47.4)	1.09	0.40–2.98
+8	8/26 (30.8)	2.17	0.82–5.71	12/26 (46.2)	0.94	0.40–2.21
Other trisomy	3/20 (15.0)	0.54	0.12–2.39	14/20 (70.0)	3.57	1.10–11.5
Abn(11q)	4/16 (25.0)	1.66	0.47–5.80	9/16 (56.3)	1.32	0.46–3.83
inv(16)	2/18 (11.1)	0.55	0.11–2.73	13/18 (72.2)	3.10	0.99–9.70
t(15;17)	6/29 (20.7)	1.16	0.42–3.24	12/29 (41.4)	0.76	0.34–1.74
Complex abnormality	3/11 (27.3)	1.22	0.26–5.67	6/11 (54.6)	1.63	0.44–6.04
Other abnormality	4/48 (8.2)	0.44	0.14–1.37	27/48 (55.1)	1.21	0.63–2.33

Table 3 Race-adjusted ORs for risk of AML associated with the joint presence of the *GSTT1* and *GSTM1* null genotypes

GSTT1 and *GSTM1* genotypes	Cases ($N = 297$) n (% of total)	Controls ($N = 152$) n (% of total)	OR	95% CI
Both null	25 (8.4)	11 (7.2)	1.42	0.64–3.17
Only *GSTT1* null	23 (7.7)	15 (9.9)	0.76	0.36–1.58
Only *GSTM1* null	134 (45.1)	64 (42.1)	1.17	0.76–1.80
Neither null	115 (38.7)	62 (40.8)	Reference	

who had neither gene deletion (race-adjusted OR, 1.42; 95% CI, 0.64–3.17) or compared with subjects who had only one of the *GSTT1* and *GSTM1* gene deletions (Table 3). There was no appreciable multiplicative interaction between *GSTT1* and *GSTM1* in relation to AML risk ($P = 0.39$).

Secondary AML was defined as AML preceded by chemotherapy, radiotherapy, or a MDS. A slightly higher proportion (20%) of secondary AML cases had the *GSTT1* null genotype compared with *de novo* cases (16%). Similarly, the *GSTM1* gene deletion had a somewhat greater association with secondary AML than with *de novo* AML. The race-adjusted OR for the association between the *GSTM1* null genotype and secondary AML was 1.80 (95% CI, 0.82–3.94), compared with 1.28 for *de novo* AML (95% CI, 0.76–2.16). Little variation was observed in the association between *GSTT1* and different FAB subtypes (Table 2). The *GSTM1* null genotype was associated with a 2-fold increased risk of FAB subtype M4 (95% CI, 1.13–4.82), but given the large number of statistical comparisons, this may also be a chance finding.

Cytogenetics were evaluable for 227 AML cases, of whom 40% had normal and 60% had abnormal cytogenetics. The most common specific abnormalities were t(15;17) (13% of evaluable cases), trisomy 8 (12%), −7/7q- (8%), inv(16) (8%), abn(11q) (7%), and −5/5q- (6%). In addition, 18 (8%) cases had a complex abnormality. The proportion of cytogenetically abnormal cases with deletions of *GSTT1* (16%) or *GSTM1* (55%) did not differ appreciably from controls (17 and 49%, respectively). Analyses of specific abnormalities suggested only a few associations, easily consistent with chance fluctuation. The *GSTT1* null genotype was associated with a 2-fold increased risk of AML with trisomy 8 (95% CI, 0.8–5.7), and the *GSTM1* null genotype was associated with a 3-fold increased risk of AML with non-8 trisomies (95% CI, 1.1–11.5) or inv(16) (95% CI, 1.0–9.7; see Table 2).

Discussion

This study found no evidence that either the *GSTT1* or *GSTM1* gene deletion is associated with the incidence of AML. These findings are compatible with four other studies (5–8) that failed to confirm findings of an increased risk of MDS (3, 4), therapy-related AML (4), and AML with dysplasia (4) associated with the *GSTT1* null genotype.

In the present study, the control group had a very similar prevalence of the *GSTT1* and *GSTM1* null genotypes compared with other populations. For example, the proportion of these controls who were *GSTT1* null (17%) or *GSTM1* null (49%),

and the proportion of white controls with the respective null genotypes (15 and 52%), corresponded closely to estimates from North Carolina, New England, and the United Kingdom (11–13). In 12 studies including >2000 white control subjects, the overall *GSTT1* and *GSTM1* null frequencies were 17 and 52%, respectively.

Secondary AML was a clinical entity of special interest because of its relation to genotoxic exposures and the MDSs. Approximately 30% of MDS cases culminate in AML, and 10–20% of AML cases have a preceding history of MDS. Sasai *et al.* (4) found an association between the *GSTT1* null genotype and *de novo* MDS (OR, 2.65; 95% CI, 1.27–5.52), therapy-related AML (OR, 4.62; 95% CI, 1.48–14.4), and AML with trilineage dysplasia (OR, 2.94; 95% CI, 1.07–8.07), but virtually none for AML without dysplasia (OR, 1.08; 95% CI, 0.34–3.43). Preudhomme *et al.* (7) found a modest association with wide confidence limits between the *GSTT1* null genotype and therapy-related MDS (OR, 1.94; 95% CI, 0.60–6.24) but virtually none for *de novo* MDS (OR, 1.13; 95% CI, 0.60–2.11). Basu *et al.* (5) found a weak association between the *GSTT1* null genotype and MDS compared with no association with AML. In the present study, data regarding *de novo* or secondary AML were available for only 136 (46%) cases. A slightly higher proportion of secondary leukemias ($n = 35$) had the *GSTT1* null genotype (20%) or the *GSTM1* null genotype (60%) compared with *de novo* cases (16 and 54%, respectively) or controls (17 and 49%, respectively), but these differences were well within the limits of chance.

Little heterogeneity was observed between the *GSTT1* or *GSTM1* gene deletions and risk of FAB subtypes or specific cytogenetic abnormalities. The data suggested possible associations between the *GSTT1* gene deletion and trisomy 8 and between the *GSTM1* gene deletion and non-8 trisomies or inv(16). These exploratory findings require verification with other data. Previous cytogenetic data for AML patients with known *GSTT1* and *GSTM1* genotypes are very sparse. In Preudhomme's study (7), the *GSTT1* null genotype was associated with a slightly increased risk of monosomy 7 (OR, 1.8) but not of trisomy 8.

The present study had a larger case group and more extensive cytogenetic data than any other study of this topic to date. The main results were relatively precise, with upper 95% confidence limits estimated <2 for the principal ORs of interest. This study also had several limitations that were common to other studies as well:

(*a*) Information on specific environmental exposures was not obtainable, and therefore interactions between *GSTT1* or *GSTM1* and known or potential GST substrates present in the environment could not be assessed. If a true association exists between GST and AML, it would be more easily detected in subpopulations with higher exposures to leukemogens that are GST substrates.

(*b*) Although there is little evidence to suggest that *GSTT1* or *GSTM1* genotype is of prognostic importance in AML, such a relationship may influence which AML patients were eligible for selection into this study, potentially biasing the results in either direction.

(*c*) Although confounding by race was controlled, population stratification of *GST* null genotype prevalence by genetic background cannot be excluded and may spuriously create or obscure an association.

(*d*) Although interaction between *GSTT1* and *GSTM1* in relation to AML risk was explored, considerably larger sample sizes would be needed for adequate power to detect interaction unless it were very large in magnitude.

(*e*) Identification of the most appropriate comparison group was difficult for this geographically diverse group of cases. Overall, however, there was no evidence in these data that geographic differences in *GSTT1* or *GSTM1* genotype frequency affected the results of this analysis.

The present study suggests that the *GSTT1* gene deletion is not associated with a substantially increased risk of AML in the general population. Two (3, 4) of seven studies to date have observed an association between the *GSTT1* gene deletion and myelodysplasia or AML. Although the present study had more data on AML subtypes than previous studies, it still had very limited power to evaluate leukemia subtypes of special interest, such as secondary AML or related cytogenetic findings such as −5 and −7. Future investigations of the *GSTT1* polymorphism and hematological malignancy should focus, when feasible, on secondary leukemias with known cytogenetics or persons with substantial exposure to GSTT1 substrates.

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