RESEARCH ARTICLE

Distributions of the *GSTM1* and *GSTT1* Null Genotypes Worldwide are Characterized by Latitudinal Clines

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Abstract

Background: Deletion types of genetic variants of glutathione S-transferase (GST) M1 and T1, the *GSTM1* null and *GSTT1* null which are risk factors for certain cancers, have been ubiquitously found in human populations but their worldwide distribution pattern is unclear. Materials and Methods: To perform a meta-analysis, a systematic search for the literature on *GSTM1* and *GSTT1* null genotypes was done to identify 63 reports for 81 human populations. Relationships between the *GSTM1* and *GSTT1* null genotype frequencies and the absolute latitude of 81 populations were tested by Spearman's rank correlation coefficient. Results: A significant positive correlation was detected between the *GSTM1* null genotype frequency and the absolute latitude (r=0.28, *p*-value <0.05), whereas the *GSTT1* null genotype frequency and absolute latitude showed a significant negative correlation (r= -0.41, *p*-value <0.01). There was no correlation between the frequencies of *GSTM1* and *GSTT1* null genotype in each population (r= -0.029, *p*-value=0.80). Conclusions: Latitudinal clines of the distribution of the *GSTM1* and *GSTT1* null genotypes may be attributed to the result of gene-environmental adaptation. No functional compensation between *GSTM1* and *GSTT1* was suggested by the lack of correlation between the null frequencies for *GSTM1* and *GSTT1*.

Keywords: *GSTM1* - *GSTT1* - null genotype - meta-analysis - latitudinal cline

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Introduction

The glutathione S-transferase (GST) gene superfamily comprises phase II detoxification enzymes that catalyze conjugation of glutathione (GSH) to xenobiotics (Sheehan et al., 2001). GSTs are expressed in response to a variety of stresses and play key roles in cellular protection against xenobiotics (McIlwain et al., 2006). GSTs are involved in the metabolic detoxification of products generated by oxidative stress, electrophilic compounds, carcinogens, environmental toxins and therapeutic drugs (Da Fonseca et al., 2010). GSTs have been classified into three families, cytosolic, mitochondrial and membrane-bound microsomal, by their cellular localization (reviewed in Frova, 2006). The human cytosolic GST family comprises seven main classes according to chromosomal localization of the genes: α, μ, ω, π, σ, θ and ζ (Hayes et al., 2005). Genetic variants of GSTs have been studied with respect to disease susceptibility and drug resistance; a deletion type of variant, null allele, has been found in the *GSTM1* (Seidegard et al., 1988) and also *GSTT1* (Pemble et al., 1994). The *GSTM1* null allele and *GSTT1* null allele are thought to be generated by a homologous recombination resulting in a 16-kb deletion spanning the complete *GSTM1* gene (Xu et al., 1998) and a 54-kb deletion spanning the complete *GSTT1* gene (Pemble et al., 1994), respectively; however, their evolutionary origins are not known. GST enzyme impairment is thought to result in inefficient detoxification, which leads to genetic damages and increased disease risks. In fact, the *GSTM1* or *GSTT1* null genotype is associated with various types of cancer (Sheehan et al., 2001; McIlwain et al., 2006), asthma (Minelli et al., 2010), diabetes (Yalin et al., 2007) and response rates to some chemotherapy (Hayes and Pulford, 1995).

The *GSTM1* and *GSTT1* null genotypes have extensively been studied in various human populations and their ubiquitous existence is well demonstrated (Garte et al., 2001; Gaspar et al., 2002; Buchard et al., 2007; Saadat, 2007; Fujihara et al., 2009; Piacentini et al., 2011). For example, the prevalence of the *GSTM1* null genotype in Caucasians, Asians and Africans was 47~57%, 42~54% and 16~36%, respectively, while the prevalence of the *GSTT1* null genotype in Caucasians was rather low as 13~26% but common in Asians (35~52%) (Garte et al., 2001). These differences in the frequencies of the *GSTM1* and *GSTT1* null genotypes among human populations may be related with population-specific disease susceptibilities. An epidemiological study on the cancer mortality and the *GSTM1* and *GSTT1* null genotypes was designed for 45 countries from five continents (Saadat, 2007); however, geographical characteristics of these null genotypes distribution are still unknown. To clarify these characteristics from the anthropological views, we have

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Table 1. *GSTM1* and *GSTT1* Null Genotype Frequencies in 81 Worldwide Populations

Population (Location)	Latitude[1]	Number	*GSTM1* null	*GSTT1* null	Reference
AFRICA					
Ibo (Abuja)	9.1	101	0.23	0.36	Ebeshi et al., 2011
Hausa (Abuja)	9.1	98	0.37	0.42	Ebeshi et al., 2011
Ethiopian (Addis Ababa)	9.0	153	0.44	0.37	Piacentini et al., 2011
Egyptian (Cairo)	30.0	200	0.56	0.30	Hamdy et al., 2003
Mandinka (Gambia)	13.5	114	0.28	0.40	Kirk et al., 2005
Fula (Gambia)	13.5	77	0.23	0.47	Kirk et al., 2005
Wollof (Gambia)	13.5	50	0.16	0.50	Kirk et al., 2005
Yoruba (Abuja)	9.1	101	0.31	0.35	Ebeshi et al., 2011
Sudanese (Khartoum)	15.5	114	0.39	0.38	Tiemersma et al., 2001
Tunisian (Mahdia)	35.5	182	0.54	0.29	Lakhdar et al., 2010
Somali (Mogadishu)	2.0	100	0.40	0.44	Buchard et al., 2007
Ovambo (Windhoek)	22.6	134	0.11	0.36	Fujihara et al., 2009
Cameroonian (Yaoundé)	3.8	126	0.28	0.47	Piacentini et al., 2011
Tunisians (Sousse)	35.8	186	0.63	0.37	Salem et al., 2011
AMERICA					
Guarani (Brazil)	23.2	51	0.04	0.12	Gaspar et al., 2002
Ache (Paraguay)	23.5	67	0.36	0.18	Gaspar et al., 2002
ASIA					
Bahrainis (Manama)	26.2	167	0.50	0.29	Salem et al., 2011
Thailander (Bangkok)	13.8	320	0.60	0.38	Pakakasama et al., 2005
Lebanese (Beirut)	33.9	141	0.53	0.38	Salem et al., 2011
Chinese (Beijing)	39.9	481	0.44	0.20	Li et al., 2012
Indian (Mumbai)	19.0	82	0.17	0.22	Nair et al., 1999
Chinese (Chengdu)	30.6	410	0.51	0.49	Jing et al., 2012
Indian (Delhi)	28.6	309	0.21	0.27	Singh et al., 2009
Chinese (Guangzhou)	23.1	412	0.47	0.48	Zhang et al., 2011
Vietnamese (Ha Nam)	20.5	100	0.42	0.30	Agusa et al., 2010
Chinese (Harbin)	45.8	226	0.46	0.49	Lu et al., 2011
Han (Henan)	33.9	212	0.51	0.50	Song et al., 2009
Pakistani (Islamabad)	33.7	162	0.36	0.10	Khan et al., 2010
Indonesian (Jakarta)	6.2	162	0.56	0.41	Amtha et al., 2009
Druze	31.8	159	0.60	0.07	Karban et al., 2011
Non-Ashkenazi Jews	31.8	172	0.55	0.22	Karban et al., 2011
Arab Moslem	31.8	101	0.56	0.22	Karban et al., 2011
Ashkenazi Jews	31.8	96	0.55	0.26	Karban et al., 2011
Chinese (Yangzhong)	32.1	419[2]	0.51	0.45	Setiawan et al., 2000
Kabul, Pashtuns	34.5	257	0.42	0.07	Saify et al., 2012
Kabul, Tajiks	34.5	217	0.48	0.25	Saify et al., 2012
Kabul, Hazaras	34.5	120	0.53	0.25	Saify et al., 2012
Kabul, Uzbeks	34.5	62	0.40	0.29	Saify et al., 2012
Kashmiri (Srinagar)	34.5	195	0.42	0.25	Malik et al., 2010
Indian (Kerala)	8.5	146	0.27	0.09	Sreeja et al., 2005
Thai (Khon Kaen)	16.4	94	0.60	0.40	Settheetham-Ishida et al., 2009
Japanese (Kitakyusyu)	33.8	126	0.44	0.44	Katoh et al., 1996
Tibetan (Lhasa)	29.4	86	0.61	0.36	Yan et al., 2006
Maharashtrian (Nagpur)	21.3	314[3]	0.35	0.13	Devi et al., 2008
Bahrainis (Manama)	26.2	167	0.50	0.29	Salem et al., 2011
Filipino (Quezon)	14.7	127	0.59	0.25	Baclig et al., 2012
Chinese (Meizhou)	23.4	512	0.62	0.48	Pan et al., 2011
Mizos (Mizoram)	23.4	204	0.48	0.46	Malakar et al., 2012
Japanese (Nagoya)	35.2	320	0.58	0.43	Niwa et al., 2005
Chinese (Qingdao)	36.1	366	0.43	0.49	Jiang et al., 2011
Saudi (Riyadh)	24.7	513	0.55	0.25	Al-Dayel et al., 2008
Korean (Seoul)	37.5	549	0.51	0.53	Uhm et al., 2007
Iranian (Shiraz)	29.6	169	0.51	0.21	Moasser et al., 2012
Southern Thai (Songkhla)	7.2	164	0.65	0.36	Kietthubthew, 2006
Southern Punjab	30.1	111	0.45	0.23	Shaikh et al., 2010
Iranian (Tehran)	35.7	336	0.28	0.21	Safarinejad et al., 2011
Japanese (Tokyo)	35.4	203	0.50	0.51	Tamaki et al., 2011
Mongolian (Ulan Bator)	47.9	207	0.46	0.26	Fujihara et al., 2009
North Indian (Lucknow)	26.9	300	0.22	0.20	Singh et al., 2010
Han (Wenzhou)	28.0	152	0.48	0.49	Chen et al., 2012
Han (Xi'an)	34.3	763	0.52	0.39	Liu et al., 2009

Turkish (Ankara)	39.9	231	0.54	0.19	Ada et al., 2012
EUROPE					
Greek (Athens)	38.0	171	0.52	0.10	Dialyna et al., 2001
German (Heidelberg)	49.4	1251[4]	0.51	0.17	Timofeeva et al., 2010
Mediterranean (Barcelona)	41.4	192	0.49	0.19	To-Figueras et al., 1997
Normanean (Basse-Normandie)	49.2	120[5]	0.49	0.26	Abbas et al., 2004
Danish (Copenhagen)	55.7	200	0.53	0.14	Buchard et al., 2007
Caucasian (Covilha)	40.2	102	0.40	0.18	Ramalhinho et al., 2011
Scottish (Aberdeen)	57.1	383	0.58	0.17	Little et al., 2006
Finnish Caucasian (Helsinki)	60.3	478	0.42	0.13	Mitrunen et al., 2001
Ukrainian (Kiev)	50.5	253	0.51	0.14	Ebrahimi et al., 2004
Slovenian (Ljubljana)	46.1	116	0.54	0.24	Dolzan, et al., 2006
Polish (Lodz)	51.8	233	0.48	0.16	Kargas et al., 2003
Spanish (Madrid)	40.4	94	0.55	0.28	Piacentini et al., 2011
Caucasian (Martin)	49.1	220	0.48	0.21	Matakova et al., 2009
Czech (Bruno)	49.1	331	0.50	0.22	Holla et al., 2006
Norvegian (Oslo)	59.9	357	0.51	0.19	Skjelbred et al., 2011
Icelander (Reykjavik)	64.1	395	0.54	0.21	Gudmundsdottir et al., 2001
Italian (Rome)	41.9	143	0.53	0.33	Piacentini et al., 2012
Italian (Florence)	43.4	546	0.50	0.17	Palli et al., 2005
Caucasian (Vienna)	48.2	305	0.55	0.17	Gundacker et al., 2009

*[1]absolute latitude; [2]418 subjects for *GSTT1*; [3]322 subjects for *GSTT1*; [4]1249 subjects for *GSTT1*; [5]115 subjects for *GSTT1*

conducted a systematic review of the literature of and a meta-analysis for the *GSTM1* and *GSTT1* null genotypes.

Materials and Methods

Publication search

To perform a meta-analysis, publications were selected with the following protocol (Figure 1). We searched for studies comprising keywords "*GSTM1 GSTT1* null population genotype NOT meta" on PubMed up to December 2012, and then used the PubMed filters "Abstract available", "English", "Human", and "MEDLINE" for the further selection. References of related studies were manually searched and added.

Inclusion/exclusion criteria

We included publications (1) reporting frequencies of the *GSTM1* and *GSTT1* null genotypes for more than 50 healthy individuals; (2) using internal control in the PCR to exclude a false null genotype or using the real-time PCR; (3) with a description of ethnic background of the subjects; (4) stating the location of the study population. We excluded publications (1) of meta-analyses and review; (2) based on the family studies; (3) for the subjects with relatively recent migrations and/or genetic admixtures. Hence a large number of studies on the population such as in the United States, Brazil, Canada, Argentina, Australia, Mexico, Puerto Rico, Hong Kong, Taiwan, Singapore, Hawaii, Shanghai, Greenland and United Kingdom were excluded. When there were multiple publications for a given population, data for the largest sample size was adopted. Latitude of each location was obtained by Google search or published maps. Decimal system of latitude was adopted. When the location of the subjected population was not clearly mentioned in the literature, we substituted the state capital for it.

Meta-analysis

Correlations between the absolute latitude and the prevalence of the *GSTM1* as well as *GSTT1* null genotype

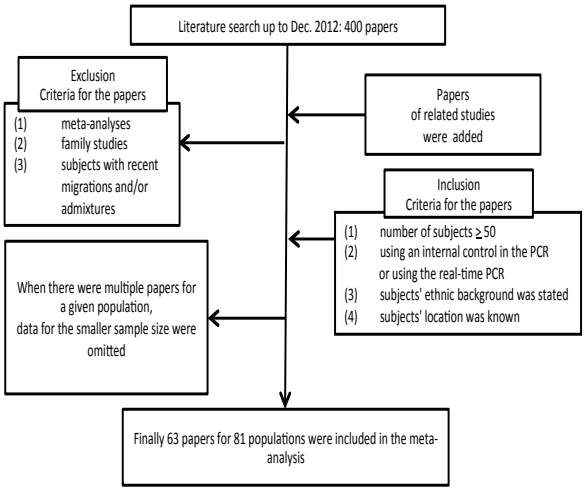

Figure 1. Flow Chart of the Selection Procedure for Literatures

for the 81 populations were tested by Spearman's rank correlation coefficient with R (version 2. 14. 1). A *p*-value less than 0.05 was considered to be significant.

Results

Starting from 400 publications in the PubMed, 63 reports for 81 populations were finally included in the study (Figure 1). These populations were located from 64.1°N to 23.5°S. Number and origin of the populations were as following; 14 from Africa, two from America, 46 from Asia and 19 from Europe. Table 1 shows the frequency of the *GSTM1* and the *GSTT1* null genotype with the absolute latitude in each population. The frequency of the *GSTM1* null genotype ranged from 0.04 in Guarani (Brazil) (Gaspar et al., 2002) to 0.65 in Southern Thais (Kietthubthew, 2006), while that of the *GSTT1* null genotype ranged from 0.07 in Druze (Israel) (Karban et al., 2011) and Pashtuns (Afghanistan) (Saify et al., 2012) to 0.53 in Korean (Korea) (Uhm et al., 2007).

A significantly positive correlation was detected between the *GSTM1* null genotype frequency and the

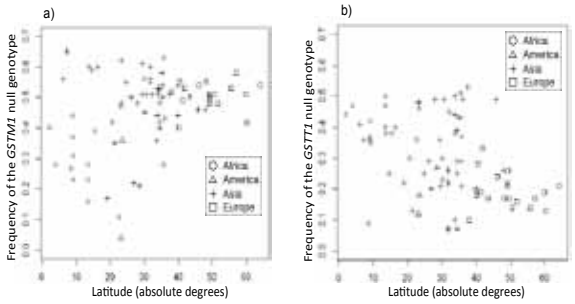

Figure 2. Latitudinal Distribution of the Null Genotype. **a)** *GSTM1* null genotype; **b)** *GSTT1* null genotype

absolute latitude (r=0.28, *p*-value<0.05, Figure 2a), whereas the *GSTT1* null genotype frequency and absolute latitude showed a significantly negative correlation (r=-0.41, *p*-value <0.01, Figure 2b). There was no correlation between the frequencies of the *GSTM1* and *GSTT1* null genotypes in each population (r =-0.029, *p*-value=0.80).

Discussion

In this study, we have visualized latitudinal clines in the distribution of the *GSTM1* null genotype and *GSTT1* null genotype; the former and the latter cline was based on the positive (r=0.28) and negative (r=-0.41) correlation between the null frequency and the absolute latitude, respectively. So far some human genotypic traits such as skin color and tumor suppressor pathway showing latitudinal clines have been attributed to adaptive consequences to the climatic environment such as temperature (Shi et al., 2009) and ultraviolet (UV) light irradiation (Jablonski and Chaplin, 2000; 2010; Shi et al., 2009). UV light induces oxidative stresses in cells (McIlwain et al., 2006) and GSTs detoxify products of oxidative stresses (Hayes et al., 2005). In case of the *GSTM1* null, we can hypothesize that peoples in Europe living in higher latitudes might have been liberated from the strong constraint of UV light toxicity and have elevated frequencies of the null allele. However, this hypothesis does not directly fit to the *GSTT1* null distribution as it showed an inverse cline to that of *GSTM1* null; certain factor(s) other than UV light toxicity should be taken into consideration.

An *in vitro* study showed that GSTT1 activity was higher in the individuals carrying the *GSTM1* null genotype (Fuciarelli et al., 2009). This can be interpreted that GSTT1 may compensate for the lack of GSTM1 activity; however, in this study, no significant correlation (r=-0.029, *p*-value=0.80) between the frequencies of the *GSTM1* and *GSTT1* null genotypes suggests no GSTT1 compensation for GSTM1 and *vice versa*. This lack of compensation is probably due to the absence of common substrates between GSTM1 and GSTT1 (Hayes et al., 2005); it is more likely to presume that not GSTT1 but GSTP1 that shares some common substrates with GSTM1 covers GSTM1 deficits. In this context, surveys for the *GSTP1* polymorphism (*Ile105Val*) of which *Val* allele shows reduced activity (Sundberg et al., 1998) are of our interest and combined genotypic analyses for the *GSTM1* and *GSTP1* are recommended to evaluate their roles in cancer susceptibility.

Relationships between the null genotype (*GSTM1* and *GSTT1*) and disease susceptibility have been documented for various cancers (McIlwain et al., 2006) with mainly the so-called conventional PCR that can distinguish the absence (null type homozygous) of the genes from the presence (wild type homozygous and heterozygous) of the genes. New methods, such as the combined long-range PCR and real-time PCR, capable of identifying three genotypes, wild/wild, null/wild and null/null, of the *GSTM1* (Roodi et al., 2004; Buchard et al., 2007) and the *GSTT1* (Sprenger et al., 2000; Buchard et al., 2007) have been developed. In fact, the combined long-range PCR for the *GSTM1* visualized that wild/wild individuals who had used to be invisible were at a higher risk for breast cancer in Europeans than in African-Americans (Roodi et al., 2004) contrary to the common hypothesis that the GSTM null is associated with increased risks for cancers (McIlwain et al., 2006). From the evolutionary views, this striking result is consistent with our observation on the *GSTM1* null distribution (Figure 2a). If the *GSTM1* wild-type allele is deleterious in the Europeans, it should have been removed from the population by the purifying selection resulting in the increase in the frequency of the null allele.

In conclusion, we have found latitudinal clines in the distribution of the *GSTM1* null genotype and *GSTT1* null genotype and a part of the distribution might be attributed to the result of gene-environmental adaptation. Of course, we cannot rule out a possible influence other than climatic environments on the null prevalence because some wide range of the frequencies was observed in the populations under low latitudes namely Africans. To reveal the backgrounds for these latitudinal clines, further studies for Southeast Asian and Oceanic populations, which are other lower latitudinal populations, are indispensable preferably with complete genotypes.

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