Genetic Polymorphisms in Xenobiotic Metabolizing Enzymes as a Determinant of Susceptibility to Environmental Carcinogens

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Mahidol University Wisdom of the Land

Gene-Environment Interaction and Susceptibility to Cardiovascular Disease, Metabolic Syndrome and Cancer in Thai population : Role of Toxicogenetic study

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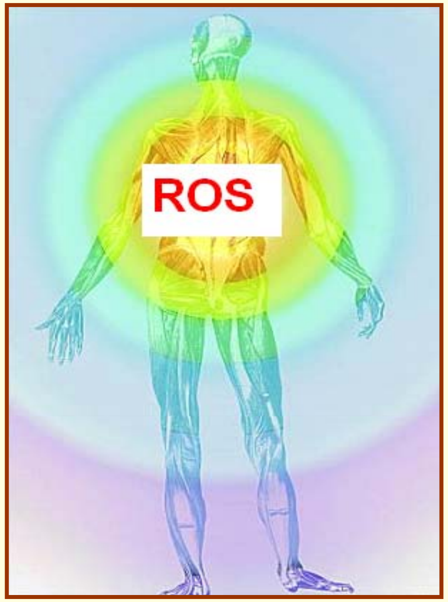
Environmental toxicants



Antioxidant activities and levels

- SOD
- Catalase
- GPx
- GSH
- Vitamin E

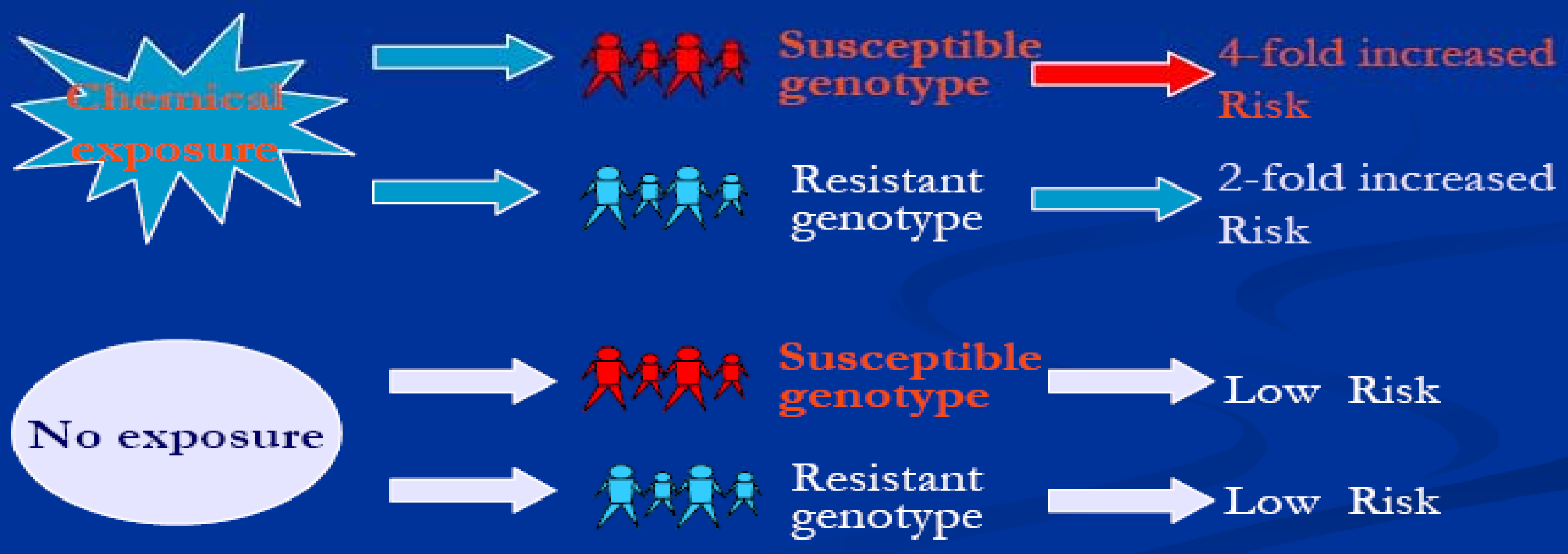
Oxidative damage

❖ **Heavy metal : Pb, Cd, Hg**

❖ **Dietary carcinogen : PAHs, HCA, Aflatoxin B1, Nitosamine, Acrylamide, etc.**

❖ **Air pollution : Metals, VOCs, etc.**

Gene-environment interaction and risk of chemical induced diseases



Research Methodology of Toxicology Unit in EGAT Project

- ❑ Exposure assessment by questionnaire
- ❑ Blood Cd and Pb
- ❑ Urine : 1-hydroxypyrene (1-OHP)

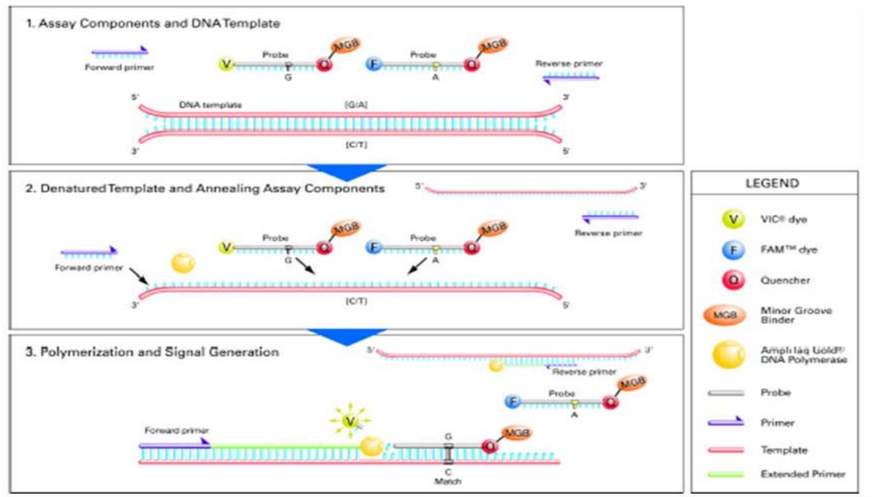
Antioxidant levels :

- ❖ **SOD (superoxide dismutase)**
- ❖ **Catalase**
- ❖ **GPx (Glutathione peroxidase)**
- ❖ **GSH (Glutathione)**
- ❖ **Vitamin E**

SNPs

↓

Real-time PCR



EGAT 2/3 : Total subjects 1,500 cases

GSTs variations : GSTM1, GSTT1 and GSTP1-105

N= 370 cases

Pb & Cd

MDA & GSH

Research Article

Provisional PDF

Genetic Variations of Glutathione S-Transferase Influence on Blood Cadmium Concentration

Nitchaphat Khansakorn, Waranya Wongwit, Prapin Tharnpoophasiam, Bunlue Hengprasith, Lorsan Suwanton, Suwanee Chanprasertyothin, Thunyachai Sura, Sming Kaojarern, Piyamit Sritara, and JINTANA SIRIVARASAI

Received 13 October 2011; Accepted 16 November 2011

Academic Editor: J. J. Stegeman

Table 1 The geometric mean of blood cadmium concentrations in a non-occupational exposed population.

Characteristics	n	Blood cadmium concentration (μg/L)	
		GM ± SE	95% CI
Total	370	0.46 ± 0.02	0.43-0.49
Gender			
male	267	0.46 ± 0.02	0.42-0.50
female	103	0.45 ± 0.03	0.40-0.50
Age (yrs)			
45- 55 yrs	144	0.45 ± 0.03	0.40-0.51
> 55 yrs	226	0.46 ± 0.02	0.42-0.50
Smoking habit			
Non-smoker	294	0.41 ± 0.02[a]	0.38-0.42
Smoker	76	0.72 ± 0.04	0.62-0.85
Alcohol consumption			
Non-drinker	178	0.44 ± 0.02	0.40-0.48
Drinker	192	0.47 ± 0.02	0.43-0.53

[a] Significantly different from smoker, $p < 0.05$, Student's t-test.

GM = Geometric mean.

95% CI = 95% Confidence interval.

Table 2. Geometric means of blood cadmium concentrations in a non-occupational exposed population categorized by different genotype.

Gene	Genotype	Frequency		Blood cadmium (μg/L)
		n	%	GM ± SE
GSTT1	Null	121	32.7	0.49±0.03
	Present	249	67.3	0.44±0.02
GSTM1	Null	213	57.6	0.47±0.02
	Present	157	42.4	0.44±0.02
GSTP1-105 rs1695	Ile/Ile	212	57.3	0.45±0.02
	Ile/Val	139	37.6	0.45±0.03
	Val/Val	19	5.1	$\boxed{0.71\pm0.08^{a,b}}$

[a,b] Significantly different from *GSTP1* Ile/Ile and Ile/Val genotypes, respectively, $p < 0.05$

Table 3. Regression coefficient for blood cadmium by *GSTP1 Val105Ile* and interaction between *GSTP1Val105Ile* and GSTT1 & GSTM1

Genotype	Blood cadmium		
	No.	β (S.E.)[a]	p-Value[b]
GSTP1 Val105Ile			
GSTP1 Ile/Ile	212	0.27 (0.19)	0.324
GSTP1 Ile/Val	139	0.35 (0.22)	0.296
GSTP1 Val/Val	19	0.59 (0.39)	0.034
GSTM1* and *GSTP1 Val105Ile			
GSTM1 +/ GSTP1 Ile/Ile	96	- 0.14 (0.23)	0.462
GSTM1 +/ GSTP1 Ile/Val and *Val/Val*	82	0.32 (0.26)	0.108
GSTM1 -/ GSTP1 Ile/Ile	126	0.29 (0.17)	0.288
GSTM1 -/ GSTP1 Ile/ Val and Val/Val	68	0.67 (0.46)	0.044
GSTT1* and *GSTP1 Val105Ile			
GSTT1 +/ GSTP1 Ile/Ile	121	0.20 (0.13)	0.142
GSTT1 +/ GSTP1 Ile/Val and Val/Val	89	0.18 (0.21)	0.296
GSTT1 -/ GSTP1 Ile/Ile	108	0.39 (0.22)	0.103
GSTT1 -/ GSTP1 Ile/Val and Val/Val	52	0.72 (0.58)	0.038

[a] Regression coefficients.

[b] p-Value were obtained by linear regression after controlling for sex, age, BMI, smoking status and alcohol consumption

Scientific Research and Essays Vol. 6(31), pp. 6540-6547, 16 December, 2011
Available online at http://www.academicjournals.org/SRE
DOI: 10.5897/SRE11.1519
ISSN 1992-2248 ©2011 Academic Journals

Full Length Research Paper

Impact of GSTM1, GSTT1, GSTP1 polymorphism and environmental lead exposure on oxidative stress biomarkers

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Accepted 22 November, 2011

Table 1. Profile of the study population and blood Pb, MDA and GSH levels.

Variable	Blood Pb (µg/dL)	Blood MDA (µmol/L)	Blood GSH (mg/dL)
All (n=370)	4.85 ± 2.71	7.40 ± 5.73	31.08 ± 7.04
Male (n=267)	5.24 ± 2.82	7.26 ± 5.41	31.09 ± 7.14
Female (n=103)	3.84 ± 2.10[a]	7.75 ± 6.50	31.04 ± 6.81
Age			
45-55 yrs (n=144)	4.99 ± 2.79	8.08 ± 6.24	31.25 ± 6.90
>55 yrs (n=226)	4.76 ± 2.66	6.96 ± 5.35	30.97 ±7.14
Smoking status			
Smokers (n=76)	6.08 ± 3.09	8.04 ± 5.67	31.02 ± 6.97
Nonsmokers (n=294)	4.54 ± 2.51[b]	7.23 ± 5.74	31.28 ±7.34
Cigarettes smoked per day			
1-9 (n=20)	5.78 ± 2.01	7.54 ± 3.89	30.18 ± 5.67
10-19 (n=32)	6.03 ± 2.95	8.02 ± 3.57	29.88 ± 7.72
≥ 20 (n=24)	6.89 ± 3.07	7.96 ± 2.99	31.25 ± 6.58
Alcohol consumption			
Yes (n=192)	5.34 ± 2.84	7.33 ± 5.50	31.13 ±6.81
No (n=178)	4.32 ± 2.46[c]	7.47 ± 5.98	31.02 ± 7.26
Frequency of alcohol consumption (drinks/week)			
1-3 (n=64)	4.94 ± 2.74	7.11 ± 4.64	31.78 ± 5.67
3-6 (n=86)	5.58 ± 3.99	7.84 ± 3.97	32.26 ± 4.87
≥ 7 (n=42)	5.99 ± 4.37	7.68 ± 5.24	31.96 ± 6.84

[a, b, c] $p<0.05$ compared to male, smokers and drinkers, respectively.

Table 2. Genotype frequencies for GSTM1, GSTT1 and GSTP1 (N=370).

Gene	Variation	Genotype	Frequency	
			Number	Percentage (%)
GSTT1	Deletion	Null	121	32.7
		Present	249	67.3
GSTM1	Deletion	Null	213	57.6
		Present	157	42.4
GSTP1-105 (rs1695)	Ile105Val	Ile/Ile	212	57.3
		Ile/Val	139	37.6
		Val/Val	19	5.1

Table 3. Blood lead level for different genotypes.

Genotype	Tertile 1		Tertile 2		Tertile 3	
	Blood Lead (< 2.99 μg/dL)	No.	Blood Lead (3.00-6.00 μg/dL)	No.	Blood Lead (> 6.00 μg/dL)	No.
GSTT1						
Null	2.79 ± 0.40	49	4.47 ± 0.50	55	8.09 ± 2.14	32
Present	2.63 ± 0.48	80	4.34 ± 0.47	91	8.69 ± 3.13	63
GSTM1						
Null	2.68 ± 0.46	75	4.44 ± 0.50	85	8.73 ± 2.58	53
Present	2.72 ± 0.45	54	4.31 ± 0.46	61	6.84 ± 2.10 [a]	42
GSTP1-105						
Ile/Ile	2.70 ± 0.48	70	4.42 ± 0.49	80	6.20 ±0.44	62
Ile/Val	2.75 ± 0.43	49	4.35 ± 0.48	62	7.42 ±1.77	28
Val/Val	2.70 ± 0.48	10	4.25 ± 0.50	4	9.15 ±3.10 [b]	5

[a, b] Significantly different from GSTM1 null genotype and GSTP1 Ile/Ile, p<0.05, respectively.

Table 4. Odds ratio for blood lead level according to smoking status and GST genotypes[a].

Genotype	Variable	Blood Pb <6 μg/dL vs. > 6 μg/dL			
		Nonsmokers		Smokers	
		OR	95% CI	OR	95% CI
GSTT1	Present	1.0	Reference	0.9	0.6-1.4
	Null	0.6	0.4-1.0	1.1	0.6-1.7
GSTM1	Present	1.0	Reference	1.2	0.7-2.0
	Null	1.4	0.9-2.4	1.5	1.0-2.2
GSTP1-105	Ile/Ile	1.0	Reference	1.1	0.7-1.8
(rs1695)	Ile/Val and Val/Val	$\boxed{1.7}$	1.1-2.6	$\boxed{1.8}$	1.1-3.1

[a] Adjusted for data of age, gender and alcohol consumption.

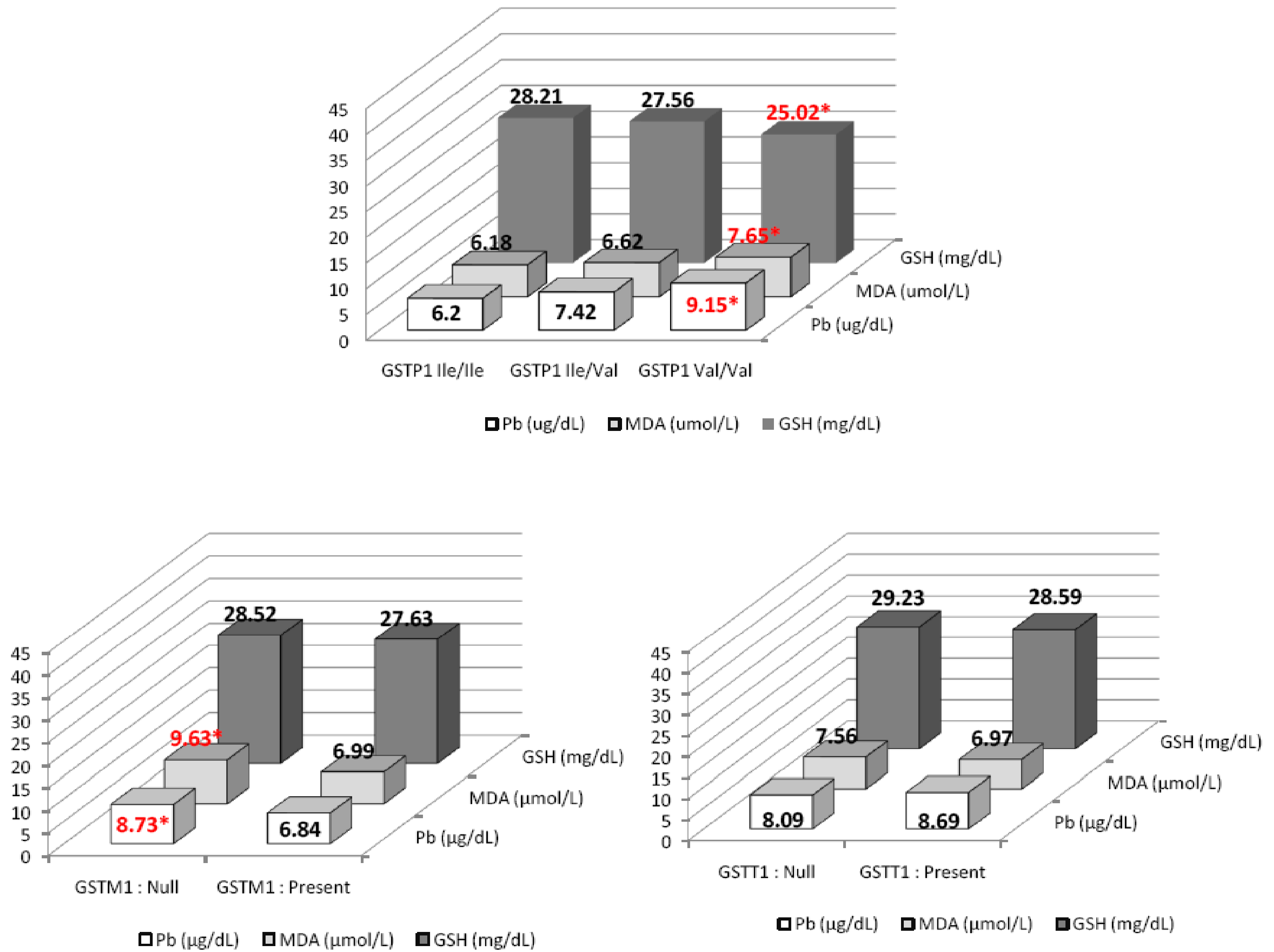
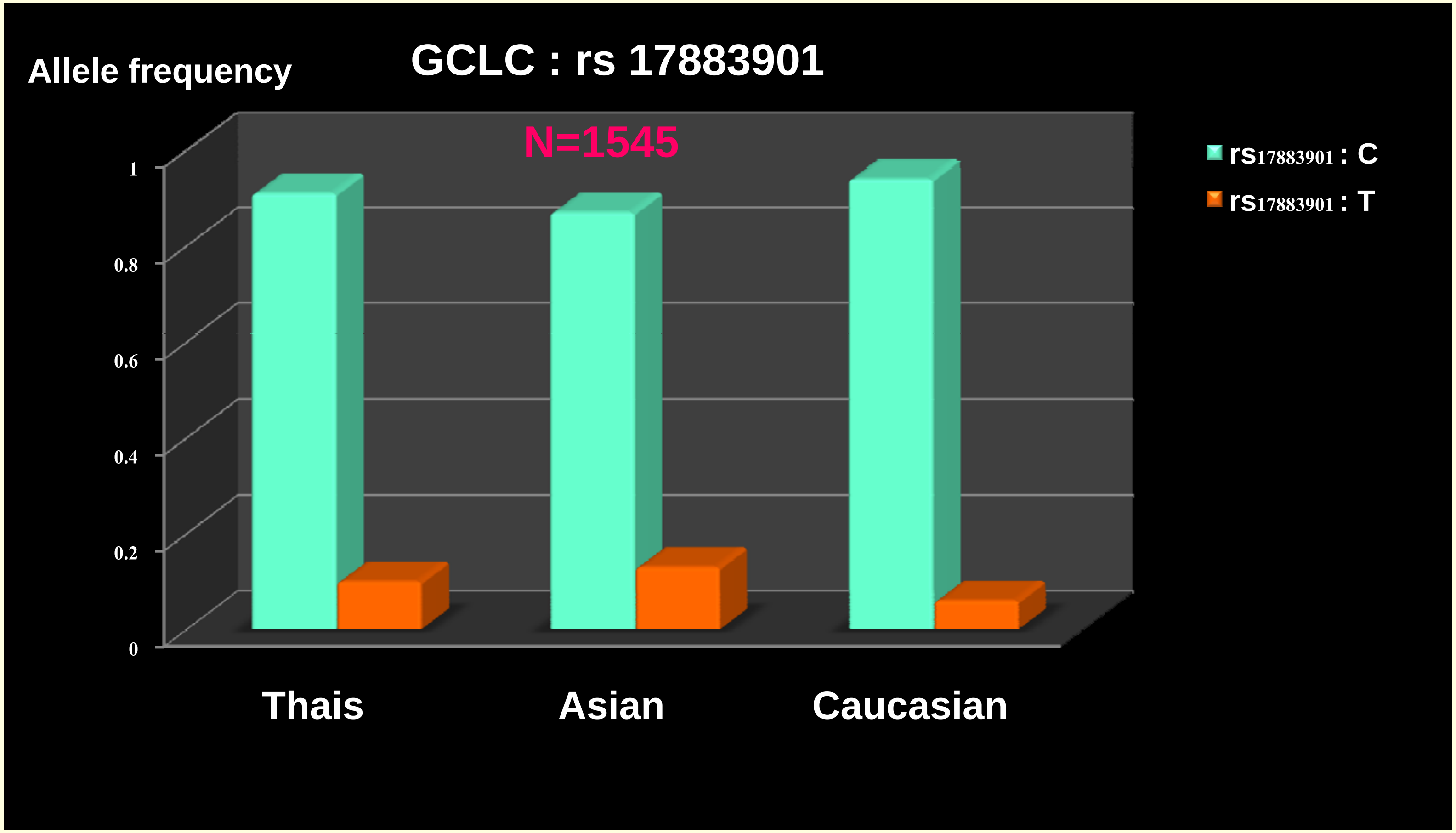
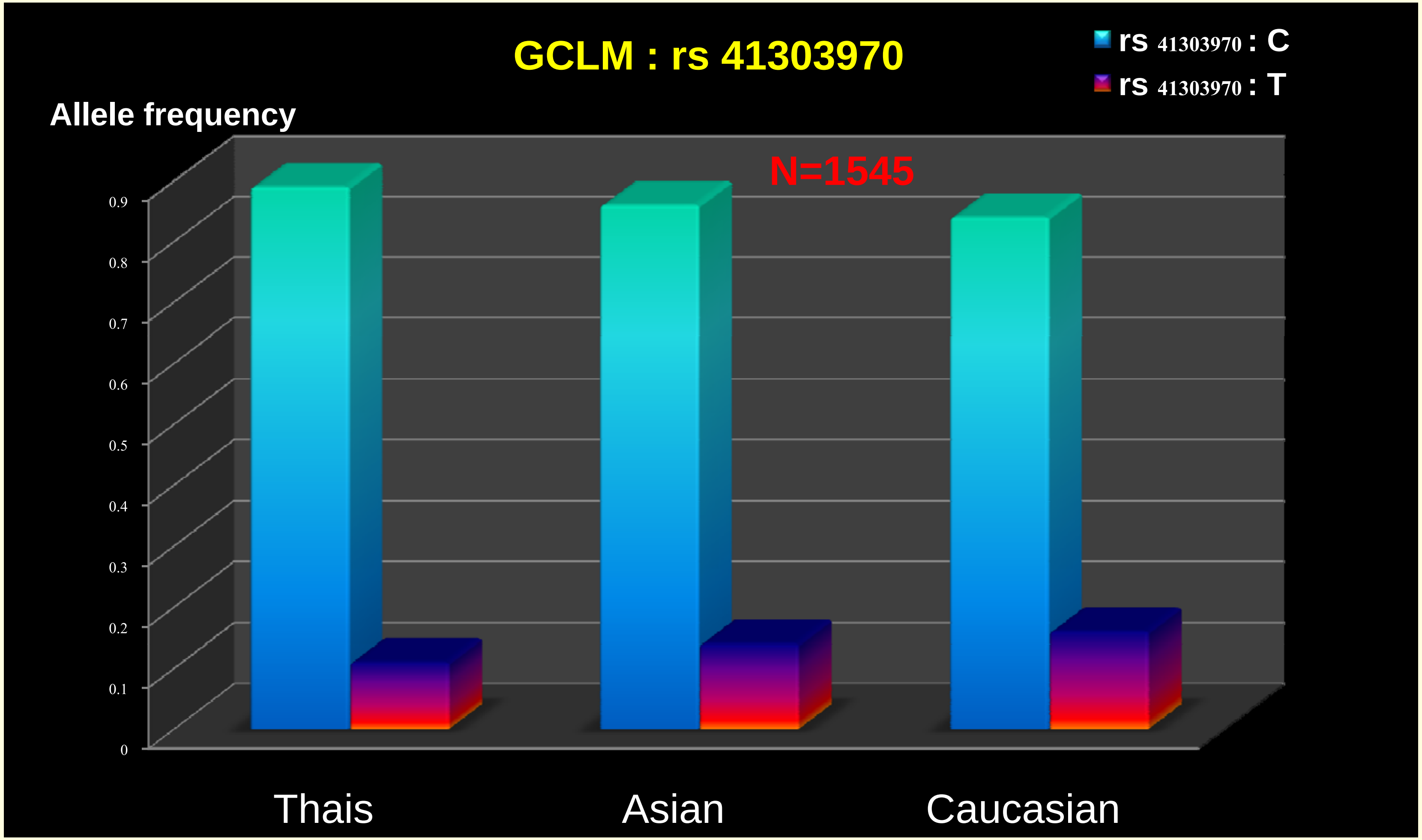


Figure 1. Genetic impact on the blood Pb, MDA and GSH levels.

GCLC
(Glutamate cysteine ligase catalytic subunit)
&
GCLM
(Glutamate cysteine ligase modifier subunit)

- First study of these SNPs in Thai population
- Association between SNPs and GSH levels
- Influence of SNPs on blood Pb and Cd levels
- Gene-gene interaction : GSTs gene and GSH related gene


Allele frequency
GCLC : rs 17883901
N=1545
1
0.8
0.6
0.4
0.2
0
rs17883901 : C
rs17883901 : T
Thais
Asian
Caucasian


GCLM : rs 41303970
rs 41303970 : C
rs 41303970 : T
Allele frequency
N=1545
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Thais
Asian
Caucasian

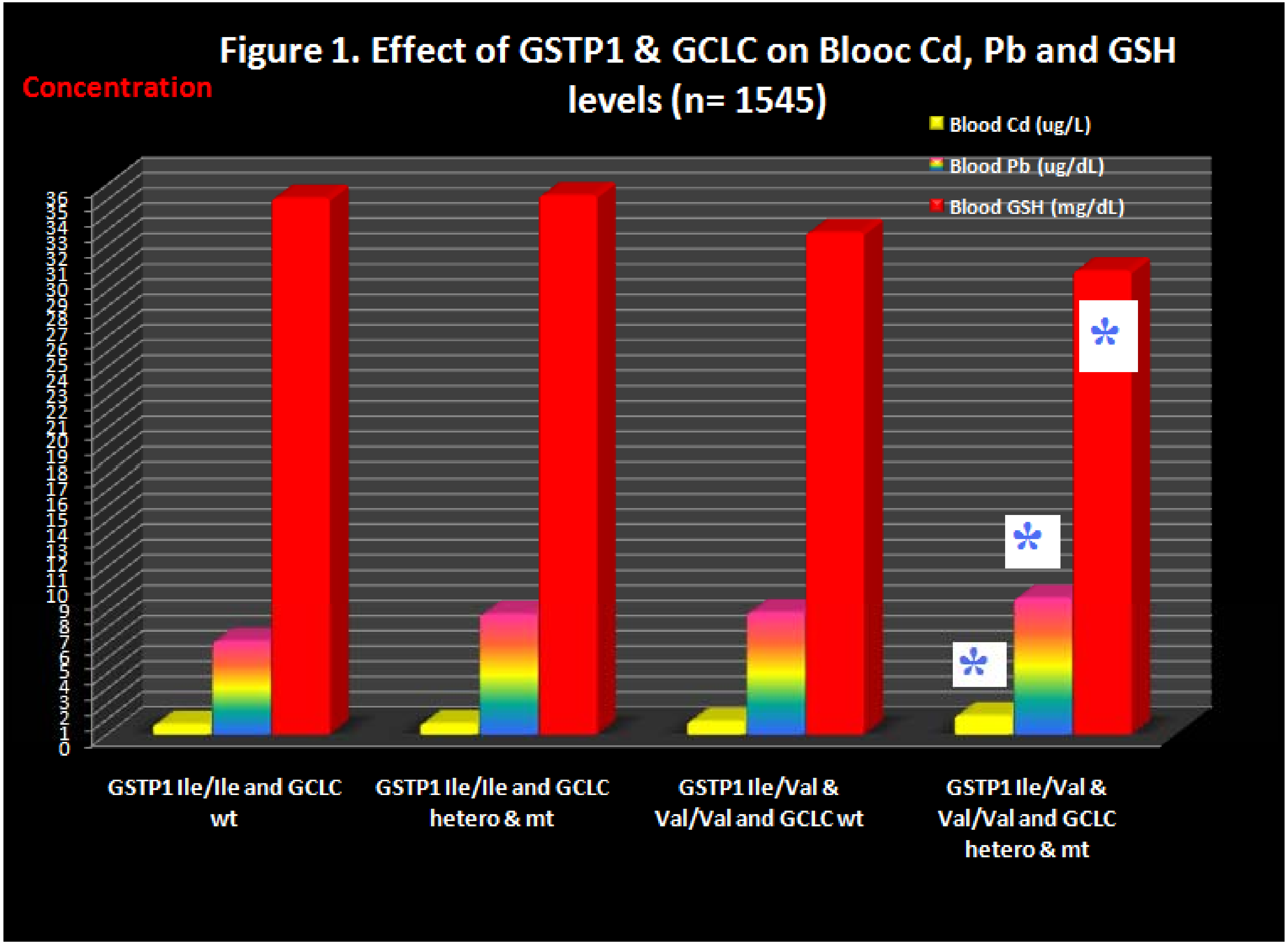


Figure 1. Effect of GSTP1 & GCLC on Blooc Cd, Pb and GSH levels (n= 1545)
Concentration
Blood Cd (ug/L)
Blood Pb (ug/dL)
Blood GSH (mg/dL)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
*
*
*
GSTP1 Ile/Ile and GCLC wt
GSTP1 Ile/Ile and GCLC hetero & mt
GSTP1 Ile/Val & Val/Val and GCLC wt
GSTP1 Ile/Val & Val/Val and GCLC hetero & mt

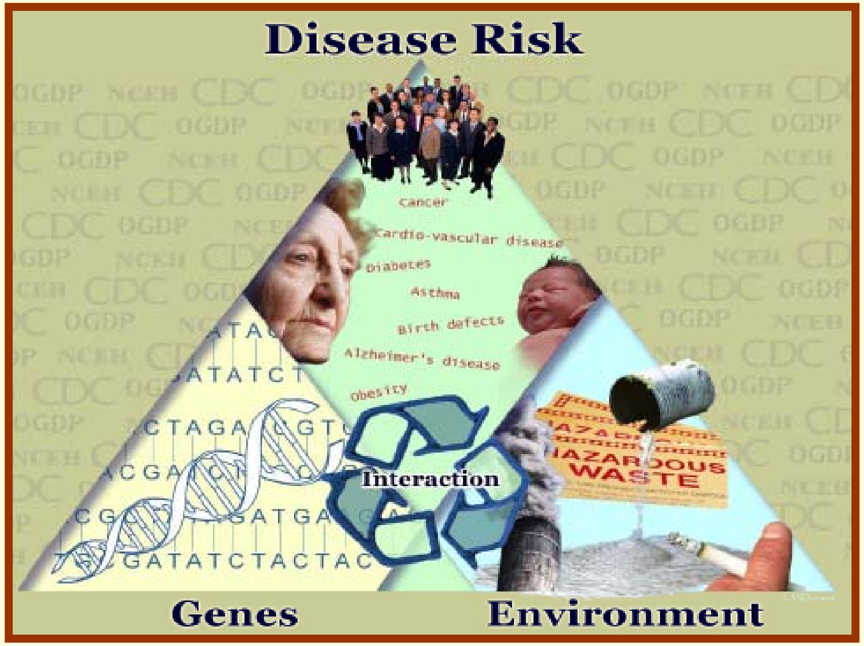
GCLC-mediated elevation GSH level

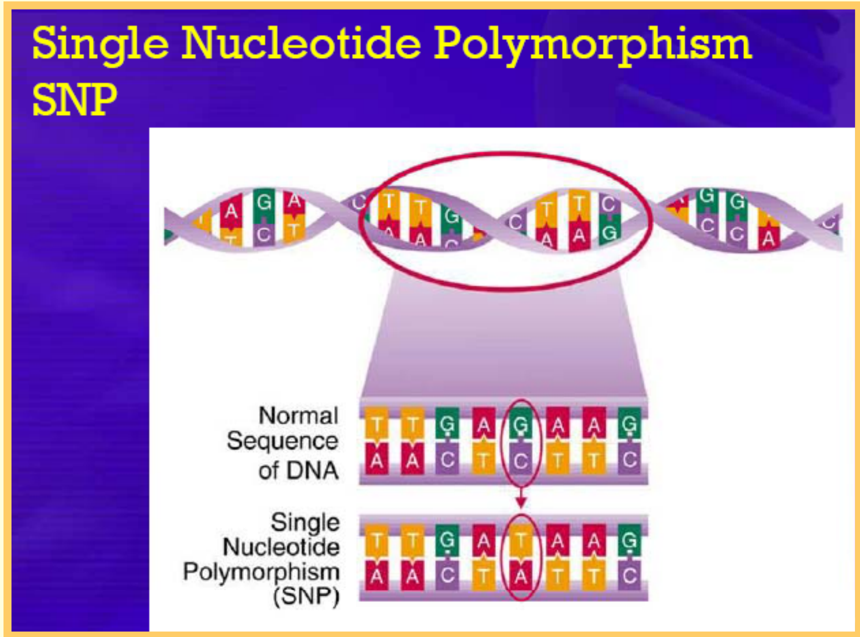
↓

Down-regulation of metal transporters (ZIP8) by reduced expression of transcription factor Sp1

↓

Effects on blood metal levels

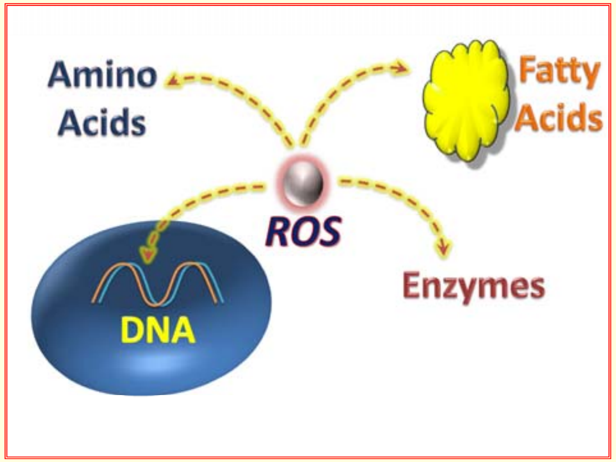




Additional information related to biomarkers of susceptibility (SNPs) give rise to more clarify the influence of gene-environment and gene-gene interactions on risks to various metabolic diseases and cancer.

ACKNOWLEDGEMENTS

The authors wish to thank the EGAT and their people for participating and establishing this study. We would like to express our gratitude to all research staffs, especially Miss Nisakron Thongmung and Ms. Yupin Wisetpanit, Office of Research Academic and Innovation, Faculty of Medicine Ramathibodi Hospital, for providing subjective data and technical assistance in specimen collection and preparation. This work was supported by the Cooperative Research Network (CRN) scholarship; the project for Higher Education Research Promotion and National Research University Development, Office of the Higher Education Commission, Ministry of Education, Thailand, and The Thailand Research Fund.



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