Genetic Polymorphisms of Xenobiotic Metabolizing Enzyme (Glutathione-S-Transferase, GSTM1 and GSTT1) and Susceptibility to Non Hodgkin's Lymphomas

Thesis

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid neoplasm. Based on the increasing evidence for the association between carcinogen-exposure-related cancer risk and xenobiotic gene polymorphisms, we have undertaken a case-control study on xenobiotic gene polymoprhisms namely glutathione-S-transferase, GSTT1 and GSTM1 in Egyptian patients with a diagnosis of diffuse large B-cell lymphoma.

The purpose of the current study was to determine the frequency of GSTT1 and GSTM1 genes polymorphism in fifty Egyptian DLBCL patients and to clarify their role in susceptibility to DLBCL. To achieve this aim, GSTT1 and GSTM1 genotyping was tested by multiplex PCR. Forty age and sex matched healthy volunteers were included in the current study as a control group. GSTT1 null genotype was detected in 64% of patients. GSTT1 null genotype was significantly higher in patients compared to controls and was associated with increased risk of DLBCL. GSTM1 null genotype and dual null genotype were detected in 44% and 34% of patients respectively and were not associated with increased risk of DLBCL.

Key words:

DLBCL, GSTT1, GSTM1, Multiplex PCR.

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Dedication

To the Soul of
My dear
Mother

To My Sweet Husband
&
Supportive Father

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LIST OF ABBREVIATIONS

95% CI	95% Confidence interval
AHR	Aryl hydrocarbon receptor
ALCL	Anaplastic large cell lymphoid
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AP-1	Activator protein -1
BCNU	Bis-chloro-methyl nitrosourea
BM	Bone marrow
BPDE	Benzo A-Pyrene-Diol-Epoxide
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
BVMOs	Baeyr-Villigar monooxygenase
CARD15	Caspase recruitment domain family
ChEH	Cholesterol epoxide hydrolase
CLL	Chronic lymphoid leukemia
CML	Chronic myeloid leukemia
CR	Complete remission
Cth	Chemotherapy
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
CYBA	Cytochrome-β-245,α-polypeptide
CYP	Cytochrome P450
DDCT	D-dopachrome tautomerase gene
DLBCL	Diffuse large B cell lymphoma
DNA	Deoxyribonucleic acid
Dnp-SG ATPase	Dinitrophenol S-GSH conjugates

DSBR	Double-strand break and repair
EBV	Epstein- Barr virus
ECA	diuretic ethacrynic acid
EH	Epoxide Hydrolase
EPHX1	Epoxide hydrolase 1
FL	Follicular lymphoma
FMO	Flavin mono oxygenase
GHRL	Gherlin
GSH	Reduced glutathione
GST	Glutathione-S-transferase
GST-alpha	Glutathione-S-transferase alpha
GSTM	Glutathione-S-transferase Mu
GST-O	Glutathione-S-transferase Omega
GSTP	Glutathione-S-transferase Pi
GSTT	Glutathione-S-transferase Theta
GSTZ1-1	Glutathione-S-transferase Zeta1-1
h GSTK1	Human Glutathione-S-transferase kappa
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HL	Hodgkin lymphoma
IL-10	Interleukin 10
IL-4	Interleukin 4
IL-4R	Interleukin 4 receptor
IL-6	Interleukin 6
LDH	Lactate dehydrogenase
LEPR	Leptin receptor
LIG4	DNA ligase IV gene

LNs	Lymph nodes
LTA	Lymphotoxin alpha
MA	Maleylacetone
MAAI	Maleylacetoacetate isomerase
MALT	Mucosa associated lymphoid tissue
MBL2	Mannose binding lectin (protein C)2
mEPH	Microsomal epoxide hydrolase
MIF	Macrophage migration inhibitory factor
MOAT	Multi specific organic anion transporter
MPO	Myeloperoxidase
MRP	Multi drug resistance protein
MSH2	mutS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)
MTHFR	Methylene tetrahydrofolate reductase
MZL	Marginal zone lymphoma
N.D	Not determined
NAT	N- acetyl transferase
NCI	National Cancer Institute
NHL	Non Hodgkin lymphoma
NOD2	Nucleotide oligomerization domain 2
NOS	Not otherwise specified
NOS2A	Nitric oxide synthase 2A gene
NPY	Neuropeptide
NSAID	Non steroidal anti inflammatory drugs
P.S	Performance status
PAH	Polycyclic aromatic hydrocarbons
PD	Progressive disease
PhiP	2-amino-1-methyl-6-phenylimidazo[4,5b]-pyridine

Plts	Platelets
PON1	Paraoxanase-1
PR	Partial remission
PRL	Prolactin
RAG1	Recombination-activating gene-1
ROS	Reactive oxygen species
Rth	Radiotherapy
She	Soluble epoxide hydrolase
SNPs	Single nucleotide polymorphisms
SOD2	Superoxide dismutase 2, mitochondrial
SULTs	Sulfotransferase
TLC	Total leucocytic count
TLR4	Toll like receptor 4
TNF	Tumor necrosis factor
TP53	Tumor protein 53
TSO	Substrate stillbene oxide
ttt	Treatment
UDP-UGT	Uridine diphosphate glycosyl transferase
WHO	World Health Organization
XMEs	Xenobiotic metabolizing enzymes
XRCC3	X-ray repair complementing defective repair in Chinese hamster cells 3

Introduction

Non-Hodgkin's lymphoma (NHL) is a heterogeneous malignancy of B- and T-cells that involves their uncontrolled clonal expansion in the periphery. B-cell lymphomas make up the majority of cases and, of these, diffuse large B-cell lymphoma (DLCL) and follicular lymphoma (FL) are the two major subtypes ***(Skibola et al., 2007)***.

The incidence of non-Hodgkin's lymphoma (NHL) has increased steadily in the past 50 years. Besides well-known risk factors, including family history, immune dysfunction, immune stimulation and infections, a number of occupational and environmental exposures have been proposed as risk factors for NHL. Associations with exposure to herbicides and pesticides, benzene and other solvents, dioxins and other potentially DNA-damaging agents have been reported, although the findings have been inconsistent ***(Shen et al., 2007)***.

DNA damage in the hematopoietic precursor cell is the essential prerequisite for the development of leukemia and the body has developed a series of mechanisms aimed at preventing such damage. One such mechanism is mediated by reactive oxygen species generated either by environmentally encountered carcinogens or endogenously as a result of oxidative mechanisms. Humans vary in their ability to detoxify intermediates, which in theory may explain differences in leukemia risk as a result of exogenous exposure ***(Bajpai et al., 2007)***.

Numerous genetic polymorphisms have been reported for glutathione-S-transferase (GST) genes, indicating a lack of functional protein or causing either increased or reduced metabolic activity ***(Dufour et al., 2005)***.

GSTs have been implicated as susceptibility genes in this context for a number of cancers including hematological malignancies like acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia ***(Bajpai et al., 2007)*** and may mediate the risk of non-Hodgkin's lymphoma ***(De Roose et al., 2006)***.

Aim of the Work

The aim of the present study is to investigate the influence of inherited genetic polymorphisms of the xenobiotic metabolizing enzymes GSTM1 and GSTT1 on the susceptibility to Non Hodgkin's Lymphoma.