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Role of Glutathione-S-Transferase gene susceptibility in patient with Bronchial asthma

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ABSTRACT

Asthma is one of the most common chronic diseases in the world which can cause considerable morbidity and a significant mortality. Hence it is important to find out the different molecular diagnostic marker which can be use for early detection as well as treatment of patient with bronchial asthma. GST biomarkers is likely become important not only as risk factors in the pathogenesis of asthma but also as determinants of responsiveness to treatment. This review represents the evidence reported the association between gene polymorphism of glutathione-s-transferases (GSTs) GSTP1, GSTM1, GSTT1 gene and bronchial asthma. The data of Indian scenario demonstrate that the Polymorphism of Glutathione-s-transferase gene *GSTT1, GSTM1* and *GSTP1* is not significantly associated with Bronchial asthma in northern Indian population due to low sample size.

Keywords: Bronchial Asthma; GST; Polymorphism

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INTRODUCTION

Asthma is one of the most common chronic diseases in the world which cause considerable morbidity and a significant mortality. It is associated with variable airways hyper-responsiveness, airflow obstruction , and chronic airway inflammation. Various risk factors are associated with the development of asthma such as Xenobiotic compounds and environmental exposure etc. previous studies shows that the prevalence of asthma is globally increases and estimated around 300 million people in the world currently have asthma. With the projected increase in the proportion of the world's population from 45-59% in 2025, there is likely to be a marked increase in the number of asthmatics worldwide over the next two decades.[1] Glutathione –S-transferase is an important anti-oxidant that protects cellular damage caused by environmental toxins as well as from ROS-mediated injury. GSH works by xenobiotics and neutralizing ROS with the help of glutathione S-transferase (GST) **.** GST biomarkers will likely become important not only as risk factors in the pathogenesis of asthma but also as determinants of responsiveness for treatment of asthmatic patients . This review represents the evidence reported the association between bronchial asthma and gene polymorphism of glutathione-s-transferases (GSTs) GSTP1, GSTM1, GSTT1 gene.

Glutathione–S-Transferase

Glutathione-*S*-transferases are considered phase II biotransformation of xenobiotics. Drugs, poisons, and other compounds are usually somewhat modified by the phase I or phase II mechanisms and finally excreted from the body. GSTs contribute to this type of metabolism by conjugating these compounds with reduced glutathione to facilitate dissolution in the aqueous cellular and extracelluar media and released from the body. Soluble glutathione S- transferase (GST) represents a superfamily of inducible enzymes, comprising at least 7 classes of cytoplasmic proteins ($\alpha,\mu,\pi,\sigma,\theta,\kappa,\zeta$) [2] which catalyze the conjugation of gluatathion (GSH) with different species of electrophillic compound. Glutathion S- transferases (GST) consists of a superfamily of dimeric phase II metabolic enzymes that catalyze the conjugation of reduced glutathione with various electrophilic enzymes [3]. The human GST genes are divided into four major subfamilies designated as GST $\propto$ or A, GST μ or m, GST θ or T and GST π or P *(Hayeset et al 1995)*. The class π GST gene exist as a single functional gene in human whereas class α, μ and θ families contain multiple distinct genes sharing ~55, 65 and 50 % homology respectively. For both GSTM1 and GSTT1 the variant allele is a deletion of the gene and individual who are homozygous for the deleted allele are said to possess the "null" genotype and do not express the

enzyme [4] and GSTP1 gene show polymorphism within its coding region of which well- known are an A to G transition at nucleotide position 1,578 causing an isoleucine to valine substitution at codon 105 (Ile^{105} Val) in exon 5, C to T base change at position 2,293 giving rise to the replacement of alanine to valine at the amino acid position 114 (Ala^{114} Val) in the exon 6 [5]. This results into the decreased enzyme activity.

Mechanism of Action:

GSTs catalyze the conjugation of reduced glutathione via the sulfhydryl group to electrophillic centers on a wide variety of substrates and then facilitates their dissolution in aqueous cellular and extra cellular media and from their out of the body. This activity is useful in the detoxification of endogenous compounds such as per oxidized lipids as well as metabolism of xenobiotics. GSTs contribute to the phase II biotransformation of xenobiotics. Drugs poison and other compounds which are not considered in either of the groups are somewhat modified by phase I and phase II mechanisms and finally excreted from the body.

GSTM family:

The mu genes are ordered, 5% GSTM4-GSTM2-GSTM1-GSTM5-GSTM3 3%, in a 20 kb cluster [6]. Three GSTM1 alleles, *GSTM* 1* 0, *GSTM* 1**A*, *GSTM* 1**B*, are described. *GSTM* 1* 0 is deleted. *GSTM* 1**A* and *GSTM* 1**B* differ by one base in exon 7 and encode monomers that form active homo- and heterodimeric enzymes. have described two Saudi Arabians with ultra rapid[7]**.** *GSTM1* activity as a result having two copies of the gene [8] identified two GSTM3 alleles (*GSTM* 3**A*, *GSTM* 3**B*) that differ by the presence of an intrinsic recognition motif for the YY1 transcription factor in *GSTM* 3**B*. *GSTM* 3**B* and *GSTM* 1**A* are in linkage disequilibrium. Thus, individuals with *GSTM* 1**A*: *GSTM* 3**B* may express more GSTM3than those with *GSTM* 1**O*: *GSTM* 3**A* or *GSTM* 1**B*: *GSTM* 3**A*, because *GSTM* 3**A* is not inducible by YY1.1.

GSTT family:

The two theta genes, GSTT1 and GSTT2, are composed of five exons with identical intron. About 20% of Caucasians are homozygote for a null allele, *GSTT* 1* 0, in GSTT1. GSTT2 lies head to head with the D-dopachrometautomerase gene. The sequence between these two genes may contain a bidirectional promoter. Both these genes have been duplicated in an inverted repeat [8]

GSTP *family:*

Four GSTP1 alleles have been identified [9]**.** The wild type allele (*GSTP* 1**A*) differs by an A:G transition at nucleotide_313 (Val105-Ala17) from *GSTP* 1**B* and from *GSTP* 1**C* by this transition and a C:Ttransition at _341 (Val105-Val17). A *GSTP* 1**D* allele (Ile105-Val17) has

also been identified. Enzymes with Val105 have a 7-fold higher efficiency for PAH diol epoxides than the enzymes with Ile105.

GSTT1, GSTM1 and GSTP1 gene polymorphisms found in asthmatic patients of different ethinic populations :

S. No	Gene	Population	Study Design	Remarks	Reference
1	GSTT1	Tunisia	Case-Control	Significance	[10]
2	GSTT1	Korean	Case-Control	Non Significance	[11]
3	GSTT1	Iran	Case-Control	Significance	[12]
4	GSTT1	Brazil	Case-Control	Non Significance	[13]
5	GSTT1	India	Case-Control	Non Significance	----
6	GSTM1	Tunisia	Case-Control	Significance	[10]
7	GSTM1	Korean	Case-Control	Significance	[11]
8	GSTM1	Iran	Case-Control	Non Significance	[12]
9	GSTM1	Brazil	Case-Control	Significance	[13]
10	GSTM1	India	Case-Control	Non Significance	----
11	GSTP1	Tunisia	Case-Control	Non Significance	[10]
12	GSTP1	Germany	Case-Control	Significance	[14]
13	GSTP1	India	Case-Control	Non Significance	-----
14	GSTP1	Germany	Case-Control	Significance	[14]

Human cytosolic GSTs have been well characterized and known to be polymorphic with different polymorphism frequencies in different ethnic groups [15]. The percentage of individuals who do not express the GSTM1 and GSTT1 enzymes due to homozygous gene deletion is higher in Caucasians (40%) and Asians (60%) in comparison to Africans (20%) about 60% of Asians, 40% of Africans and 20% of Caucasians do not express the GSTM1 and GSTT1 enzyme[16].

CONCLUSION

It has been suggested that variant alleles in the GSTM1, GSTT1 and GSTP1 genes are unlikely to convey moderate increases in the susceptibility to Bronchial asthma although the possibility of a small effect cannot be ruled out. Taking care of bronchial asthma patients will remain a daily task for decades. It will be important to find out the different molecular diagnostic marker for early predication as well as treatment of bronchial asthma patients in Indian population. The data from our study in demonstrate that the Polymorphism of Glutathione-s-transferase gene (*GSTT1, GSTM1, GSTP1*) is not significantly associated with Bronchial asthma in northern Indian population due to low sample size and hence it is suggested to conduct more study with large samples size.

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