Glutathione S transferase theta1 and mu1 gene polymorphisms and phenotypic expression of asthma in Egyptian children: a case–control study

Nihal El Rifai1,3*, Nadia Moustafa1, Nelly Degheidy1 and Manal Wilson2

Abstract

Background: Asthma is the result of a complex interaction between environmental factors and genetic variants that confer susceptibility. The glutathione S-transferases (GSTT1 and GSTM1) are phase II enzymes thought to protect the airways from oxidative stress. Few and contradictory data are available on the association between asthma development and GSTT1 and GSTM1 polymorphisms in different ethnic groups. The current study aimed to investigate whether these polymorphisms are associated with asthma development in the Egyptian population.

Methods: The cross-sectional study was performed on 94 asthmatic children 6-12 yrs and 90 matched healthy controls. Candidates were subjected to clinical evaluation and measurement of absolute blood eosinophilic count, total serum IgE, and GSTT1 and GSTM1 genotype by multiplex PCR technique.

Results: The results for GSTT1 null genotype were 87.2% and 97.2% for asthmatic children and controls respectively and showed to be significantly more in controls (P =0.007, OR: 0.683, CI: 0.034-0.715). The results for GSTM1 null genotype were 50% and 61.1% for asthmatic children and controls respectively and showed to be nonsignificant (p = 0.130, OR: 1.000, CI: 0.54-1.86). Also, no association was detected between GSTT1 and GSTM1 polymorphisms and atopic conditions or asthma severity.

Conclusion: The significant detection of GSTT1 null genotype more in controls than in asthmatics with no association with other atopic manifestations or asthma severity and the lack of association detected between GSTM1 polymorphism in relation to asthma, atopy or asthma severity confirm the uncertain role of those genes in the development of asthma.

Keywords: Asthma, Children, Egyptian, Glutathione S-transferase, Polymorphism

Introduction

Asthma is a disorder of the airways characterized by several symptoms such as airflow obstruction, airway inflammation, and hyper responsiveness [1]. The study of genetic factors involved in complex pathologies such as asthma is arduous, not only because of human genetic variability, or incomplete penetrance, but also because, in complex disease studies, the importance and strength of gene to gene and gene to environment interactions need to be considered [2]. The prevalence of candidate gene polymorphisms for asthma varies considerably worldwide, and accordingly, ethnicity should be considered as a factor that might act on and influence asthma development. Previous data based on intra- and inter-population frequency differences suggest that the association between a given genetic polymorphism and asthma cannot be extrapolated from one ethnic group to another [3].

Phase II detoxification enzymes, particularly classes of GSTs, play an important role in inflammatory responses triggered by xenobiotic or reactive oxygen compounds [4]. The GSTM1 and GSTT1 are two important phase II enzymes that protect the airways from oxidative stress [5]. They utilize as substrates a wide variety of products of oxidative stress [6]. The inability of GST variant enzymes to detoxify reactive oxygen species contributes to the activation of the inflammatory process, bronchoconstriction, and the exacerbation of asthma symptoms [4]. In particular, GSTM1 and GSTT1 null polymorphisms...
may influence the pathogenesis of respiratory diseases. Numerous studies have documented associations between genes implicated in the oxidative stress response and respiratory phenotypes, but data suggest that they may not be consistent across ethnic groups owing to differences in intra- and inter-ethnic allele frequencies [7].

The aim of the current study was to detect the presence of an association between GSTM1 and GSTT1 polymorphisms and asthma, atopy or asthma severity.

Methods
The present cross-sectional case–control study is conducted on a group of Egyptian asthmatic children (n: 94) and their age and sex matched healthy controls (n: 90) from September 2012 to June 2013. Patients were recruited from the allergy clinic of Cairo university specialized pediatric hospital where they were following up after being diagnosed according to GINA guidelines criteria of asthma classification [8]. All patients were subjected to a questionnaire containing a detailed history and clinical examination with emphasis on age, sex, family history, presence of atopic manifestations and asthma severity classification according to GINA Guidelines [8]. The following investigations were performed for all patients and controls.

Total immunoglobulin E (IgE) and Prick test assays
Atopy was defined by a positive history of atopic manifestations, positive skin prick test (wheat diameter ≥3 mm) to at least one of the following Aeroallergens (Dermatophagoides Farinae, hay Dust, Dermato-pteronyssinus, Alternaria Tenuis, Moulds II, Candida Albicans, Cat epithelia, Hen's egg, Dog epithelia, Grasses/cereals, Cow's milk in the presence of positive histamine control and negative physiological saline control using reagents obtained from Allergopharma D21462 Reinbek, Germany) and by the quantitative determination of human total IgE in serum using the DiaMed Eurogen IgE quantitative technique (Positive values were taken to be ≥200 IU/ml). Among the 94 asthmatic children there were 67 atopic and 27 non-atopic children.

Pulmonary function tests assay
Spirometric measurements using a Jaeger Master Screen Spirometry system (Jaeger Co) were done and included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and forced expiratory flow between 25% and 75% expired volume (FEF25-75). Short-acting bronchodilators were stopped at least 8 h before the test. All pulmonary function data were collected at a single visit. A minimum of 3 results within 10% of each other were recorded, and the result with the highest FEV1 was analyzed. The participants were not suffering from asthma exacerbations or other acute illnesses at the time of the measurement of pulmonary function. The lung function test results were expressed as a percentage of that predicted.

The personal, family, medical history and clinical presentation of controls were free of any atopic or allergic diseases with negative skin prick tests, normal total IgE values, normal lung function tests.

Genotyping of GSTT1 and GSTM1
100 ng of DNA were amplified in a-50 ul multiplex reaction mixture containing 0.90 pmol of each of the following GSTT1 primers (GSTT1-Forward: GAACTCCCTG AAAAGCTAAAAGC and GSTT1-Reverse: GTTGGCCT CAAATATACGGTG) and GSTM1 primers (GSTM1-Forward: TTCCCTCACTGGTCCTCAGAT and GST M1-Reverse: TCACGGGATCATGGCCAGCA). As an internal control, the beta-globulin gene was also amplified using the following amplification sequence (Forward primer: GCCCTCTGTAACAAAGTCCTAC and Reverse primer: GCCCTAAAAAAGATAACGCAATC) [9]. The amplification reaction consisted of 0.9 pmol of each primer added to 12.5 u PCR master mix which contains 3.5 mM MgCl2, 200 uM dNTPs, 5 ul 10X PCR buffer, and 2U TaqDNA polymerase (Fermentas).

The PCR protocol included: initial melting temperature of 94°C (5 minutes), amplification by 35 cycles of 20 seconds at 94°C, 20 seconds at 64°C, and 30 second at 72°C) then final extension at 72°C for 7 minutes. Analysis of PCR products on agarose gels where a fragment of 215 pb indicated the presence of GSTM1, a fragment of 480 pb indicated the presence of GSTT1 and a fragment of 280 pb indicated the positive internal control B globulin. The subjects were classified as either (+), when at least one specimen of the gene was detected, or (–) when they showed a null genotype.

Ethical considerations
The aim and nature of the study was explained for each candidate and/or parent before inclusion. An informed written consent was obtained from parents/surrogates before enrollment. Children old enough were asked for consent. Cairo University Hospital Research Ethical Committee approved the work and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Seoul 2008).

Statistical analysis
Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student’s t test for independent samples when comparing 2 groups of normally distributed data and Mann Whitney test when comparing 2 groups of non-
normal data. Kruskal Wallis test with posthoc multiple 2-group comparisons was used to compare numerical data between more than 2 groups. For comparing categorical data, Chi square ($\chi^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. Odds ratio with its 95% CI was used to present the relation between haplotypes in cases and controls. Haldane modification was used when the occurrence of any haplotypes was zero. $p$ values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

**Results**

We investigated 94 children with asthma, approximately 67% of whom were atopic, and 90 age and sex matched healthy controls. Table 1 summarizes the characteristics of both groups. Age was found to be significantly higher in controls ($p = 0.025$). Male sex was found to be significantly higher in asthmatics ($p = 0.019$). No significant differences were found between asthmatic patients and healthy controls for any of the other characteristics analyzed. Data regarding the genotype frequencies of the GSTT1 and GSTM1 homozygous deletions in asthmatics and controls are also shown in Table 1. GSTT1 null genotype was found to be significantly higher in controls than in asthmatics ($p = 0.007$, CI = 0.683, OR = 0.034-0.714). No significant difference in the genotype distribution of the GSTM1 gene was found between asthmatics and controls. No significant differences in the genotype distributions of the GSTT1 or GSTM1 genes were found between atopic and nonatopic asthmatics ($p = 0.706$ and 0.820 respectively) as shown in Table 2. Also, no significant differences in the genotype distributions of the GSTT1 or GSTM1 genes were found between asthmatics stratified by disease severity ($p = 0.236$ and 0.892 respectively) as shown in Table 3.

**Discussion**

It was recently recognized that GSTs play an active role in oxidative defenses and members of this superfamily may be determinants of respiratory health [10]. The presence of the GSTT1 null polymorphism was 87.2% and 97.2% in asthmatics and controls respectively and the results showed to be significantly higher in controls ($P = 0.007$, OR:0.683, CI: 0.034 -0.715). The results for GSTM1 were 50% and 61.1% respectively and showed to be nonsignificant ($p = 0.130$, OR: 1.000, CI: 0.539-1.857).

**Table 1 Characteristics and genotype distributions in asthmatics and controls**

|                      | Asthmatics | Controls | P-value | OR   | 95% CI     |
|----------------------|------------|----------|---------|------|------------|
| Age (Mean ± SD), years | 7.65 ± 1.916 | 8.27 ± 1.785 | 0.025* |      |            |
| Sex                  |            |          |         |      |            |
| Male                 | 62 (66%)   | 44 (48.9%) | 0.019* |      |            |
| Female               | 32 (34%)   | 46 (51.1%) |        |      |            |
| Spirometry           |            |          |         |      |            |
| FEV1 (%predicted)**  | 97 ± 6.2   |          |         |      |            |
| FVC (%predicted)***  | 96 ± 8.2   |          |         |      |            |
| Disease severity     |            |          |         |      |            |
| Mild persistent      | 21 (22%)   |          |         |      |            |
| Moderate persistent  | 36 (38.3%) |          |         |      |            |
| Severe persistent    | 37 (39.3%) |          |         |      |            |
| Atopy                |            |          |         |      |            |
| Atopic               | 67 (71.3%) |          |         |      |            |
| Non atopic           | 27 (28.7%) | 90 (100%) |         |      |            |
| Passive smoking exposure | 39 (41.5%) | 28 (31.1%) | 0.168 |      |            |
| GSTT1                |            |          |         |      |            |
| Null                 | 82 (87.2%) | 88 (97.9%) |         |      |            |
| Present              | 12 (12.8%) | 2 (2.2%)   | 0.007* | 0.683 | 0.034-0.715|
| GSTM1                |            |          |         |      |            |
| Null                 | 47 (50%)   | 55 (61.1%) |         |      |            |
| Present              | 47 (50%)   | 35 (38.9%) | 0.130 | 1.000 | 0.539-1.857|

*Data are expressed as no. (%) of patients unless otherwise indicated.

*P*-value less than 0.05 is considered statistically significant.

**FEV1**: forced expiratory volume in 1 second, **FVC**: forced vital capacity.
However, an increased risk was seen in individuals with 
by several studies in different populations [2,12-16,18].

The differences in the prevalence of asthma in different ethnic groups reflect and 
highlight genetic variances with a significant coverage of 
environmental conditions. The study declared that rapid 
change in asthma prevalence is not linked to genetic 
changes in populations because these mechanisms are 
too slow to explain this scenario and the effect of envi-
ronmental exposures and interactions between genetic 
factors and environmental conditions are still a matter 
of debate [26].

The current study revealed that the frequencies of 
GSTT1 and GSTM1 null genotypes in controls were 
97.8% and 60.1% respectively. The frequencies previously 
reported in the Egyptian population (15% and 44% re-
spectively among 34 subjects) [27] and in another study 
a higher frequencies was reported (25.50% and 55.50% 
respectively) [28]. According to our results, the fre-
quency of the GSTM1 null genotype (60.1%) was slightly 
higher than the previous Egyptian studies, comparable 
to Caucasians (50.4% -58%), Europeans (39.00-62.00%) 
and White Americans (35.00-62.00%). However, the fre-
quency of the GSTT1 null genotype (97.8%) was extremely 
higher than the range of the previous Egyptian studies, comparable 
to Caucasians (50.4% -58%), Europeans (39.00-62.00%) and 
Caucasian- Americans (10.00-26.00%).

Differences in gene frequencies among various ethnic 
groups, may explain the differences encountered. A pre-
vious study that attempted to investigate the prevalence 
of important allelic variants of several genes including 
GST gene in the Egyptian population denoted that Egypt 
is unique geographically, as it is located centrally to the 
three continents of Africa, Europe and Asia, so its popu-
lation is highly affected by the rapid pace of intercontinen-
tal transportation and large-scale immigration and that 
throughout history, the Greeks, Romans, Arabs, Turks, 
French and British have all ruled Egypt and mixed with its 
people, so that modern Egypt now is an amalgam of all 
these legacies. So, there is a considerable genetic admix-
ture in the Egyptian population [28]. This genetic admix-
ture explains more the differences encountered between 
the results of the current study done in Cairo- central 
Egypt- and that performed in Zagazig- northern Egypt.

The present study compared the GSTT1and GSTM1 
null genotypes among asthmatic patients with the levels 
of asthma severity whether mild (87.5% and 50% re-
spectively), moderate (80.6% and 52.8% respectively) or 
severe persistent (94.1% and 47.1% respectively) and it

| Table 2 Genotype distributions in atopic asthmatics and non-atopic asthmaticsa |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Atopic asthmatics n = 67 (%) | Non-atopic asthmatics n = 27 (%) | P-value |
| GSTT1                       |                             |                             |          |
| Null                        | 59 (88.1%)                  | 23 (85.2%)                  | 0.706    |
| Present                     | 8 (11.9%)                   | 4 (14.8%)                   |          |
| GSTM1                       |                             |                             |          |
| Null                        | 33 (49.3%)                  | 14 (51.9%)                  | 0.820    |
| Present                     | 34 (50.7%)                  | 13 (48.1%)                  |          |

aData are expressed as no. (%) of patients unless otherwise indicated.

A systematic review and meta-analysis for the effects of 
GST genes on asthma demonstrated that a large Avon 
Longitudinal Study of Parents and Children found a 
protective effect on asthma of the GSTT1 null allele 
in mothers (OR: 0.71; 95% CI: 0.57–0.90 and 0.84; 0.63–1.12, for heterozygotes and null homozygotes, 
respectively, compared with wild-type homozygotes) and 
children (0.91; 0.76–1.11 and 0.89; 0.70–1.13) [11]. No 
association of the disease with GSTT1 null genotype 
was noted by several studies in different populations 
[2,12-20]. However, in contrary to our findings an in-
creased risk was seen in individuals with this genotype 
in some studies [3,21-24]. Similarly, a study performed 
on Egyptian population in Zagazig -located in northern 
Egypt- showed that asthmatic children had a significant 
lower prevalence of GSTT1 null genotype than the control 
group (P = 0.003). However, a higher prevalence of 
the GSTM1 null genotype was observed in the asthmatic 
group [25]. As our study was performed in Cairo- the 
capital of Egypt located in the centre- the enrolled patients 
were referred from upper Egypt that's why a difference in 
GSTM1 null genotype frequencies among asthmatics and 
controls in the two studies.

In agreement with the current study results, no associ-
ation of the disease with GSTM1 null genotype was noted 
by several studies in different populations [2,12-16,18]. 
However, an increased risk was seen in individuals with 
this genotype in some reports [3,17,19-24]. The fact that 
asthma pathogenesis is a result of interactions between 
multiple genetic and environmental factors highlight that 
exposure to environmental chemical agents may explain 
the differences encountered.

| Table 3 Genotype distributions in asthmatics stratified by 
disease severitya |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Mild persistent n = 24 (%) | Moderate persistent n = 36 (%) | Severe persistent N = 34 (%) | P-value |
| GSTT1                       |                             |                             |                             |          |
| Null                        | 21 (87.5%)                  | 29 (80.6%)                  | 32 (94.1%)                  |          |
| Present                     | 3 (12.5%)                   | 7 (19.4%)                   | 2 (5.9%)                   | 0.236    |
| GSTM1                       |                             |                             |                             |          |
| Null                        | 12 (50%)                    | 19 (52.8%)                  | 16 (47.1%)                  |          |
| Present                     | 12 (50%)                    | 17 (47.2%)                  | 18 (52.9%)                  | 0.892    |

aData are expressed as no. (%) of patients unless otherwise indicated.
revealed no statistical significance (P value: 0.236 and 0.892 respectively). These findings were supported by several studies [12,14,15,29,30].

Regarding the genetic polymorphisms of GSTT1 and GSTM1 among atopic asthmatic patients and non-atopic asthmatics, no significant statistical difference in GSTT1 and GSTM1 polymorphisms was noted between the two groups (P value: 0.706 and 0.820 respectively). In agreement with the current study, a study done on Egyptian population in zagazig announced that there is no significant association found between atopy and GSTT1 polymorphism. However, they found that the GSTM1 null genotype was significantly higher in atopic asthmatic cases than in nonatopic asthmatic subjects (P = 0.01) [25].

Comparison of our results with other studies indicates that GSTT1 and GSTM1 null genotypes were not universally associated with the asthma phenotypes. The genetic basis of asthma may differ between different ethnic groups. Future studies of large size should focus on interactions of GST genes with environmental oxidative exposures and with other genes involved in antioxidant pathways. Quality of study conduct and reporting need to be improved to increase credibility of the evidence accumulating over time.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
NMR, NKG and MMW - Designed, conducted and analyzed the study, NAM and NMR - Analyzed the data and drafted the manuscript. All authors reviewed and approved the manuscript.

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Author details
1Department of Pediatrics, Faculty of Medicine, Cairo University, Giza, Egypt. 2Department of Clinical Pathology, Faculty of Medicine, Cairo University, Giza, Egypt. 3New University Children’s Hospital (Abu El Reish), 4 - Gamil Salem St. Doki, Cairo, Egypt.

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