CLINICAL STUDY

Implication of glutathione S-transferase M1 and T1 polymorphisms in the development of senile cataract among Egyptians

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Abstract: *Objectives:* To determine the effect of glutathione S-transferases M1 and T1 polymorphisms on the risk of senile cataract among Egyptians.
Background: The glutathione S-transferases (GSTs) are polymorphic enzymes that are important in the protection against oxidative damage.
Methods: Using a multiplex polymerase chain reaction (PCR), GSTM1 and GSTT1 gene polymorphisms were evaluated in 53 Egyptians with senile cataract and in 73 healthy individuals of the control group.
Results: The frequency of GSTM1-positive individuals among the senile cataract group was significantly higher than in controls. The risk among the GSTM1-positive individuals of developing senile cataract was even higher in females. It is also increased with combination of "GSTM1-positive and GSTT1-positive" genotypes. However the combination of "GSTM1-null, GSTT1-positive" was found to be protective (OR=0.47; 95 % CI: 0.22−0.99; p=0.045).
Conclusion: The GSTMI-positive genotype and the combined "GSTM1-positive /GSTT1-positive" genotype may be associated with an increased risk of development of senile cataract among Egyptians. However, the "GSTM1-null/GSTT1-positive" genotype was found to be protective. Therefore, when evaluating the role of a particular GST gene in disease susceptibility, the whole pattern of different biotransformation enzymes should be taken into account *(Tab. 4, Fig. 1, Ref. 36).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: glutathione S-transferase, polymorphism, activity, oxidative stress, senile cataract.

Cataract, or opacification of the lens, is one of the most common causes of loss of useful vision among Egyptians (1). Currently, surgery is the only approach for the treatment of cataract, and the etiology of age-related changes in the lens is not fully understood (2).

Oxidative stress has been identified as one of the major causes of age-related cataract. Generation of reactive oxygen species (ROS) resulting in degradation, cross linking, and aggregation of lens proteins, is regarded as an important factor in cataractogenesis. Cellular defense mechanisms protecting against the toxic effects of oxidative insult must therefore play an important role in the defense against development of cataract (3).

Glutathione is the most abundant non-protein intracellular thiol, with multiple roles as antioxidant agent. Reduced glutathione (GSH) acts to scavenge reactive oxygen species as well to regenerate other antioxidants from their oxidized forms (4). The decreased level of GSH would enhance photo-oxidation and

induce lipid peroxidation with Malodialdehyde (MDA) as a final product (5). It has been hypothesized that protein S-thiolation, or the formation of protein-thiol mixed disulfides, is the earlier damage to lens proteins during age-related cataractogenesis. Glutatione-S-transferase (GST) dethiolates protein-S-S- glutathione in the human lens (3). It is one of the enzymes that are important in the protection of the eye from oxidative damage. Beside detoxifying exogenous electrophilic xenobiotics, these transferases inactivate endogenous end products formed as secondary metabolites during oxidative stress (6).

The GST isoenzymes expressed in human tissues comprise alpha, mu, pi, theta, kappa, sigma, zeta and omega gene families. Human lens tissue has been shown to express classes mu, theta, and pi. Because many GST genes are polymorphic, there has been considerable interest in determining whether particular allelic variants are associated with altered risk of a variety of pathologies like senile cataract (7).

GSTM, GSTT and GSTP have been found to have functional polymorphisms that are frequently present in the general population (8). GSTM1 and GSTT1 polymorphisms are the most common polymorphisms of GST enzymes in the human population with major ethnic differences. In contrast with GSTP1, polymorphism in GSTM1 and GSTT1 genes can lead to total absence of the enzymatic activity (9). Therefore, the aim of this study was

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to investigate the distribution of GSTM1 and GSTT1 polymorphisms together with enzymatic activity in patients with age-related cataract and healthy controls to explore the possible association between different GST variants and the risk of senile cataract development among Egyptian patients.

Methods

A case control study included 53 patients with senile cataract selected consecutively and had cataract surgery at Research Institute of Ophthalmology (RIO). Patients with secondary cataract, diabetes mellitus or other systemic diseases were excluded. Seventy-three normal subjects who were volunteers matched according to age and sex, with normal ocular and systemic examination were selected as a control group. All patients and controls were subjected to personal and family history taking and general examination for exclusion of associated systemic disorders. Ophthalmological evaluation included best corrected visual acuity, dilated slit-lamp biomicroscopy for cataract diagnosis, grading of opacity and exclusion of any local etiology of cataract.

Venous blood samples (6ml) were obtained from all subjects and divided into three tubes; 3 ml was taken on EDTA and submitted to genomic DNA extraction from peripheral blood leucocytes using QIA amp DNA mini kit (QIAGEN, Inc., Germany). 2 ml was taken in dry clean tubes for serum separation and determination of glutathione S-transeferase activity and malondialdehyde level. Finally, 1 ml was taken on ACD for GSH determination.

Analysis of GSTM1 and GSTT1 polymorphisms

The GSTM1 and GSTT1 genetic polymorphisms were evaluated using multiplex polymerase chain reaction (PCR) technique as described before (10). Primers for GSTM1 were 5'-GAACTC-CCTGAAAAGCTAAAGC and 5'-GTTGGGCTCAAATATAC-GGTGG while for GSTT1 were 5'-TTCCTTACTGGTCCTCAC-ATCTC and 5'-TCACCGGATCATGGCCAGCA. The beta globin locus was used as an internal control to avoid false negative readings. Primers for beta globin were 5'-CAACTTCATCCACG-TTCACC and 5'-GAAGAGCCAAGGACAGGTAC. PCR reaction was carried out in a total volume of 25 µl containing 10 pmol of each primer, 2.5 mmol/L of $MgCl_2$, 0.2 mmol/L each deoxy-nucleotide triphosphate, 1 unit of Taq polymerase, and 100 ng of genomic DNA. Amplification was performed by initial denaturation at 94 °C for 5 min, followed by 30 cycles at 94 °C for 1 min, 64 °C for 1 min and 72 °C for 1 min and a final extension of 72 °C for 7 min.

The amplified products were identified by electrophoresis in a 1.5 % agarose gel and stained with 0.5µg/ml ethidium bromide. The product lengths were 215 bp, 480 bp, and 268 bp for GSTM1, GSTT1 and beta globin, respectively. Absence of PCR product for GSTM1 or GSTT1 in the presence of the β-globin band was indicative of a null genotype for GSTM1 or GSTT1. Individuals with one or two copies of the relevant gene were classified as a "present" genotype and those with homozygous deletions as a "null" genotype.

Glutathione S-transeferase assay

GST activity in serum was assayed according to the method of Habig et al (11) using chlorodinitrobenzene (CDNB) as a substrate. The activity of the enzyme in serum was expressed as u/L.

Reduced glutathione (GSH) measurement

GSH was measured according to the method of Beutler et al (12), which is based on the reduction of 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) with glutathione to produce a yellow compound.

Malondialdehyde (MDA) measurement

Serum malondialdehyde concentration was determined by measuring the pink-colored chromophore upon reaction with thiobarbituric acid at 535 nm according to Satoh (13). The results were expressed as nmol/ml.

Statistical analysis

Ages, glutathione-S-transferases activity, reduced glutathione (GSH) and malondialdehyde (MDA) serum levels of patients, and control groups were compared with Student's t test. Odd ratios (OR) and confidence intervals (CI) were used to compare differences in gender, association between GSTMI and GSTT1 genotypes and risk of senile cataract and association between cataract and combinations of GSTM1 and GSTT1 genotypes. Statistical significance was set at $p < 0.05$. Analysis was performed using SPSS v.10 statistical analysis software.

Tab. 1. Demographic data of senile cataract patients and controls.

	Senile cataract	Controls	OR	95%CI	p value
Number of patients	53	73	–	–	–
Gender					
Male, n (%)	22 (42%)	31 (42.5%)			
Female, n (%)	31 (58%)	42 (57.5%)	1.04	0.51–2.13	>0.05
Age (years)					
Range	(45–78)	(44–80)	–	–	>0.05
Mean±SD	61.0±7.8	60.13±8.81	–	–	

Results

Ophthamological examination revealed that 30 patients (16.6 % males and 83.4 % females), had mature cataracts, while 23 patients (73.9 % males and 26.1 % females) had immature cataracts. The demographic data of the patients and controls were shown in Table (1). The two groups were not significantly different with respect to age (p>0.05) and gender (p>0.05; OR= 1.04; 95 % CI, 0.51–2.13). The association between GSTM1and GSTT1 genotypes and the risk of development of senile cataract in the patients and controls were shown in Table 2. Although

there was a statistically significant relationship between GSTM1 genotype and the risk of cataract development in patients, (p= 0.029: OR=2.22, 95 % CI, 1.08–4.57) the stratification by sex of the subjects revealed that this significance is only in female patients with (OR=3.41 and p=0.012). However the increase in GSTM1 genotype in patients was not statistically significant in males (p=0.688; OR=1.26).

Considering the possible additive effect of different GST genotypes the association between genotype profile and cataract risk was examined (Tab. 3). The combination of "GSTM1 positive, GSTT1 positive" had a significantly higher risk for devel-

Tab. 2. Association between GST genotypes and senile cataract risk.

Genotype	Sex	Cataract (%)	Control (%)	OR	95% CI	p value
GSTM1	Both sexes					
Positive		30 (57%)	27 (37%)	2.22	1.08–4.57	0.029*
Null		23 (43%)	46 (63%)			
GSTT1						
Positive		37 (70%)	52 (71%)	0.93	0.43–2.03	0.863
Null		16 (30%)	21 (29%)			
GSTM1	females					
Positive		21 (68%)	16 (38%)	3.41	1.28–9.07	0.012*
Null		10 (32%)	26 (62%)			
GSTT1						
Positive		22 (71%)	29 (69%)	1.096	0.397–3.02	0.86
Null		9 (29%)	13 (31%)			
GSTM1	males					
Positive		9 (41%)	11 (35%)	1.26	0.41–3.87	0.688
Null		13 (59%)	20 (65%)			
GSTT1						
Positive		15 (68%)	23 (74%)	0.75	0.22–2.49	0.632
Null		7 (32%)	8 (26%)			

* p<0.05 is significant

Tab. 3. Association between cataract development and combinations of GSTM1 and GSTT1 genotypes.

Genotype combination		Cataract n (%)	Control n (%)	OR	95% CI	p value
GSTM1	GSTT1					
Positive	Positive	21 (40%)	17 (25%)	2.16	0.998–4.68	0.049*
	Male	5 (10%)	7 (10%)			
	Female	16 (30%)	10 (13%)	0.45	0.11–1.79	0.252
Positive	Null	9 (17%)	10 (14%)	1.46	0.54–3.96	0.461
	Male	4 (8%)	4 (6%)			
	Female	5 (9%)	6 (8%)	1.2	0.19–7.44	0.845
Null	Positive	16 (30%)	35 (48%)	0.47	0.22–0.99	0.045*
	Male	10 (19%)	16 (22%)			
	Female	6 (11%)	19 (26%)	1.98	0.59–6.64	0.266
Null	Null	7 (13%)	11 (15%)	0.86	0.31–2.38	0.768
	Male	3 (6%)	4 (5%)			
	Female	4 (7%)	7 (10%)	1.31	0.19–9.10	0.783

* p<0.05 is significant

Tab. 4. Glutathione S-transferase (GST) activity; reduced glutathione (GSH) and malondialdehyde (MDA) levels in senile cataract patients and control subjects.

	Senile cataract (n=53)	Control (n=73)
GST(U/L)		
Range	(2.53−9.80)	(7.03−19.68)
Mean±SD	6.1±1.76*	11.46±2.80
GSH (mg/dl erythrocytes)		
Range	(20−77)	(61−109)
Mean±SD	43.91±15.7*	79.37±13.02
MDA (nmol/ml)		
Range	5.3−7.5	(0.72−5.76)
Mean±SD	6.37±0.54*	2.82±1.48

* p<0.001 significant relative to control

Fig. 1. Agarose gel electrophoresis of PCR amplification products of GST M1 and T1 polymorphisms. The 480 bp band corresponds to GSTT1, 268 bp to β-globin and 215 bp to GSTM1. Lanes 1, 3, 6 and 8: GSTT1 positive/GSTM1 positive. Lanes 2 and 5: GSTM1 positive/GSTT1 null. Lanes 7 and 9: GSTT1 positive/GSTM1 null. Lane 4: GSTM1 null/GSTT1 null .M: φx 174/HaeIIII ladder.

oping cataract than individuals with other combinations (OR= 2.16; 95 % CI, 0.998−4.68 and p=0.049). However the combination of "GSTM1 null, GSTT1 positive" was found to protect from the development of senile cataract (OR=0.47; 95 % CI: 0.22−0.99; p=0.045). The study also showed a significantly decreased serum activity of GST, a decreased blood level of reduced glutathione (GSH) and an increased level of malondialdehyde (MDA) in senile cataract patients relative to controls (p<0.001) (Tab. 4). Figure 1 showed agarose gel electrophoresis of PCR amplification products of GST M1 and T1 polymorphisms.

Discussion

Oxidative damage can result in a number of molecular changes that contribute to the development of cataract. Crystallins and other proteins in lens fiber cells do not turn over and must serve the lens for a lifetime. Thus, the lens must have efficient reducing and detoxification systems (14). Recent biochemical and epidemiological studies have led to the conclusion that polymorphic GSTs are important in the metabolism and induction of numerous known or suspected endogenous and exogenous compounds (15). GSTs, the first enzymes in the mercapturic acid pathway, catalyze the nucleophilic addition of the thiol of GSH to many possibly harmful compounds, and this is important for detoxification of xenobiotics and for protection of lens and other tissues from oxidative damage. Cataractogenesis is a highly complex multifactorial process, and oxidative damage of the lens is the major risk factor for the development of senile cataract (16). On the basis of the fact that allelic variants of GSTs have different ability to conjugate substances to glutathione, the role of GST polymorphism in several diseases, including eye diseases as cataract, has been hypothesized (17, 18). Average or increased enzyme activity may protect susceptible tissues from electrophilic toxic metabolites by facilitating their conjugation and subsequent elimination. Decreased or deficient GST enzyme activity may result in poorer elimination of toxic compounds and therefore results in increased risk of toxicity, leading to the formation of a tumor or disease (19).
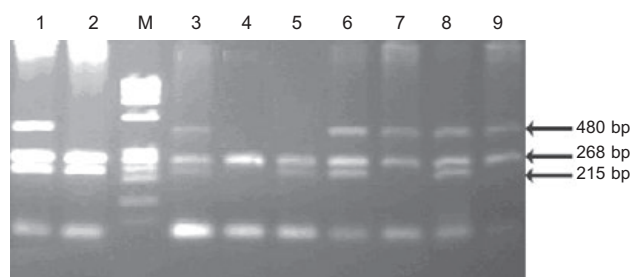
To our knowledge, the present study is the first attempt to examine the possible association between polymorphic GST genotypes and senile cataract in Egyptian patients.

Contrary to the hypothesis of the protective role of GSTs, we found approximately a two-fold increased risk of senile cataract associated with GSTM1 genotype (OR=2.22). There were several reasons helping in the conclusion that the GSTMI gene is involved in modifying the genetic susceptibility to senile cataract. Firstly, the risk of developing senile cataract associated with the GSTM1 genotype was remarkably higher in females (p=0.012; OR, 3.41, CI 95 %, 1.28−9.07) as compared to males (p=0.688; OR, 1.26, CI 95 %, 0.41−3.87) in the present study. Females were found to be at an increased risk of developing senile cataract and more severely affected than males (20, 21, 22). Also, there was a significantly increased risk of developing senile cataract among the combination of GSTM1 GSTT1 genotype (p=0.049; OR, 2.16, CI 95 %, 0.998−4.68).

These results support the hypothesis that different mechanisms may be implicated during the development of cataract (16). The exact molecular mechanisms, by which the expressing genotypes of GSTM1 and GSTT1 loci conduce to increase the cataract risk, remain to be elucidated in subsequent studies. Although GSTs are generally recognized as detoxifying enzymes, they may also be involved in generation and activation of toxic compounds (23, 24). Possibly, during cataractogenesis the GSTM1 and GSTT1 enzymes take part in activation and formation of some toxic metabolites derived from nutrition, drug metabolism, or environmental pollution. The formed toxic metabolites can induce changes in the protein structure, thus favoring the aggregation of lens proteins and promoting the development of cataract (25). Juronen and his colleagues (14) found that the risk of GSTM1-positive phenotype was significantly higher in cortical cataract group than in controls with odds ratio of 1.88 and p=0.004, and this risk was increased in carriers of the combined GSTM1--positive/ GSTT1-positive phenotype (OR=1.99, p=0.002).They supposed that interethnic differences in senile cataract incidence could partly be explained by differences in gene frequencies of polymorphic glutathione-S-transferases. However, Alberti et al

(26) documented a lack of association between glutathione-S-
-transferase M1 genotype and age-related cataract in the Italian
population, and an association between homozygous deletion of
GSTM1 and cataract was found in a Japanese population (18).
The apparent discrepancy could be explained by the possibility
that the results reflect differences in genetic (including GST poly-
morphism), nutritional, and environmental backgrounds of the
populations studied. Abu-Amero and his colleagues (27) stud-
ied glutathione S-transferase M1 and T1 polymorphisms in Arab
glaucoma patients, which is also an ophthalmic disease related
to oxidative stress. Their results indicate a possible variable as-
sociation between various GSTM1 and GSTT1 genotypes and
glaucoma in this population.

Previous studies showed that GSTM1 null individuals ex-
press less GSTM3 and possibly other GST Mu-class enzymes
than subjects with the GSTM1 positive genotype (28, 29). The
protective role of the GSTM1null genotype against senile cata-
ract found by this study may be connected with the suppression
of other GST Mu-class isoenzymes. The GSTM1 deletion oc-
curring in the GST Mu gene cluster probably leads to a decreased
expression or deficiency in other GST Mu class enzymes as well,
and can cause a selective activation of other detoxifying enzymes.
It has been suggested that multiple detoxification enzymes may
be involved in the metabolism of a given compound (30). The
other biotransformation enzymes have probably the same sub-
strate specificity as GST Mu-enzymes, but metabolites formed
could be non-toxic.

The significant decreased level of reduced glutathione in se-
nile cataract patients relative to controls detected in this study
($p<0.001$) would enhance photo-oxidation and induce lipid
peroxidation as indicated by the significant increased level of
malondialdehyde (MDA). MDA was known to play a role in
lens opacification, and can form cross-links between membrane
lipids and proteins (5).

The observations of the present study are generally in agree-
ment with previous studies, which concluded that the decrease
in erythrocyte glutathione is associated with cataract formation
(31, 32). Since glutathione stabilizes the GST enzyme (33), and
it is assumed that the deficiency in GST activity in the plasma of
the cataract patients is due to the instability of this enzyme in the
absence of adequate GSH levels. On the other hand, in spite of
that, some authors claimed that the GST activity is significantly
decreased in cataractous lenses compared with normal clear age-
matched lenses; a large inter-individual variation in GST activ-
ity of human lenses has been observed (34). Murata and his col-
leagues (35) demonstrated that, mammalian Mu-class lens en-
zymes are activated by various oxidative stress agents. Due to
severe oxidative stress, the activation of Mu class of GST lens
isoenzyme may be involved in activation or formation of some
toxic metabolites that induce changes in the crystallin structure,
thus favouring aggregation of lens protein and promoting the
pathogenesis of cataract.

The relationship between polymorphic GSTs with the other
cataractogenic genetic and environmental factors is highly com-
plicated. A number of studies, including the present one suggest

that when evaluating the role of a particular GST gene in any
disease susceptibility, the whole pattern of different biotransfor-
mation enzymes should be taken into account as much as pos-
sible, because multiple detoxification enzymes may be involved
in the metabolism of a given compound (36), and forming me-
tabolites may be affected differently. Extensive research is re-
quired to ascertain as to how exactly the GST genotype affects
the individual susceptibility to cataract and which detoxifying
enzymes and environmental factors are responsible for the de-
velopment of cataract. The importance to evaluate this matter
further is related to the possibility of developing a non-invasive
diagnostic tool for analyzing genotypes and predicting the inter-
individual susceptibility to the disease.

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