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ORIGINAL ARTICLE / *ARTICLE ORIGINAL*

# GSTM1 and GSTT1 polymorphisms, tobacco use as risk factors for nasopharyngeal carcinoma in maghreb population — A case-control study

## Polymorphismes GSTM1 et GSTT1 ainsi que tabagisme comme facteurs de risque du carcinome nasopharyngé dans la population maghrébine — Étude cas-témoin

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**Abstract** Nasopharyngeal carcinoma (NPC) has known environmental risk factors, notably smoking, and enzymes that biotransform carcinogens. The interindividual differences observed in the metabolism of tobacco carcinogens substances have been attributed to the genetic polymorphism of genes, which code for enzymes involved in detoxification. Polymorphic deletions of GSTM1 and GSTT1 genes involved in the detoxification of potentially carcinogenic agents may be a risk factor for NPC. To investigate the roles of genetic variations of GSTM1 and GSTT1 in NPC susceptibility in the Northern African population, we conducted a case–control study of 132 NPC cases and 200 controls. DNA was isolated from blood for cases and controls. GSTM1 and GSTT1 deletion variants were genotyped by multiplex PCR assays. Allelic frequencies between the two groups were compared using a $\chi^2$ test, and odds ratio (OR) with 95% confidence intervals were calculated. The results indicate that an excess of the *GSTM1* null genotype was observed in cases compared with controls, 50% *versus* 33%. The genotypic frequency of GSTM1 null genotype between controls and patients was significantly different. This genotype confers an increased risk of NPC [OR = 2.18; CI 95% (1.23–5.33). The association between GSTM1 and increased NPC risk in this cases-controls study was present among both men [OR = 2.59 ; CI95% (1.81–4.32)] and smokers. No significant association was observed between null GSTT1 genotype and the risk of CNP.

**Keywords** Nasopharyngeal carcinoma · Glutathione transferase · Tobacco

**Résumé** Le carcinome nasopharyngé (NPC) est lié à des facteurs de risque environnementaux connus, notamment le tabagisme et des enzymes qui biotransforment les agents cancérigènes. Les différences entre individus observées dans le métabolisme des substances cancérigènes du tabac ont été attribuées au polymorphisme génétique des gènes, dont le code pour les enzymes impliquait une détoxication. Les délétions polymorphiques des gènes *GSTM1* et *GSTT1* impliqués dans la détoxication des agents potentiellement cancérigènes pourraient constituer un facteur de risque du NPC. Pour analyser le rôle des variations génétiques des gènes *GSTM1* et *GSTT1* dans la vulnérabilité au NPC de la population nord-africaine, nous avons mené une étude cas-témoin sur 132 cas de NPC et 200 témoins. L'ADN a été isolé du sang pour les cas et pour les témoins. Les variantes par délétion des gènes *GSTM1* et *GSTT1* ont été génotypées par analyse PCR multiplexe. Les fréquences alléliques entre les deux groupes ont été comparées à l'aide d'un test $\chi^2$ et les taux de probabilité (OR) ont été calculés avec des intervalles de confiance de 95 %. Les résultats indiquent qu'un excès de génotype GSTM1 nul a été observé dans les cas par rapport aux témoins, 50 versus 33 %. La fréquence génotypique du génotype GSTM1 nul entre les témoins et les patients était sensiblement différente. Ce génotype confère un risque

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accru de NPC (OR = 2,18 ; IC 95 % : [1,23–5,33]). L'association entre GSTM1 et risque accru de NPC dans cette étude cas-témoin était présente à la fois sur les hommes (OR = 2,59 ; IC 95 % : [1,81–4,32]) et sur les fumeurs. Aucune association significative n'a été observée entre le génotype GSTT1 nul et le risque de CNP.

**Mots clés** Carcinome nasopharyngé · Glutathion-transférase · Tabac

## Introduction

Nasopharyngeal carcinoma (NPC) is a fast-growing tumor characterized by a high frequency of nodal and distant metastasis at diagnosis. NPC represents in Algeria and Tunisia the first most common aero digestive ways cancers in women and the second most common tumor in men [1,2]. The most common histological type is undifferentiated nasopharyngeal carcinoma types (UNCTs).

Nasopharyngeal carcinoma is thought to be caused by the combined effects of EBV, environmental carcinogens, and genetic susceptibility. Case–control studies have indicated a strong role for environmental factors [3,4], but smoking and alcohol drinking are considered as independent risk factors [5].

Xenobiotics and chemical compounds present in tobacco smoke undergo metabolic activation by liver enzymes. Two groups of enzymes are involved in the process of biometabolization of chemical compounds: the enzymes of oxidative metabolism (Phase I) and conjugating enzymes (Phase II). Phase I oxidative enzymes, mainly the families pertaining to the cytochrome P-450 superfamily (CYPs), convert many compounds into highly reactive metabolites. On the other hand, Phase II enzymes act deactivating Phase I products, making metabolites hydrophilic and liable to excretion as a result of their conjugation with the endogenous substrate (glutathione, sulphate, glucose, acetate) by means of the action of glutathione S-transferases (GSTs) and N-acetyltransferases (NATs).

Glutathione S-transferases constitute a super family of ubiquitous, multifunctional enzymes, which play a key role in cellular detoxification of exogenous chemical carcinogens, such as aromatic polycyclic hydrocarbons present in the tobacco. They comprise four classes of genes (α, μ, π, and θ) and each class, on their turn, include various genes [6].

Polymorphisms in genes that codify GSTM1 and GSTT1 may alter their expression or function and result in activation or detoxification of carcinogenic compounds.

The polymorphisms of the GSTM1 and GSTT1 genes involved may result in differences in the enzymatic activity, possibly favoring mechanisms that increase the susceptibility to cancer [7].

GSTM1 and GSTT1 are known to be highly polymorphic. This genetic variation may change an individual's susceptibility to carcinogens and toxins, as well as affect the toxicity and efficacy of certain drugs [4]. GSTM1 is located on chromosome1p13.3 and is a homologous recombination.

Involving left and right 4.2-kb repeats, resulting in a 16-kb deletion containing the entire GSTM1 gene. GSTT1 is located at 22q11.2 and, like GSTM1, is a deletion produced by a homologous recombination event involving left and right 403-bp repeats, resulting in a f54-kb deletion containing the entire GSTT1 gene [5]. Homozygous deletions of these genes, referred to as GSTM1 null and GSTT1 null, respectively, result in lack of enzyme activity [8,9].

Studies relating these polymorphisms of deletion with the occurrence of nasopharyngeal carcinoma diverge between themselves: some demonstrate the association of these neoplasias with the null genotype of GSTM1, while others do not. The same occurs with the null genotype of GSTT1, showing an association with the disease or not [10–13].

Here, we conducted a case–control study with 132 nasopharyngeal carcinoma cases and 200 controls to determine whether the deletions of the GSTM1 or GSTT1 genes are associated with nasopharyngeal carcinoma risk in Northern Africa, in an attempt to define genetic factors involved in the susceptibility to this cancer, which seems to be strongly associated with tobacco consumptions.

## Material and methods

### Study groups

The patients were recruited at Salah Azaiez Institut in Tunisia and in the Otorhinolaryngology and Head and Neck Surgery service in a university hospital in Constantine and in Khenchela in Algeria. This group consisted of 132 individuals. All were histologically verified to have a nasopharyngeal carcinoma. UNCTs were predominant (89%). The healthy group consisted of 200 individuals without any prior diagnosis of cancer recruited among the familial surrounding. Controls were frequency matched with case on age, gender, and tobacco consumption. Informed consent was obtained from patients and controls.

### Methods

#### *Genotyping*

DNA was isolated from leukocytes in 5 ml of peripheral blood. The presence of the GSTM1 null and GSTT1 null polymorphism was screened using a multiplex PCR using three sets of primers to amplify a 215-bp sequence of the *GSTM1* gene, a 380-bp sequence of the albumin gene, and a 480-bp segment of the *GSTT1* gene (Fig. 1). Presence or absence of the albumin band was used to determine failed PCR. This procedure was described by Jong et al. [14] (Table 1). The 50 µl reaction mixture contained 0.25 µg of genomic DNA, 0.45 pmol/µl for each primer, 1X Taq buffer (50 mM Kcl, 20 mM tris Hcl pH 8.4, 5 mM Mgcl2); 200 µM each dNTP, 2U of Taq DNA polymerase. Cycling conditions consisted of 5'at 94° for initial denaturation and 2'at 64° for initial hybridation followed by 30 cycles: at 72°C for 1min (elongation), at 94°C for 20 sec (denaturation), at 64°C for 20 sec (hybridation), and final extension at 72° for 7'. A 10 µl of each PCR product was visualized on an agarose gel at 1% with ethidium bromide staining.

### *Statistical analysis*

The $\chi^2$ test was used to assess the distribution of allele frequencies between groups. Odds ratio (OR) and their 95% confidence intervals (CI) were calculated using epi-info logiciel to estimate the relative risk association with certain genotype.

## Results

The deletion polymorphisms for GSTM1 and GSTT1 were genotyped in 132 nasopharyngeal carcinoma cases and 200 controls. The analyzed distributions of the alleles in

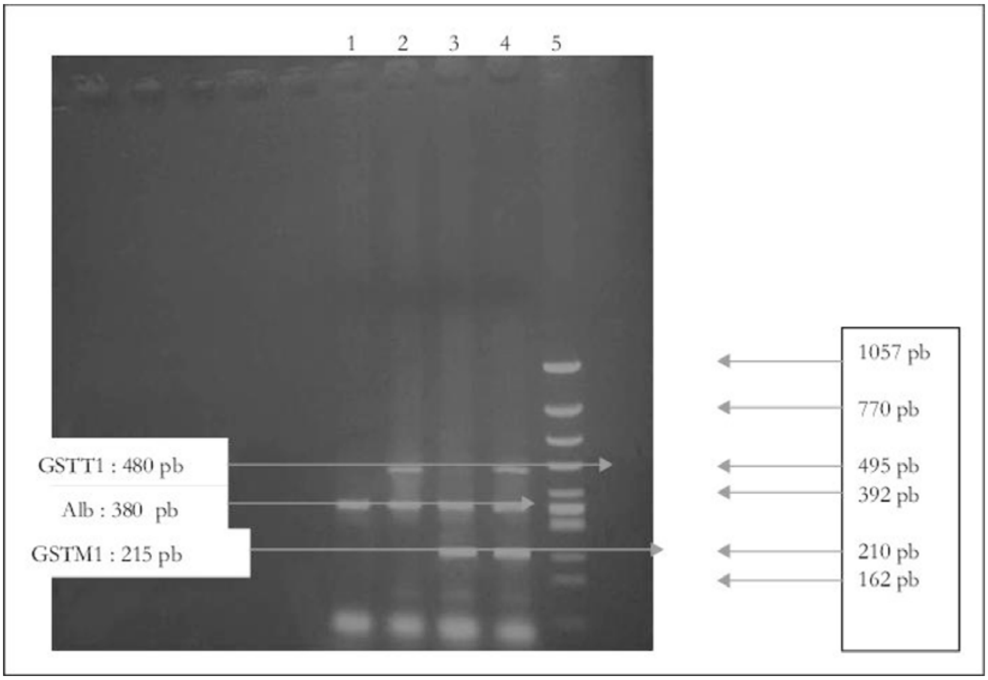

**Fig. 1** Multiplex PCR of GSTM1and GSTT1. **1**) GSTM1 (0/0)/GSTT1 (0/0); **2**) GSTM1 (0/0)/GSTT1 (+) ; **3**) GSTM1 (+)/GSTT1 (0/0) **4**) GSTM1 (+)/GSTT1 (+) ; **5**) molecular weight marker

**Table 1** Primer for amplification of GSTM1, GSTT1 genes.

| Genes | PRIMER | Fragment size |
|---|---|---|
| GSTM1 | 5'-GAACTCCCTGAAAAGCTAAAGC-3'<br>5'-GTTGGGCTCAAATATACGGTGG-3' | 215 pb |
| GSTT1 | 5'-TTCCTCACTGGTCCTCACATCTC-3'<br>5'-TCACCGGATCATGGCCAGCA-3' | 480 pb |
| ALB | 5'-GCCCTCTGCTAACAAGTCCTAC- 3'<br>5'-GCCCTAAAAAGAAAATCGCCAATC-3' | 380 pb |

patients and control individuals were found to be in Hardy–Weinberg equilibrium.

In this study, male individuals were dominant in the group of patients (82 men and 50 women), with mean age of 47 years. All were histologically verified to have a nasopharyngeal carcinoma. The healthy group without any prior diagnosis of cancer were recruited among the familial surrounding. The control group is represented by 59% of male individuals and with a mean age of 49 years (Table 2). Controls were frequency matched with cases on age, gender, and tobacco consumption. Informed consent was obtained from patients and controls.

Table 3 lists the genotype distribution of the GSTM1 and GSTT1 in the total cohort. The GSTM1 and GSTT1 null genotypes were detected in 50% and 33% of the patients, respectively. There was no significant difference (P = 0.39–0.88) in the GSTT1 null genotype between patients and cases males and females.

The odds ration value for the association of GSTM1, GSTT1, and the nasopharyngeal carcinoma suggested an association between GSTM1 0/0 and the NPC.

Odds ratio for NPC associated with GSTM1 null genotype are presented in Table 4 and were adjusted for age, gender, and cigarettes. Table 4 showed a little variation in risk according to men who were homozygous for the null GSTM1 genotype compared with women. Distribution according to age showed that the most elevated risk was observed in subjects with 20–40 years of age (OR = 6.12 CI 95%[4.71–14.6]). A less important risk was observed among those of 60 years older. Similarly, the higher risk was observed among tobacco-user patients (OR = 3.21 CI 95% [2.01–3.86]).

Table 5 presents the results of the combined genotypes analysis, in which GSTM1 null/GSTM1+ presents an increase for the risk of head and neck cancer (OR= 6.94; CI 95% [1.98–14.94]; p = 0.0066].

**Table 2** Distribution of demographic factors and tobacco use among patients and controls.

| Characteristics | Cases 132 | Controls 200 |
|---|---|---|
| Average of age | 47 years | 49 years |
| Sex (men/women) | 82/50 | 118/82 |
| Number of smokers/non smokers | 50/82 | 44/156 |
| 20–40 years | 30 | 34 |
| 40–60 years | 70 | 104 |
| +60 years | 32 | 62 |

**Table 3** Genotype distribution of GSTM1 0/0 and GSTT1 0/0 in control individuals and NPC patients.

| Genotypes | Patients (132) | | Controls (200) | | *p* | OR (95% CI) |
|---|---|---|---|---|---|---|
| | Nb | % | Nb | % | | |
| GSTMI *0/0* | 66 | 50 | 66 | 33 | <0.05 | 2.18 (1.23–5.33) |
| GSTT1 *0/0* | 32 | 24.24 | 40 | 20 | NS | 1.08 (0.6–2.32) |

NS: not significant.

## Discussion

The GST is an important detoxifying phase II enzyme. Null mutations of GSTM1 and GSTT1 are known to abolish enzyme activities and therefore have been linked with increasing incidence of certain cancers, most likely due to increased susceptibilities to environmental toxins and carcinogens. In this study, the effects of the GSTM1 and GSTT1 null genotypes were examined for association with nasopharyngeal carcinoma risk. Previous evidence suggests that GSTM1 and GSTT1 polymorphisms may have a close association with increased susceptibility to various carcinomas.

Our results suggest that genetic deletion of GSTM1 may contribute to increased susceptibility to NPC, when compared with a group of individuals with no history of neoplasia. whereas GSTT1 polymorphism may not.

Previous meta-analyses indicate that GSTM1 deficiency might have a significant association with increased risks of breast cancer [15] and lung cancer in Chinese people [16]. Analyses concerning oral cancer suggest that GSTM1 null genotype increases the oral cancer risk in Asians but not Caucasians [17]. However, a number of meta-analyses suggest no marked associations of GSTM1 null mutations with other cancers in many ethnic groups [10,17,18].

Previous studies on the interaction of GSTM1 and GSTT1 with smoking in tobacco-associated cancer have shown that the deletion of the GSTM1 and GSTT1 genes may increase cancer risk in smokers [19]. Further studies on the effects of smoking and GSTTM1 and GSTT1genotypes will clarify the role of smoking-gene interactions in nasopharyngeal carcinoma.

However, the conclusion about the relationship between GSTM1 null, NPC, and the history of smoking is not clear. Some previous studies found this association without any relation to tobacco consumption [12,19], whereas, other one have reported that increasing risk of NPC was linked to GSTM1 null genotype and smoking status [12,13]. Our results confirm finding indicating that tobacco use is a strong risk factor in NPC.

**Table 4** Genotype distribution of GSTM1 0/0 in case and control adjusting for gender, age and smoking.

| | **Patients (132)** | | **Controls (200)** | | **P** | **OR (95%CI)** |
|---|---|---|---|---|---|---|
| | **GSTM10/0** | **GSTM1+/+** | **GSTM10/0** | **GSTM1+/+** | | |
| **All subjects** | 66 | 66 | 68 | 132 | < 0.05 | 2.18 (1.23–5.33) |
| **1-gender** | | | | | | |
| Men | 48 | 40 | 48 | 68 | < 0.05 | 2.59 (1.81–4.32) |
| Women | 18 | 26 | 18 | 66 | <0.05 | 2.35 (1.51–2.98) |
| **2-age** | | | | | | |
| 20–40 years | 14 | 16 | 2 | 32 | < 0.05 | **6.12 (4.71–14.6)** |
| 40–60 years | 34 | 36 | 52 | 52 | NS | 0.87 (0.62–1.22) |
| +60 years | 18 | 14 | 12 | 50 | < 0.05 | **5.35 (3.35–6.44)** |
| **3-tobacco** | | | | | | |
| Smokers | 30 | 20 | 14 | 30 | < 0.05 | 3.21 (2.01–3.86) |
| Never | 34 | 48 | 52 | 104 | < 0.05 | 1.41 (0.9–1.88) |

NS: not significant.

**Table 5** Frequency of combined genotypes in nasopharyngeal carcinoma patients and in the control group.

| **Genotypes** | **OR (IC 95%)** | **P** |
|---|---|---|
| **GSTM1 null / GSTT1null** | 1.92 (0.61–6.28) | 0.3404 |
| **GSTM1+/ GSTT1 null** | 1.01 (0.34–2.36) | 0.7626 |
| **GSTM1 null / GSTT1+** | 6.94 (1.98–14.94) | 0.0066 |

Otherwise, in our study, gender can modify the risk associated with GSTM1 null genotype. We report that smoking may be responsible for the increased risk in males because GST genes have been reported to detoxify nicotine and smoke [20]. Whereas, other studies conducted in American population showed a strong relation between women and NPC [11,14]. The sex differences reported here could possibly result from differences in expression or regulation of GSTM1 involved in the metabolism of carcinogens [21,22]. The increase of the risk for men, observed in our work, could be explained by a difference of sociocultural context and all smokers was men.

Fluctuated risk among developing NPC in patients with GSTM1 null genotype, noted in Table 3, showed a stronger predictor of risk in patients at the age of 20–40 years and at the age of 60 years, but this same polymorphism was the protector in patients at the age of 40–60 years.

There are several explanations for this original finding:

- Smoker patients at the age of 20–40 years represent 26.26% of smoker population. For this group, an increased risk of NPC with GSTM1 null genotype (OR=8 ; 95% CI [6.03–19.08]) was detected. It is possible that a lower amount of smoking or a brief exposition to tobacco smoke generate an important expression of carcinogenic mutations.
- Patients at the age of 20–40 years would present a genetic factor (have to identify) of regulation and expression of oncogenes, this factor would probably influence the increased risk of NPC.
- The contrast to the estimated cancer risk among individuals at the age of 40–60 years with the same null genotype could be due to a hormonal influence. The increase of the risk for men accentuated this hypothesis.
- The increased risk among patients at 60 years older confirms that a longer exposure to environmental carcinogen contributes to the development of NPC.

Null genotype of GSTT1 has been suggested to associate with risks of a number of cancers. Previous meta-analyses suggest marked associations of GSTT1 deletion with lung cancer [17], gastric cancer in Caucasians [23], colorectal cancer [24], and head and neck cancers including the oral cavity, the laryngeal and the pharyngeal cancers [20]. In this study, GSTT1 deficiency is unlikely to act as a risk factor for NPC. This discrepancy might be due to major ethnic differences existing in frequency distribution.

GSTM1/GSTT1 double deletions have been reported to confer a higher risk for head and neck squamous cell carcinoma [12,13,20]. Similar increases in risk for other cancers have been reported for the combined genotypes of GSTM1 null and GSTT1 null [25,26].

In our analysis, we have evidenced that the GSTM1 null/ GSTT1+ combined genotype provides a greater susceptibility for the development of NPC, similar results to those found by other authors [13,26]. There was no association between this type of neoplasia and the null combined genotypes null GSTT1 and null GSTM1, as observed by Suzen et al. [27]. On the other hand, similar study has shown a correlation between the double null genotype GSTT1 and GSTM1 with same or different cancer among men [28,29].

**Conflict of interest:** the authors have no conflicts of interest to declare.

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