Genetic polymorphisms in glutathione-S-transferases are associated with anxiety and mood disorders in nicotine dependence

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\textbf{Background} Nicotine dependence is associated with an increased risk of mood and anxiety disorders and suicide. The primary hypothesis of this study was to identify whether the polymorphisms of two glutathione-S-transferase enzymes (GSTM1 and GSTT1 genes) predict an increased risk of mood and anxiety disorders in smokers with nicotine dependence.

\textbf{Materials and methods} Smokers were recruited at the Centre of Treatment for Smokers. The instruments were a sociodemographic questionnaire, Fagerström Test for Nicotine Dependence, diagnoses of mood disorder and nicotine dependence according to DSM-IV (SCID-IV), and the Alcohol, Smoking and Substance Involvement Screening Test. Anxiety disorder was assessed based on the treatment report. Laboratory assessment included glutathione-S-transferases M1 (GSTM1) and T1 (GSTT1), which were detected by a multiplex-PCR protocol.

\textbf{Results} Compared with individuals who had both GSTM1 and GSTT1 genes, a higher frequency of at least one deletion of the GSTM1 and GSTT1 genes was identified in anxious smokers [odds ratio (OR) = 2.21, 95% confidence interval (CI) = 1.05–4.65, \( P = 0.034 \)], but there was no association with bipolar and unipolar depression (\( P = 0.943 \)). Compared with nonanxious smokers, anxious smokers had a greater risk for mood disorders (OR = 4.67; 95% CI = 2.24–9.92, \( P < 0.001 \)), lung disease (OR = 6.78, 95% CI = 1.95–23.58, \( P < 0.003 \)), and suicide attempts (OR = 17.01, 95% CI = 2.23–129.91, \( P < 0.006 \)).

\textbf{Conclusion} This study suggests that at least one deletion of the GSTM1 and GSTT1 genes represents a risk factor for anxious smokers. These two genes may modify the capacity for the detoxification potential against oxidative stress. \textit{Psychiatr Genet} 24:87–93 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Psychiatric Genetics 2014, 24:87–93

Keywords: anxiety disorder, genetic polymorphisms, glutathione-S-transferase, mood disorder, nicotine dependence

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Received 3 March 2013 Revised 3 March 2013 Accepted 25 October 2013

\textbf{Introduction} The relationship between nicotine dependence and anxiety disorders has been established in epidemiological and clinical studies. Cigarette smoking is associated with an increased risk of anxiety disorders. In the National Comorbidity Survey, nearly 61.3% of individuals with a lifetime history of panic disorder and 68.4% with generalized anxiety disorders were current or past smokers, whereas only 39% of smokers had no mental disorders (Lasser \textit{et al.}, 2000; Ziedonis \textit{et al.}, 2008).

The nexus between co-occurring disorders such as smoking, depression, and anxiety is not clear. Depression and anxiety may increase the risks of smoking, and smoking may increase the risks of depression and anxiety. A history of previous psychiatric disorders increases the risk of early onset of smoking, and contributes to progression from daily smoking to nicotine dependence (Breslau \textit{et al.}, 2004). Depression and anxiety symptoms have been associated with a greater risk for the onset of smoking behaviors (Patton \textit{et al.}, 1998). In contrast, other studies have found evidence that smoking increases the risk for the onset of depression and anxiety disorders (Pasco \textit{et al.}, 2008; Boden \textit{et al.}, 2010; Moylan \textit{et al.}, 2012). Smoking appears to increase the risk of the development of mood disorders, anxiety disorders, and suicide.
substances in tobacco smoke (Kim et al., 2008). Genes involved in cellular protection against inflammation and oxidative stress damage from various toxic compounds and products of oxidative stress are implicated as a risk factor for a wide range of tobacco-related diseases, including susceptibility to coronary heart disease (Li et al., 2000; Wang et al., 2008; Wang et al., 2010), cerebrovascular diseases (Um et al., 2006), lung cancer (Schneider et al., 2004; Lam et al., 2009), and COPD (Xue et al., 2012). In contrast, another study did not find an association between GSTM1/GSTT1 null genotype and risk of ischemic heart disease (Norskov et al., 2009).

In the light of these findings, the current study examines the role of GSTM1 and GSTT1 genes in smokers with anxiety and mood disorders. These two genes may modify the capacity for the detoxification potential against oxidative stress. We hypothesized that at least one deletion of the GSTM1 and GSTT1 genes compared with people who had both GSTM1 and GSTT1 genes is associated with a greater risk for anxiety and mood disorders in smokers.

Materials and methods

Study population

Smokers (n = 151) were recruited from outpatients at the Centre of Treatment for Smokers, at University Hospital of Londrina, State University of Londrina (UEL) (Parana, Brazil). The controls were never-smokers (n = 191) and were recruited from staff at UEL. This research was approved by the Ethics Research Committee at State University of Londrina, and all participants gave written informed consent to participate in the study. The study was conducted from March 2011 to July 2012. Smokers were men and women aged 18–60 years of all ethnicities.

Genotyping

Genomic DNA was extracted from 200 μl of peripheral blood cells of all participants using the Biopur Kit (Biometrix Diagnostic, Curitiba, Brazil) according to the manufacturer’s instructions. After precipitation with
ethanol, the DNA pellet was resuspended in 50 µl of Biopur Kit specific buffer, quantified by spectrophotometry, and stored at freezer –80°C for later use in genotyping analyses.

The genetic polymorphisms were studied using multiplex PCR protocol (Abdel-Rahman et al., 1996) with modifications: 80–100 ng of DNA was amplified in a total volume of 25 µl reaction containing 20 mmol/l Tris-HCl; 50 mmol/l KCl; 1.5 mmol/l MgCl2; 2 mmol/l of each deoxynucleotide triphosphate; 1 pmol of each primer; and 1.25 U of AmpliTaq DNA polymerase. PCR was carried out in a PTC-100 Termocycler (MJ Research Inc., Minnesota, USA), after 5 min of pretreatment at 94°C, 30 cycles of 1 min at 94°C, 1 min at 59°C, and 30 s at 72°C, followed by 5 min at 72°C. The PCR products were analyzed by electrophoresis on 10% acrylamide gel and detected by a nonradioisotopic technique using a commercially available silver staining method.

The genotype was coded according to GSTM1/GSTT1 complete gene deletion polymorphisms: (a) GSTT1 present and GSTM1 absent or GSTT1 absent and GSTM1 present (at least one gene deleted), (b) both genes present, and (c) both genes deleted.

The multiplex PCR assay cannot discriminate the heterozygous presence of the allele from the homozygous presence. However, the distributions of these two genotypes were similar to those reported in another study (Cornelis et al., 2007).

The absence of a 215 bp fragment in the electrophoretic profile indicates the GSTM1 null genotype, and the absence of a 480 bp fragment indicates the GSTT1 null genotype. A fragment of 312 bp related to a non-polymorphic fragment of the CYP1A1 gene was used as an internal control in all reactions. Negative controls were analyzed with each experiment.

Statistical analyses
Comparisons were made between smokers with and without anxiety disorders for sociodemographic and clinical characteristics, and the laboratory measurements, using appropriate parametric tests where data were normally distributed and nonparametric statistical tests for categorical or excluded non-normal data. All associations between smokers with and without anxiety disorders and genetic polymorphisms, mood disorders, lung disease, and suicide attempts were performed using contingency tables to calculate the odds ratios (OR) and the 95% confidence interval (CI). All tests were two-tailed and a $P$-value of 0.05 was used for statistical significance.

Results
Characteristics of participants
In examining sociodemographic variables, anxious smokers did not differ with respect to marital status, age, years of education, and ethnicity. There were significantly more women among the anxious smokers compared with the nonanxious smokers ($P < 0.01$). Women sought more treatment for smoking cessation and exhibited higher rates of anxiety disorders than men. The mean age for all groups was 46.25 years. There were no significant differences with respect to years smoked, pack years, scores on FTND scale, and age of onset of smoking between anxious and nonanxious smokers (Table 1).

Clinical characteristics
Anxious smokers had significantly more lung disease, suicide attempts, psychiatric and psychological treatment, use of sedative and sleeping pills, and mood disorders than nonanxious smokers ($P < 0.01$). There were no significant differences with respect to diabetes, hypertension, cardiovascular diseases, alcohol risk, and BMI (kg/m²) between anxious and nonanxious smokers (Table 2).

| Table 1 Sociodemographic characteristics of smokers with and without anxiety disorders |
|---------------------------------|---------------------------------|------------------------------|
| Characteristics                 | Smokers with anxiety (n=59 [%]) | Smokers without anxiety (n=55 [%]) | $P$-value* |
| Sex                             |                                 |                              |            |
| Male                            | 26 (27.1)                       | 29 (52.7)                    | 0.002*     |
| Female                          | 70 (72.9)                       | 26 (47.3)                    |            |
| Age (years)                     |                                 |                              | 0.570      |
| 18–29                           | 5 (5.2)                         | 5 (9.1)                      |            |
| 30–39                           | 11 (11.5)                       | 9 (16.4)                     |            |
| 40–49                           | 37 (38.5)                       | 17 (30.9)                    |            |
| 50–60                           | 43 (44.3)                       | 24 (43.6)                    |            |
| Ethnicity                       |                                 |                              | 0.181      |
| White                           | 62 (64.6)                       | 40 (72.7)                    |            |
| African                         | 13 (13.5)                       | 4 (7.3)                      |            |
| Asian                           | 1 (1.0)                         | 3 (5.5)                      |            |
| Mixed                           | 20 (20.8)                       | 8 (14.5)                     |            |
| Marital status                  |                                 |                              | 0.385      |
| Single                          | 15 (15.6)                       | 8 (14.5)                     |            |
| Stable relationship             | 55 (57.3)                       | 38 (69.1)                    |            |
| Divorced/                      |                                 |                              |            |
| separated                      | 20 (20.8)                       | 8 (14.5)                     |            |
| Widow                           | 6 (6.3)                         | 1 (1.8)                      |            |
| Years of education              |                                 |                              | 0.307      |
| ≤ 12                            | 67 (72.0)                       | 43 (79.6)                    |            |
| > 13                           | 26 (28.0)                       | 11 (20.4)                    |            |
| Smoking (mean±SD)               |                                 |                              |            |
| Age first smoked                | 14.8±3.7                        | 15.0±3.4                     | 0.681      |
| Years of smoking               | 31.9±9.4                        | 31.4±10.3                    | 0.762      |
| Cigarettes/day                  | 22.2±12.9                      | 20.5±10.7                    | 0.383      |
| Pack/year                      | 33.9±21.2                      | 32.6±20.8                    | 0.715      |
| Fagerström scale               | 6.0±2.3                        | 5.3±2.0                      | 0.050      |

Tests are adjusted for all pairwise comparisons within a row using the Bonferroni correction.

*The $P$-value is based on the Pearson $r^2$-test for categorical variables and the independent sample $t$-test for the continuous variables.

*Statistically significant difference. In this and subsequent tables $P$-values should be interpreted with caution where some cells have values <5.
were performed, using pooled smokers and never-smokers. Comparisons between the anxious and nonanxious groups revealed significant associations between \textit{GSTM1/GSTT1} genotypes and unipolar and bipolar smokers ($P = 0.0943$) (Table 3).

The relationship between smoking, mood disorders, lung disease, suicide attempts, \textit{GSTM1/GSTT1} genetic polymorphism, and anxiety disorders is shown in Table 4.

The results showed that anxiety disorders were significantly associated with mood disorders (OR = 4.67, 95% CI = 2.84–7.19, $P < 0.0001$), lung disease (OR = 6.78, 95% CI = 1.95–23.58, $P < 0.0026$), and suicide attempts (OR = 17.01, 95% CI = 2.23–129.91, $P < 0.006$).

Comparisons between the anxious and nonanxious groups were performed, using pooled smokers and never-smokers ($n = 342$), to estimate OR with 95% CI and the combined effects of GST genotypes. There was a positive association between anxiety and smokers (OR = 4.55, 95% CI = 2.84–7.19, $P < 0.0000$), mood disorders (OR = 6.32, 95% CI = 3.90–10.17, $P < 0.0000$), lung disease (OR = 3.12, 95% CI = 1.61–6.03, $P < 0.001$), and suicide attempts (OR = 18.34, 95% CI = 4.26–78.96, $P < 0.0000$).

**Discussion**

Our data confirm results from previous studies in showing that anxious smokers exhibited having higher rates of suicide attempts than nonanxious smokers. Smokers who attempted suicide exhibited 17.0 more likelihood of having anxiety compared with smokers who did not attempt suicide. This striking finding is consistent with the hypothesis that individuals who are nicotine dependent are more likely to be anxious, depressive, and suicidal (Pedersen and von Soest, 2009; Berlin et al., 2011). Previous studies have reported that smoking is associated with a risk of suicidal behavior and depressive disorders (Malone et al., 2003; Breslau et al., 2005; McGee et al., 2005; Hughes, 2008; Goodwin et al., 2013). Other studies have found associations between prior smoking or nicotine dependence and subsequent suicidal behavior, which were independent of depression (Boden et al., 2008; Bronisch et al., 2008).

The smoking and suicide nexus may be explained, in part, by inflammation and oxidative stress. Individuals with suicidal behavior had significantly higher levels of nitric oxide metabolites (products of nitrates and nitrates) and lipid hydroperoxides (a biomarker of oxidative damage to lipids or lipid peroxidation) and lower levels of plasma total antioxidant potential TRAP (a biomarker...
of total antioxidant defenses) than those without a history of suicide attempts (Vargas et al., 2013b, in press). Proinflammatory cytokines have been implicated in depressive smokers (Nunes et al., 2012). Inflammation and oxidative stress is a mechanism activating production of kynurenine, which may deplete tryptophan, leading to reduced levels of serotonin. Increased plasma kynurenine levels were found in suicide attempters (Sublette et al., 2011). Decreased levels of serotonin were related to suicidal behavior in depressed smokers (Malone et al., 2003).

Co-occurring affective, anxiety disorders, and nicotine dependence share pathways that may explain these disorders. First, monoamine oxidases (MAO) catalyze the metabolism of dopamine, norepinephrine, and serotonin. Cigarette smoke inhibits the activity of MAO type A and type B (Benowitz, 2010). Lowered MAO activity, which may play a role in central nervous system serotonin metabolism, could modulate, in part, the link between cigarette smoking and suicidal behavior (Breslau et al., 2005). Second, this comorbidity can potentially be explained by one disorder being an epiphenomenon of the other and by a partly shared genetic etiology (Middeldorp et al., 2005). Finally, there are alterations of neurotransmitters by inflammation and oxidative stress, and cigarette smoking and mood disorders are associated with increased levels of inflammation and oxidative stress (Rytilä et al., 2006; Yanbaeva et al., 2007; Berk et al., 2011; Maes et al., 2011).

Smokers who had mood disorders exhibited 4.67 times the risk of having anxiety compared with smokers who did not have a mood disorder. The relationship between mood and anxiety disorders was associated with several markers of clinical severity, including earlier age of onset, greater number of depressive episodes, and higher prevalence of attempted suicide, when compared with mood disorder without comorbid anxiety (Goes et al., 2012). Comorbidity of anxiety and bipolar/unipolar disorders, suicidal behavior, substance abuse, and familial history may be explained by heavy familial-genetic loading for affective illness (Dilsaver et al., 2006). Individuals with anxiety and depressive disorders have increased rates of smoking compared with those without mental disorders or depression (Lasser et al., 2000).

In the present study, smokers who had lung disease exhibited 6.78 times the risk of having anxiety compared with smokers who did not have lung disease. This finding was consistent with previous studies that have reported a link between anxiety, depression, and lung disease (Di Marco et al., 2006; Goodwin et al., 2012). Therefore, it is necessary to consider the cumulative effects of depressive and anxiety disorders, physical illnesses, and smoking on suicide rates. Patients with some pulmonary diseases have an increased risk of mood and anxiety disorders (Dome et al., 2010). The association between lung disease (COPD) and anxiety in smokers may be accounted for by the higher rate of the null variant of the enzyme genes in the anxiety group. Because the association between the polymorphisms and anxiety in smokers is uncertain it is probably most reasonable to conjecture that the increased rate of lung disease is due to the enzyme deficiency rather than to anxiety.

Our study also provides evidence for the association between at least one deletion of the GSTM1 and GSTT1 genes in anxious smokers, compared with those who had the presence of both GSTM1 and GSTT1 genes. However, we did not find significant differences for these polymorphisms in unipolar and bipolar smokers. These results are in accordance with another study that did not find an association of nicotine acetylcholine receptor gene of smokers with depression, but found that it was positively associated with the prevalence of both anxious and depressive smokers (Bjørngaard et al., 2012).

Some limitations of the study need to be mentioned. First, these results should be confirmed using a larger sample size. Because of the small sample size, the possibility of type II statistical errors cannot be excluded. Second, all participants were recruited from the Centre for Smoking Cessation. We did not compare smokers with nonsmokers recruited from the same geographic area and rigorously matched with the smokers for age and sex of the GSTM1 and GSTT1 genes. However, there were no significant differences between smokers and nonsmokers for the GSTM1/GSTT1 gene polymorphisms reported in another study (Saadat and Mohabatkar, 2004). Third, there is a considerable overlap between symptoms of anxiety and mood disorders that needs to be interpreted with caution, and assessments of anxiety disorders were based on reported treatment. We did not find differences for mood disorders; however, further research is needed to clarify this issue. Finally, this study was conducted on cross-sectional data, and thus results can only determine associations, not causality.

A bidirectional relationship might exist between neurotransmitter activity, inflammation, and oxidative stress status in nicotine dependence and depressive disorders (Nunes et al., 2013). Our data strengthen the hypothesis of a role of GSTM1 and GSTT1 for the detoxification potential against oxidative stress in anxious smokers that exhibited higher rates of suicide attempts and mood disorders than nonanxious smokers.

Taken all together, the results suggest that both or at least one deletion of the GSTM1 and GSTT1 genes represent a risk factor for anxious smokers with co-occurrence with lung diseases, suicide attempts, sedative use, and mood disorders. The impact on health risks of this comorbidity suggests that we need to aggressively target smoking cessation as a part of routine care (Berk, 2007). Moreover, it is necessary to develop more effective therapeutic targets.
to reduce morbidity and mortality due to the co-occurrence of nicotine dependence and anxiety and mood disorders and sedative use.

Acknowledgements

The authors gratefully acknowledge the Health Sciences Postgraduate Program, the genetic laboratory and clinical analyses laboratory at State University of Londrina (Brazil), and the Barwon Psychiatric Research Unit, Deakin University (Geelong, Australia).

This study was supported by the Health Sciences Postgraduate Program at Londrina State University, Paraná, Brazil (ULE), the Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES), and the Ministry for Science and Technology of Brazil (CNPq).

Conflicts of interest

There are no conflicts of interest.

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Title:
Genetic polymorphisms in glutathione-S-transferases are associated with anxiety and mood disorders in nicotine dependence

Date:
2014-06-01

Citation:
Vargas Nunes, S. O., Pizzo de Castro, M. R., Ehara Watanabe, M. A., Guembarovski, R. L., Vargas, H. O., Vissoci Reiche, E. M., Morimoto, H. K., Dodd, S. & Berk, M. (2014). Genetic polymorphisms in glutathione-S-transferases are associated with anxiety and mood disorders in nicotine dependence. PSYCHIATRIC GENETICS, 24 (3), pp.87-93. https://doi.org/10.1097/YPG.0000000000000023.

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