Distribution of the Val108/158Met polymorphism of the COMT gene in healthy Mexican population

Thelma Beatriz González-Castro a, Carlos Tovilla-Zárate b,⁎, Isela Juárez-Rojop a, Sherezada Pool García c, Alma Genis d, Humberto Nicolini d, Lilia López Narváez e,f

a Universidad Juárez Autónoma de Tabasco, División Académica de Ciencias de la Salud, Villahermosa, Tabasco, México
b Universidad Juárez Autónoma de Tabasco, División Académica Multidisciplinaria de Comalcalco, Comalcalco, Tabasco, México
c Grupo de Estudios Médicos y Familiares Carracci, México, D.F., México
d CIGEN, Centro de Investigación Genómica, Comalcalco, Tabasco, México
e Hospital General de Yajalón, Yajalón, Chiapas, México
f CIGEN, Centro de Investigación Genómica, Comalcalco, Tabasco, México

Abstract

Catechol-O-methyltransferase (COMT) inactivates the catecholamines adrenaline, noradrenaline and dopamine. On the other hand, some studies have reported that the enzymatic activity of COMT is partly genetically determined. With regard to the COMT gene, the most studied polymorphism is the functional variant Val108/158Met (rs4680), which results in substantial three- to four-fold variations in enzyme activity. To date, the rs4680 polymorphism of COMT has been associated with a number of disorders. In addition, this polymorphism has been found to have important differences in frequency according to the studied population. Therefore, the aim of the present study was to evaluate the frequency of a common single nucleotide polymorphism (SNP) Val108/158Met of the COMT gene in the Mexican population. Accordingly, we recruited 431 healthy volunteers. Our sample consisted of 111 healthy individuals from Mexico City and 320 individuals from the state of Tabasco, Mexico. We observed that Met was the most common allele, ranging from 57% (Tabasco) to 85% (Mexico City). In addition, we analyzed the frequency of Val108/158Met polymorphism of Caucasian (54% Met allele), Asian (29% Met allele) and African (34% Met allele) populations separately and also in comparison with Mexican (63% Met allele) population. In conclusion, the distribution of the Val108/158Met polymorphism distinguishes the Mexican population studied from other populations, but it is necessary to increase the size of the sample to get more conclusive results.

© 2013 The Authors. Published by Elsevier B.V. All rights reserved.
such as schizophrenia, alcohol dependence, suicidal behavior, psychotic and affective disorders, as well as in other situations such as smoking, cognitive processing and post-menopausal breast cancer risk (Baud et al., 2007; Calati et al., 2011; Cheng et al., 2006; Colilla et al., 2005; Ehrlich et al., 2010; Illi et al., 2010; Kia-Keating et al., 2007; Kocabas et al., 2010; Lee and Kim, 2011; Liou et al., 2001; Martínez-Ramírez et al., 2012; Nedic et al., 2011; Nikolac et al., 2013; Nolan et al., 2000; Ohara et al., 1998; Ono et al., 2004; Oppen-Rhein et al., 2008; Perroud et al., 2010; Pivac et al., 2011; Roten et al., 2011; Russ et al., 2000; Takizawa et al., 2009; Vargas-Alarcón et al., 2007; Wedren et al., 2003; Zalsman et al., 2008). The important single nucleotide polymorphism has been genotyped in most of the populations worldwide. However, the COMT gene has been studied in several association studies with inconclusive results. One of the possible explanations for the discrepancies in the outcomes may be that the distribution of the frequency of the COMT gene varies according to the populations (Hatizmanolis et al., 2013; Sheik et al., 2013; Wardle et al., 2013). In consequence, the distribution of the genotype and allele frequencies of the COMT gene in a certain population is a relevant issue. Therefore, as one of our samples we chose the population of Tabasco, Mexico, which is a closed population. The aim of this study was to investigate the distribution of allele and genotype frequencies of the Val108/158 polymorphism in Mexico City and in the state of Tabasco and to compare our findings with other populations.

2. Material and methods

2.1. Subjects

In order to evaluate the genotype and allele frequency of the polymorphism Val108/158Met in the Mexican population we included a sample consisting of 111 healthy individuals recruited from the Carracci Medical Group in Mexico City and 320 subjects randomly recruited when they attended the Blood Donor Center in the municipalities of Comalcalco in the state of Tabasco, Mexico. Part of the sample of the Tabasco population was taken from previous reports (Tovilla-Zárate et al., 2011, 2013). We included a total of 431 healthy volunteers in the present study; all the participants were Mexican Mestizos, and to reduce ethnic variation and stratification effects, we selected subjects that descended from two Mexican generations. The exclusion criteria for both populations (Mexico City and Tabasco) were the following: current substance abuse, history of substance dependence, history of neurobiological disease, intellectual disability or other concomitant medical ailment.

2.2. Description of the populations

2.2.1. Population A or Tabasco population

Tabasco is one of the 31 states comprising the 32 federal entities which constitute Mexico. It is located in the southeast of the country along the Gulf of Mexico. It has as boundaries the states of Campeche, Chiapas and Veracruz, as well as the country of Guatemala. The Tabasco population is considered to have been originated from late Mesoamerican cultures. The state of Tabasco is divided into 17 municipalities, but our subjects came solely from the one called Comalcalco (Fig. 1). Only subjects of Mestizo Mexican descent were included in this study.

2.2.2. Population B or Mexico City population

Mexico City is the capital of Mexico. It is a federal entity that together with the 31 Mexican states conform a federation. The growth of the city has extended beyond its limits and has infiltrated 59 municipalities in the state of Mexico and 1 in the state of Hidalgo. Although we included only Mexican individuals descending from Mexican parents and grandparents, this population is less closed than the one of Tabasco (Fig. 1). Only subjects of Mexican Mestizo descent were included in this study.

2.3. Ethics statement

After they were given a verbal and written explanation of the research objectives, all subjects signed an informed consent to participate in the study. They did not receive any economical remuneration. This study complied with the principles convened in the Helsinki Declaration. In addition, this study was approved by the ethics committee so-called DAMC-UJAT Ethics and Research Committee (UJAT-DAMC-2012-02) of the University of Tabasco.

2.4. Genotype assays

Genomic DNA was extracted from peripheral blood leukocytes using a modified version of the protocol by Lahiri (Lahiri and Nurnberger, 1991). The genotypes of the COMT Val108/158Met polymorphism were analyzed in all subjects using a polymerase chain reaction (PCR) end-point method. The final volume of the PCR reaction was 5 μl and consisted of 20 ng genomic DNA, 2.5 Fl TaqMan Master Mix, and 0.125 Fl 20× Assay. The amplification was performed in 96-well plates using the TaqMan Universal Thermal Cycling Protocol. After the PCR end-point was reached, fluorescence intensity was measured with the 7500 Real-Time PCR system using SDS version 2.1 software (Applied Biosystems). An allelic discrimination was performed resulting in the clear identification of three genotypes for the COMT Val108/158Met polymorphism. All genotyping was carried out blind to patient outcome. As a quality control in our genotyping analyses we used random blind duplicates. Genotype assays were previously reported elsewhere (Tovilla-Zárate et al., 2011).

2.5. Statistical analysis

We measured frequencies and percentages of the genotypes and alleles using the SPSS statistical program version 11.5. Similarly, we used the THESIAS software v. 3.1. Chi-square statistics were used for testing goodness of fit to the Hardy–Weinberg equilibrium.

3. Results

The distribution of genotype and allele frequencies of the Val108/158Met polymorphism in the Mexican population of our study is shown in Table 1. The frequencies of these studies in the Mexican population were in Hardy–Weinberg equilibrium. Table 2 shows the genotype and allele frequencies in Caucasian, African and Asian populations that were studied in relation to the Val108/158Met polymorphism. Likewise, all these frequencies were in Hardy–Weinberg equilibrium.

4. Discussion

The aim of the present study was to estimate allele and genotype frequencies of the Val108/158Met polymorphism in a Mexican population. The Met allele in this polymorphism is associated with a three- to four-fold decrease in COMT activity, whereas the Val allele is related to its highest activity. Data from several studies have established that the Val108/158 Met polymorphism plays an important role in many diseases such as schizophrenia, alcohol dependence, suicidal behavior, psychotic and affective disorders, as well as in studies concerning smoking, cognitive processing and post-menopausal breast cancer risk. Hence, it is relevant to study the Val108/158Met polymorphism in different populations.

Table 1 shows genotype and allele frequencies observed in the two populations. Met was the most common allele ranging from 57% (Tabasco) to 85% (Mexico City). We compared the analysis with
previous papers reported in the healthy Mexican population until May 2013 (Martínez-Ramírez et al., 2012; Vargas-Alarcón et al., 2007; both having women samples). In the study by Martínez-Ramírez et al. (2012) the more frequent allele was Met by 65% and the Val allele exhibited a lower frequency (35%). This study included individuals from all over Mexico. With regard to the study of Vargas-Alarcón et al. (2007), the frequencies for the Val and Met alleles were 67% and 33%, respectively. Our results are in agreement with the study by Martínez-Ramírez et al. (2012) which reported a higher frequency for the Met allele (65%) than for the Val allele (35%). Conversely, when we compared our results with Vargas-Alarcón et al. (2007), they reported that the allele with higher frequency was Val (67%). One possible explanation could be the difference in genetic heterogeneity in the population even though both belong to the same country. Vargas-Alarcón et al. (2007) included in their study individuals from different states of Mexico, whereas our sample was more homogeneous.

Allele and genotype frequencies of these polymorphisms in Mexican individuals were compared to those reported in other populations — Caucasian, Asian, and African. We performed an analysis of the genotype and allele frequencies of the Val108/158Met polymorphism with studies comprising healthy individuals as controls. The pooled results of Caucasian populations showed that the Met allele had a frequency of 54% and Val allele frequency of 46%; the Asian population exhibited a frequency of 29% for the Met allele and 71% for the Val allele, and the African population presented a frequency of 34% for the Met allele and 67% for the Val allele. These control subjects were recruited from different ethnic and populations (Table 2). We obtained similar results for the Met allele frequency between the pooled results of the various control groups and the Mexican population, but we observed a minor discrepancy with the Mexico City sample. Our results contradict the allele frequencies when compared to the studies in Asian and African populations and the study by Vargas-Alarcón et al. (2007). The possible explanation for this discrepancy could be the sample size. Our sample size for both Tabasco and Mexico City populations was larger when compared to the other studies in Mexican subjects mentioned above.

Among the limitations of our study lies the fact that the subjects were not randomly recruited to be a representative sample of a specific ethnic group. Besides, we did not calculate the sample size. Finally, we did not present an association report.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
<th>p</th>
<th>Allele</th>
<th>Frequency</th>
<th>p</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tabasco (Tovilla-Zárate)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met-Met n (%)</td>
<td>106 (0.33)</td>
<td>&lt;0.0001</td>
<td>Met n (%)</td>
<td>367 (0.57)</td>
<td>&lt;0.0001</td>
<td>0.90</td>
</tr>
<tr>
<td>Met-Val n (%)</td>
<td>155 (0.48)</td>
<td></td>
<td>Val n (%)</td>
<td>273 (0.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-Val n (%)</td>
<td>59 (0.19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>320</td>
<td></td>
<td>Total</td>
<td>640</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mexico City (Tovilla-Zárate)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met-Met n (%)</td>
<td>79 (0.71)</td>
<td>&lt;0.0001</td>
<td>Met n (%)</td>
<td>189 (0.85)</td>
<td>&lt;0.0001</td>
<td>0.45</td>
</tr>
<tr>
<td>Met-Val n (%)</td>
<td>31 (0.28)</td>
<td></td>
<td>Val n (%)</td>
<td>33 (0.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-Val n (%)</td>
<td>1 (0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td></td>
<td>Total</td>
<td>222</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mexico City (Martínez-Ramírez)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met-Met n (%)</td>
<td>68 (0.45)</td>
<td>0.60</td>
<td>Met n (%)</td>
<td>195 (0.65)</td>
<td>0.39</td>
<td>0.10</td>
</tr>
<tr>
<td>Met-Val n (%)</td>
<td>59 (0.39)</td>
<td></td>
<td>Val n (%)</td>
<td>105 (0.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-Val n (%)</td>
<td>23 (0.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>150</td>
<td></td>
<td>Total</td>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mexico City (Vargas-Alarcón)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met-Met n (%)</td>
<td>4 (0.12)</td>
<td>0.81</td>
<td>Met n (%)</td>
<td>22 (0.33)</td>
<td>&lt;0.0001</td>
<td>0.79</td>
</tr>
<tr>
<td>Met-Val n (%)</td>
<td>14 (0.42)</td>
<td></td>
<td>Val n (%)</td>
<td>44 (0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-Val n (%)</td>
<td>15 (0.46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td></td>
<td>Total</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall Mexican population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met-Met n (%)</td>
<td>257 (0.42)</td>
<td></td>
<td>Met n (%)</td>
<td>773 (0.63)</td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>Met-Val n (%)</td>
<td>259 (0.42)</td>
<td></td>
<td>Val n (%)</td>
<td>455 (0.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-Val n (%)</td>
<td>98 (0.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>614</td>
<td></td>
<td>Total</td>
<td>1228</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The p value was calculated when we compared each population vs pool of frequencies of the rest of Mexican population.

Example: Tabasco population (Tovilla-Zarate) vs Mexico city (Tovilla-zarate)+Mexico city (Martínez-Ramírez)+Mexico city (Vargas-Alarcón).
The authors declare not to have any competing interests.

In summary, the distribution of the Val108/158Met polymorphism distinguishes the Mexican population studied from other groups including Africans, Asians and Caucasians. The alleles of Val108/158Met are associated with the development of different diseases; hence the knowledge of the distribution of these alleles could be important for the understanding of its genetic role in a specific population.

Conflict of interest

The authors declare not to have any competing interests.

Authors' contributions

TZZ and GCTB conceived the study, participated in its design, and helped to draft the manuscript. TZZ, JRI, LNL and NH helped to perform the statistical analysis and to draft the manuscript. PGS and VSMP recruited participants and helped with data integration and analysis. GA, TZZ and HN coordinated and supervised the integration of data.

Acknowledgments

The authors gratefully acknowledge our research volunteers who helped to recruit the participants in this study. The collection of data and the genotyping of subjects were carried out thanks to the support of grants UJAT-DAMC-2012-02 and CONACYT CB-2012-01-177459.

References


Perroud, N., et al., 2010. COMT but not serotonin-related genes modulates the influence of childhood abuse on anger traits. Genes Brain Behav. 9, 193–202.


