Pharmacogenetics of Catechol-O-Methyltransferase: Frequency of Low Activity Allele in a Ghanaian Population

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Catechol-O-methyltransferase (COMT) catalyses the O-methylation of neurotransmitters, catechol hormones and drugs such as levodopa and methyldopa. Ethnic differences in COMT activity have been observed in several populations. Previous studies suggest that the g1947G>A low activity allele is less common in individuals of African origin. COMT genotyping was performed using a mini-sequencing method in 195 healthy Ghanaians with a frequency of the homozygous g1947G>A of 6%. This study provides confirmation that the low activity COMT allele is less common in individuals of African origin. This finding may be important clinically with regards to the treatment of many neuropsychiatric disorders and in the pathophysiology of various human disorders including estrogen-induced cancers, Parkinson’s disease, depression and hypertension. © 2000 Wiley-Liss, Inc.

KEY WORDS: catechol-O-methyltransferase; COMT; ethnic variation; SNP; Ghanaian; African

INTRODUCTION

Catechol-O-methyltransferase (COMT; MIM#116790) catalyses the O-methylation of neurotransmitters, catechol hormones and drugs such as levodopa, methyldopa and isoprenaline (Weinshilboum et al, 1999). COMT is an important gene for a number of neurologic and psychiatric disorders that involve noradrenergic or

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dopaminergic systems (Kunugi et al., 1997). O-methylation by COMT also inactivates catechol estrogens and reduced COMT has been associated with an increased risk of breast cancer (Huang et al., 1999). This polymorphic enzyme may also have pharmacogenetic significance with regard to individual differences in the metabolism of a variety of catechol drugs, as has been demonstrated for methyl dopa and levodopa (Weinshilboum et al., 1999).

COMT enzyme activity in erythrocytes (RBC) and liver has a trimodal distribution. The inheritance of human RBC COMT activity is controlled by a single genetic locus with alleles for low activity and high activity. Population studies have demonstrated genotype frequency of 25% high activity, 50% intermediate, and 25% low activity in Caucasians (Weinshilboum et al., 1999; McLeod et al., 1994). COMT phenotype frequency has been attributed to a G→A single nucleotide polymorphism (SNP) at nucleotide 1947 (g1947G>A), corresponding to valine to methionine change at codon 108 (V108M) and codon 158 (V158M) of the soluble and membrane bound COMT proteins, respectively (Lundstrom et al., 1995, Lotta et al., 1995, Lachman et al., 1996).

Ethnic differences in COMT activity have been observed in African Americans, the Saami people of Northern Norway, Oriental individuals and Kenyans (McLeod et al., 1994; McLeod et al., 1998). RBC COMT activity was 40% higher in African Americans than Caucasians, with African American individuals having a 7% frequency of the low activity phenotype (McLeod et al., 1994). Using a molecular approach, a significantly lower frequency of homozygous low activity individuals (g1947G>A) was observed in the Kenyan population (9%) than in the Caucasian (31%) or Southwest Asian (27%) populations (McLeod et al., 1998).

A remaining question is whether the significant difference in COMT genotype frequency observed in East African populations occurs in other Africans. COMT genotyping was performed in 195 Ghanaian subjects and confirms that the COMT low activity allele is less common in individuals of African origin.

Materials and Methods

After obtaining written informed consent, whole blood samples were collected from 195 healthy Ghanaian blood donors (100 men; 95 women; age 17-57 years, mean 25.6 years). The study was approved by the University of Ghana Medical School Ethical Committee. DNA was extracted from 5ml whole blood using a sodium perchlorate/chloroform extraction method (Nucleon Biosciences, U.K.). Genotyping of COMT codon 108/158 was performed using a previously described mini-sequencing method and PCR primers (Syvänen et al., 1997; McLeod et al., 1998). Comparison was made between Ghanaian allele frequency and genotype and that found for Kenyan, Southwest Asian and Caucasian subjects evaluated in the same laboratory. The difference in allele or genotype frequency between the Caucasian, Kenyan, Southwest Asians, Chinese and Ghanaians and between the Ga, Fante and Ewe tribes of Ghana were determined using a chi-square test.

Results

The allele frequency for g1947G>A was 0.26 amongst the 390 Ghanaian alleles (Table 1). The genotype frequency for homozygous g1947G>A individuals in the 195 Ghanaians studied was 6%, heterozygotes 39% and homozygous g1947G 55% (Table 1). This is in Hardy-Weinberg equilibrium. The data to date demonstrates that the population distribution of low activity COMT genotypes is clearly different between ethnic groups, with greatest similarity between the East and West Africans (Table 1). Including literature data, Kenyan, Ghanaian, Chinese and Taiwanese have a similar homozygous g1947G>A genotype frequency (range 0.03-0.09;Table 1). In contrast, Caucasians in the U.K., USA and Finland, as well as, Southwest Asians have higher frequencies of the g1947G>A genotype (range 0.22-0.31,Table 1). The difference between the Caucasians and African/Asian groups is significant (p<0.001).

Among the 195 Ghanaians studied, 115 were from the three largest Ghanaian tribes (Ga n=46; Fanti n=37; Ewe n=32). However there is no significant difference between the allele frequency among these subjects (p=0.23). The difference in genotype frequency between the three tribes did not reach significance (p=0.08,Table 2).

Discussion

The frequency of a homozygous g1947G>A genotype in West African subjects (Ghanaian) (6%) is nearly identical to RBC COMT analysis among African American individuals in which 7% had the low activity phenotype (McLeod et al., 1994). This frequency is also similar to that found in East Africans with a 9% homozygous g1947G>A genotype (McLeod et al., 1998). In contrast, 22-31% of Caucasians are homozygous for the g1947G>A (Table 1). This data provides confirmation that the low activity catechol-O-methyltransferase allele
is less common in African individuals than the Caucasian population. This is also consistent with a recent survey of COMT g1947G>A in world populations (Palmatier et al, 1999).

Table 1 Interethnic differences in the genotype and allele frequencies of the COMT gene polymorphism

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>H</th>
<th>L</th>
<th>H/H</th>
<th>H/L</th>
<th>L/L</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghanaians</td>
<td>195</td>
<td>0.74</td>
<td>0.26</td>
<td>0.55</td>
<td>0.39</td>
<td>0.06</td>
<td>This study</td>
</tr>
<tr>
<td>Kenyans</td>
<td>102</td>
<td>0.68</td>
<td>0.32</td>
<td>0.44</td>
<td>0.47</td>
<td>0.09</td>
<td>McLeod et al, 1998</td>
</tr>
<tr>
<td>Caucasians, U.K</td>
<td>265</td>
<td>0.45</td>
<td>0.54</td>
<td>0.22</td>
<td>0.47</td>
<td>0.31</td>
<td>McLeod et al, 1998</td>
</tr>
<tr>
<td>Caucasians, USA</td>
<td>129</td>
<td>0.51</td>
<td>0.49</td>
<td>0.24</td>
<td>0.54</td>
<td>0.22</td>
<td>Karayiorgou et al, 1998</td>
</tr>
<tr>
<td>Caucasians, Finland</td>
<td>3140</td>
<td>0.51</td>
<td>0.49</td>
<td>0.26</td>
<td>0.50</td>
<td>0.24</td>
<td>Syvänen et al, 1997</td>
</tr>
<tr>
<td>Southwest Asians</td>
<td>99</td>
<td>0.51</td>
<td>0.49</td>
<td>0.29</td>
<td>0.43</td>
<td>0.27</td>
<td>McLeod et al, 1998</td>
</tr>
<tr>
<td>Taiwanese</td>
<td>99</td>
<td>0.73</td>
<td>0.27</td>
<td>0.53</td>
<td>0.40</td>
<td>0.07</td>
<td>Chen et al, 1997</td>
</tr>
<tr>
<td>Taiwanese</td>
<td>125</td>
<td>0.75</td>
<td>0.25</td>
<td>0.53</td>
<td>0.44</td>
<td>0.03</td>
<td>Huang et al, 1999</td>
</tr>
<tr>
<td>Japanese</td>
<td>153</td>
<td>0.71</td>
<td>0.29</td>
<td>0.48</td>
<td>0.46</td>
<td>0.06</td>
<td>Kunugi et al, 1997</td>
</tr>
<tr>
<td>Chinese</td>
<td>98</td>
<td>0.82</td>
<td>0.18</td>
<td>0.67</td>
<td>0.30</td>
<td>0.03</td>
<td>Li et al, 1997</td>
</tr>
</tbody>
</table>

(H-high activity allele [g1947G], L-low activity allele[g1947G>A], n=number of subjects)

These results have implications for disease risk and treatment response. Regulation of human COMT gene expression may be important in the pathophysiology of various human disorders including estrogen-induced cancers, Parkinson's disease, depression and hypertension. The COMT SNP has been associated with violence in schizophrenia and suggested to have a role in other neuropsychiatric disorders (Lachman et al, 1998).

Recent studies suggest that the COMT SNP is associated with an increased risk of breast cancer (Huang et al, 1999; Lavigne et al, 1997). Methylation by COMT is the principal pathway for the inactivation of catechol estrogens, which are hypothesised to participate in estrogen-induced carcinogenesis. Patient COMT genotype may contribute to the subsequent development of breast cancer in women who have other risk factors, such as a family history of breast cancer, early age at menarche, late age of first full term pregnancy, smoking and high body mass index (Lavigne et al, 1997). The low frequency of COMT g1947G>A may help explain the lower incidence and lower risk of breast cancer in black women compared to white women (Moormeier et al, 1996).

Table 2 COMT Allele and genotype frequency in Ghanaian tribes

<table>
<thead>
<tr>
<th>Tribe</th>
<th>n</th>
<th>H</th>
<th>L</th>
<th>H/H</th>
<th>H/L</th>
<th>L/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ga</td>
<td>92</td>
<td>0.80</td>
<td>0.20</td>
<td>0.63</td>
<td>0.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Fante</td>
<td>74</td>
<td>0.77</td>
<td>0.23</td>
<td>0.57</td>
<td>0.40</td>
<td>0.03</td>
</tr>
<tr>
<td>Ewe</td>
<td>64</td>
<td>0.70</td>
<td>0.30</td>
<td>0.50</td>
<td>0.41</td>
<td>0.09</td>
</tr>
</tbody>
</table>

(H-high activity allele, L-low activity allele, n=number of alleles)

REFERENCES


4 Ameyaw et al.


