Allele frequency differences of cytochrome P450 polymorphisms in a sample of New Zealand Māori

Rod A Lea, Rebecca L Roberts, Michael R Green, Martin A Kennedy, Geoffrey K Chambers

Abstract

Aims To determine the prevalence of functional alleles for drug metabolising genes in a sample of Māori and compare allele frequencies with Caucasian estimates.

Procedures DNA from 60 Māori volunteers was genotyped for cytochrome P450 polymorphisms—CYP2A6, CYP2C9, CYP2C19, and CYP2D6—and allele frequencies calculated and compared with Caucasian estimates.

Results Absolute allele frequency differences between Māori and Caucasian groups ranged from 1% to 16% for the polymorphisms tested.

Conclusions Functional allele frequencies of drug metabolising genes differed between Māori and European groups warranting larger general population surveys. These findings may also bear thinking about when conducting pharmacogenetic studies or clinical trials in New Zealand cohorts because patients with Māori ancestry may respond differently to certain medicines based on genotype.

The cytochrome P450 (CYP) enzymes play a central role in the metabolism of commonly prescribed drugs such as antidepressants, beta blockers, antipsychotics, and nicotine replacement therapy (NRT). Many of the CYP genes are known to contain polymorphisms that are associated with variation in drug response among individuals. Allele frequencies of some of these polymorphisms are known to vary considerably across different racial groups, and this may be important for understanding variation in drug response among patients with different ancestral backgrounds.

The Māori population of New Zealand (NZ) represents the final link in a long chain of island-hopping voyages stretching across the South Pacific Ocean. It is believed this population originated from small groups of common ancestors ~1000 years ago and, within the geographic isolation of NZ, underwent rapid growth until the arrival of European colonisers in the 1800s.

Considering this unusual genetic history it is reasonable to expect that the Māori population developed substantially different allele frequencies compared to other human populations. The intermarriage with Europeans over the last 8–10 generations has further modified the genomic structure of the Māori population, such that an estimated 40% of the modern Māori gene pool consists of Caucasian genes.¹

Little research has been conducted on pharmacokinetics or pharmacogenetics of drugs in the Māori population. In 1995, Wanwimolruk et al, phenotyped CYP2D6 and CYP2C19 in a sample of Māori using debrisoquine and proguanil as substrate drugs, respectively. These researchers found that the prevalence of poor metabolisers (PMs)
for debrisoquine was not higher in Māori compared to Caucasians. However the frequency of the PM phenotype for proguanil was increased in Māori.  

Recently, we assessed nicotine metabolism via the CYP2A6 enzyme in a sample of smokers and found evidence that Māori metabolise nicotine at a slower rate than Caucasians. These findings suggest that genetic variants, influencing CYP2C19 and CYP2A6 activity, may play a role in predicting relevant drug response in Māori.

Here we have determined the prevalence of functionally relevant alleles in the CYP2C9, CYP2C19, CYP2D6, and CYP2A6 genes in a sample of Māori volunteers and compared these frequencies to those previously reported for Caucasians. We also discuss the findings in terms of possible clinical relevance to Māori as well as pharmacogenetic association studies in this admixed population.

**Methods**

The sample (n=60) was selected from a pre-existing bank of DNA housed at Victoria University of Wellington. DNA samples were originally collected through the Blood Transfusion Service in Wellington.

Participants were unrelated by first-degree and classified as “Māori” by self-report using:
- The 2001 census definition for ethnicity, and
- An ancestral definition—i.e. having 8 Māori great grandparents.

As such, this sample might be considered more representative of the ancestral (non-admixed) Māori population then the modern day general (and admixed) Māori population. Ethics approval was granted by the Wellington Ethics Committee in 2004.

We tested CYP2A6 variants that have been previously associated with slow nicotine metabolism and that have an allele frequency of greater than 2% in Caucasians (i.e. CYP2A6*4, CYP2A6*7, and CYP2A6*9). Genotyping of CYP2A6 variants was performed as described in Lea et al, 2005. We also genotyped the commonly studied variants in CYP2C9 and CYP2C19, CYP2D6 genes according to the methods described in Sullivan-Klose et al, 1996; Roberts et al, 2006; Goldstein et al, 1996. P-values were determined using Fisher's Exact Tests by comparing data from the Māori sample to previously published Caucasian data.

**Results**

Table 1 shows the CYP allele frequencies observed for the Māori sample as well as absolute frequency differences compared to previously published estimates in Caucasian samples (see references in Table 1). Across all variants tested the absolute difference values ranged from less than 1% to 16%. The largest differences were observed for CYP2C9*2, CYP2D6*4, and CYP2A6*9 (>11%). For the Māori sample, the PM alleles (i.e. *2 and *3) were less prevalent for CYP2A9 and more prevalent for CYP2C19 compared to Caucasian (p<0.05).

The distributions for CYP2D6 alleles were different between the groups due to lower frequency of *4 and *41 alleles and higher frequencies of *10 alleles in Māori (p<0.05). For CYP2A6 variants the slow metabolising alleles (*4 and *9) were more prevalent in Māori compared to Caucasian (p<0.001).

**Discussion**

This study determined allele frequencies for functionally relevant CYP gene variants in a sample of Māori selected to be fairly representative of the non-admixed Māori population. The rationale for the research is based on the premise that the unique genetic history of Māori has significantly modified the allele frequencies at these loci, particularly compared to Caucasian, and that this may partially explain variation in drug response of this indigenous population.
Table 1. Frequencies of variant cytochrome P450 alleles in Māori and Caucasian samples

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Common Drugs Metabolised</th>
<th>Allele Frequency (%)</th>
<th>Difference</th>
<th>P-value*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maori</td>
<td>Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*2</td>
<td>NSAIDs, Angiotensin II</td>
<td>1.7</td>
<td>11*</td>
<td>9.3</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>*3</td>
<td>Blockers, Sulfonylureas</td>
<td>0.8</td>
<td>7*</td>
<td>6.2</td>
<td>0.002</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*2</td>
<td>Proton pump Inhibitors, Anti-epilepsies</td>
<td>24</td>
<td>15</td>
<td>9</td>
<td>0.001</td>
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<tr>
<td></td>
<td>*3</td>
<td></td>
<td>1.7</td>
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</tr>
<tr>
<td>CYP2D6</td>
<td>*5</td>
<td>Antidepressants,</td>
<td>0.9</td>
<td>1</td>
<td>0.1</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>*4</td>
<td></td>
<td>7.9</td>
<td>19.5</td>
<td>11.6</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>*5</td>
<td></td>
<td>1.8</td>
<td>4.1</td>
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<tr>
<td></td>
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<td></td>
<td>0</td>
<td>2</td>
<td>2</td>
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</tr>
<tr>
<td></td>
<td>*10</td>
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<td>6.1</td>
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<tr>
<td></td>
<td>*41</td>
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<td>3.5</td>
<td>20*</td>
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<td>1.1</td>
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<tr>
<td></td>
<td>*9</td>
<td></td>
<td>1.9</td>
<td>7.1</td>
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</tbody>
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*P values determined by comparing Māori allele frequencies to published Caucasian frequencies using Fisher's Exact Test; #Values are the lower of the range published for European (i.e. British, Italian, Spanish, and Swedish).

Our results showed that substantial differences exist for alleles of CYP2C9, CYP2C19, and CYP2D6 polymorphisms between Māori and Caucasian groups. The increased prevalence of PM alleles for CYP2C19 in Māori is consistent with the phenotypic results of Wanwimolruk et al (1995).²

These findings may ultimately have implications for clinicians prescribing commonly used drugs metabolised via these enzymes such as fluoxetine and warfarin. For example, if a patient with Māori ancestry has a different likelihood of possessing variant CYP450 alleles this might alter their risk of adverse events or otherwise influence successful treatment outcomes.

We also found evidence for a higher frequency of CYP2A6 alleles (*4 and *9) in the Māori sample compared to Caucasian. These alleles have been previously associated with slower acting CYP2A6 and nicotine clearance in smokers: ~80% of nicotine is metabolised via CYP2A6. There is also evidence that slow-acting CYP2A6 may modify response to nicotine patch therapy and likelihood of smoking cessation.¹¹ Therefore, knowledge of increased frequency of the slow-acting CYP2A6 alleles in Māori might benefit the smoking-cessation programmes and clinicians when screening smokers for likely success using standard dose nicotine replacement patches.

It is important to note that due to the fact that the Māori sample studied here was selected to possess as little non-Māori ancestry as possible our allele frequencies should not be interpreted to be estimates of the general Māori population. Studies of much larger random Māori samples are required before evidence-based decisions can be made about these genetic markers in terms of clinical practice.
The present day Māori population exhibits significant genetic admixture largely as a result of intermarriage with Caucasians of European origin. This unique genetic structure presents both problems and advantages for pharmacogenetics studies involving this population. When conducting genetic association studies or clinical trials of drug response in NZ care should be taken to control for ancestry-specific genetic variation within the study cohort to avoid false or misleading results.

Depending on the study design this may be achieved by genotyping relevant functional polymorphisms such as the CYP markers investigated here (e.g. clinical trial) and/or by using genomic control markers—i.e. DNA markers that can estimate degree of Māori/European ancestry (e.g. genetic association studies of cases and controls).

If DNA is not available or difficult to obtain, as is the case for many clinical trials or epidemiological studies, we suggest self reported ancestry of the patient based on grandparental information could be used as a proxy for estimating and controlling for variation in genomic ancestry.

Recently admixed populations such as Māori also make it possible to map genes associated with differential drug response or disease susceptibility using a method known as mapping by admixture linkage disequilibrium (MALD). This method exploits the new allelic associations that are formed among adjacent polymorphisms when two genetically distinct populations mix and can identify ancestry-specific alleles that may contribute to ethnic differences in heritable traits like drug response.

In conclusion, this study is the first to report frequencies of functionally important CYP alleles in a sample of Māori and has shown that potentially important differences exist when compared to Caucasians. These data provide a compelling rationale for conducting further large-scale pharmacogenetic research involving Māori.

Competing interests: None known.

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Acknowledgements: The authors acknowledge the participants of the study and the financial support of the Foundation of Research Science and Technology and Health Research Council of New Zealand.

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References


