Is the prevalence of \textit{CYP2C19} genetic variants different in Pacific people than in New Zealand Europeans?

Nuala Helsby, Michael Goldthorpe, Peter Gow, Janak de Zoysa

**Abstract**

**Aim** To undertake a preliminary assessment of the prevalence of \textit{CYP2C19} ultra-rapid and poor metaboliser genetic variants in Pacific people compared with NZ Europeans.

**Method** Individuals who self-identified as either Pacific people (n=14) or NZ European (n=12) were genotyped for the *2, *3 or *17 functional variants of \textit{CYP2C19}.

**Results** There was a significantly lower frequency (P<0.01) of the \textit{CYP2C19*17} allele in Pacific people compared with NZ Europeans. No \textit{CYP2C19*17} variant alleles were detected in Pacific people in this preliminary study.

**Conclusions** The presence of \textit{CYP2C19*17} may be low in Pacific people and may lead to altered efficiency at metabolising some common drugs such as omeprazole. Further studies to confirm this preliminary finding are warranted.

The human liver cytochrome P450 enzyme, \textit{CYP2C19}, is involved in the metabolism of drugs from an extensive range of therapeutic classes, including omeprazole, diazepam and proguanil.\textsuperscript{1} Individuals who are homozygous for the loss of function variants (\textit{CYP2C19*2} and \textit{CYP2C19*3}) are “poor metabolisers” of these drugs.\textsuperscript{2} Recent reports indicate that an additional variant (\textit{CYP2C19*17}) is associated with ultra-rapid metabolism of these drugs.\textsuperscript{3,4}

Up to 5\% of Caucasians are \textit{CYP2C19} genotypic poor metabolisers\textsuperscript{5} and between 18–22\% of Caucasians are carriers of the \textit{CYP2C19*17} allele.\textsuperscript{3,6} A genotyping approach for pharmacogenes such as \textit{CYP2C19} is often advocated to "personalise therapy" in individuals with variant alleles.

In contrast to Caucasian populations, however, there have been no reports regarding the prevalence of \textit{CYP2C19} variant alleles in Pacific people.

**Methods**

Following informed consent a cohort of New Zealand (NZ) lupus nephritis patients were genotyped for the \textit{CYP2C19} genetic polymorphism as part of a larger study to determine the role of pharmacogenetics in the response to cyclophosphamide therapy. Ethics approval for this study was obtained from the Northern X Regional Ethics Committee. Of this larger cohort of 41 patients, 14 subjects self identified as Pacific people (6 Samoan, 4 Tongan, 1 Cook Islander, and 3 Fijian) and 12 subjects identified as NZ European (Table 1).

DNA was prepared from blood samples using the PAXgene blood DNA kit (Qiagen, Hilden, Germany). \textit{CYP2C19} genotype was determined by PCR-RFLP analysis of the two major loss of function allelic variants (\textit{CYP2C19*2} and \textit{CYP2C19*3}) and the gain of function variant (\textit{CYP2C19*17}) using previously published methods.\textsuperscript{3,7} Statistical differences in allele frequencies were determined using Fishers exact test (two- tailed) using Graphpad Prism (v5.02).
Results

Six (of the 14) Pacific people were carriers of CYP2C19 (*2 or *3) loss of function variants (Table 1) while three (of the 12) NZ Caucasians were heterozygote carriers of the *2 variant (including one subject who was homozygous variant (*2/*2). No NZ European subjects had the *3 variant. The frequency of the loss of function variant alleles, though higher (21.4%) in Pacific people, was not significantly different from the frequency in NZ Europeans (16.6%).

Using the Hardy-Weinberg equation (p^2 + 2pq + q^2=1) the expected frequency of CYP2C19 loss of function homozygous (poor metaboliser) subjects in Pacific people in this small sample is 3.6%.

Table 1. CYP2C19 genotypes of subjects who self identified as Samoan, Tongan, Cook Islander, Fijian, or NZ European

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>CYP2C19 genotype</th>
<th>Ethnicity</th>
<th>CYP2C19 genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samoan</td>
<td>*1/*2</td>
<td>NZ European</td>
<td>*1/*17</td>
</tr>
<tr>
<td>Samoan</td>
<td>*1/*1</td>
<td>NZ European</td>
<td>*1/*2</td>
</tr>
<tr>
<td>Samoan</td>
<td>*1/*1</td>
<td>NZ European</td>
<td>*1/*17</td>
</tr>
<tr>
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<td>*1/*3</td>
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<td>*1/*1</td>
</tr>
<tr>
<td>Samoan</td>
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<td>NZ European</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Samoan</td>
<td>*1/*1</td>
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<td>*1/*17</td>
</tr>
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<td>NZ European</td>
<td>*2/*2</td>
</tr>
<tr>
<td>Tongan</td>
<td>*1/*1</td>
<td>NZ European</td>
<td>*1/*17</td>
</tr>
<tr>
<td>Tongan</td>
<td>*1/*2</td>
<td>NZ European</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Cook Islander</td>
<td>*1/*2</td>
<td>NZ European</td>
<td>*17/*17</td>
</tr>
<tr>
<td>Fijian</td>
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<td>NZ European</td>
<td>*1/*17</td>
</tr>
<tr>
<td>Fijian</td>
<td>*1/*2</td>
<td>NZ European</td>
<td>*1/*17</td>
</tr>
<tr>
<td>Fijian</td>
<td>*1/*3</td>
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</tbody>
</table>

In contrast, the frequency of CYP2C19*17 was significantly lower (P=0.0053) in Pacific people than in NZ Europeans (Table 1). No CYP2C19*17 variant alleles were detected in samples from Pacific people whereas in NZ Europeans two subjects were homozygous variant for CYP2C19*17 and four subjects were heterozygous carriers of this variant.

Hence the overall pattern of CYP2C19 variant alleles differs in Pacific people compared with NZ Europeans (Figure 1).
Figure 1. The frequency of individual CYP2C19 alleles in Pacific people and New Zealand (NZ) Europeans

![Bar chart showing frequency of CYP2C19 alleles](chart.png)

Note: *1 is the wild type allele, the *17 variant is associated with “ultra-rapid metaboliser” status, the *2 and *3 variants are associated with a loss of function “poor metaboliser” status.

Conclusions

No reports of the prevalence of CYP2C19 genetic variants in Pacific people have been published previously. However, a study that measured CYP2C19 activity, using the probe drug proguanil, reported that 13.6% of “Polynesian” subjects had a poor metaboliser status.

The predicted frequency of CYP2C19 loss of function homozygous poor metabolisers in the current small study of Pacific people is much lower at 3.6%. However, a significantly increased frequency of the CYP2C19*2 variant in Maori compared with Caucasians has been reported, with 25.7% of Maori subjects CYP2C19 loss of function carriers. This is similar to the prevalence of heterozygote carriers identified in the current small study in Pacific people. However, possibly due to the small sample size in this preliminary study we did not observe a significant difference between Pacific people and NZ Europeans in the prevalence of CYP2C19 loss of function carriers. Hence, further studies with a larger sample size are warranted to confirm the frequency of CYP2C19 loss of function variants in Pacific people.

The CYP2C19*17 variant has only recently been identified as a novel gain of function SNP which results in an ultra-rapid metaboliser phenotype. Prior to this study no information about the incidence of this variant in Pacific people had been reported. The incidence of this allele in NZ Europeans was 33%, which is higher than the prevalence reported in other Caucasian groups (18-22%). In contrast, this allelic variant is reported to be low in Japanese (1.3%) and Chinese (4.4%). Since CYP2C19*17 was not detected in this small study of Pacific people it is possible that...
ultra rapid metabolism of drugs which are substrates for CYP2C19, such as omeprazole, clopidogrel and diazepam, will not be observed in these populations.

There are a number of limitations to this preliminary study, in particular the small sample size. Moreover, the Pacific peoples in the study included both Melanesian and Polynesian individuals, and ethnic diversity within Pacific peoples should not be overlooked in future studies. In addition, the participants in this study were lupus nephritis patients who had received, or were about to receive, cyclophosphamide treatment. The CYP2C19 pharmacogene plays a significant role in the bioactivation of this drug\textsuperscript{11} and may adversely affect therapeutic outcome. As such the prevalence of CYP2C19 allelic variants in lupus nephritis patients may differ from that observed in healthy subjects.

In conclusion, there appears to be a difference in the pattern of CYP2C19 genetic variants in Pacific people compared with Caucasians. Further studies to confirm this preliminary finding are necessary.

\textbf{Competing interests:} None known.

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