Association between cytochrome P450 2C19 polymorphism and clinical outcomes in Chinese patients with coronary artery disease

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1. Introduction

Cytochrome P450 (CYP)2C19 is expressed in vascular endothelium and metabolizes arachidonic acid to biologically active epoxyeicosatrienoic acids, which play a key role in regulating vascular tone. The frequent genetic functional variant 681G > A (∗2) of cytochrome CYP2C19 is an important contributor to the wide variability between individuals of the antiplatelet effect of clopidogrel and predict cardiac events in Caucasian patients with acute coronary syndromes (ACS) [1–4]. Importantly, the CYP2C19∗2 loss-of-function allelic variant (681A allele) has been shown to encode for a deficient drug-metabolizing enzyme [5].

The frequency of CYP2C19∗2 variant allele is reported to be higher in Chinese populations than in Caucasians [6,7]. However, the relationship between the genetic polymorphism of CYP2C19 and cardiovascular prognosis in patients of Chinese ancestry has been hitherto unexplored. This study was designed to test the hypothesis that the CYP2C19∗2 loss-of-function allelic variant could predict clinical outcomes in Chinese patients with coronary artery disease (CAD).

2. Materials and methods

This study complied with the ethical guidelines of the Declaration of Helsinki, and was approved by the local Institutional Review Board. Informed consent was obtained from all participants.

2.1. Study participants

This study was conducted between July 2008 and September 2009 in the West China Hospital, Chengdu, China. All consecutive patients with angiographically-proven CAD (ACS or stable angina) who were 18 years of age or older were considered for participation. The diagnosis of ACS was based on the following criteria: (1) a greater than 50% stenosis in at least one epicardial coronary artery; (2) symptoms of ischemia that increased or occurred at rest, and (3)
Table 1  
General characteristics of the study participants at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire cohort (N = 654)</th>
<th>CYP2C19 polymorphism</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>*2/*2 (N = 57)</td>
<td>*1/*2 (N = 291)</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.17 ± 10.63</td>
<td>64.61 ± 9.62</td>
<td>66.07 ± 10.22</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>533 (81.5)</td>
<td>47 (82.5)</td>
<td>231 (79.4)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>369 (56.4)</td>
<td>32 (59.1)</td>
<td>162 (55.7)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>127 (19.4)</td>
<td>16 (28.1)</td>
<td>69 (23.7)</td>
</tr>
<tr>
<td>Previous or current smokers, n (%)</td>
<td>395 (60.4)</td>
<td>37 (64.9)</td>
<td>171 (58.8)</td>
</tr>
<tr>
<td>Previous PCI or CABG, n (%)</td>
<td>103 (15.7)</td>
<td>11 (19.3)</td>
<td>48 (16.5)</td>
</tr>
<tr>
<td>Previous drug treatment, n (%)</td>
<td>497 (76)</td>
<td>39 (68.4)</td>
<td>216 (74.2)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>533 (81.5)</td>
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<td>231 (79.4)</td>
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</tbody>
</table>

Diabetes was diagnosed in patients who had previously undergone dietary treatment, had received additional oral anti-diabetic or insulin medication, or had a current fasting blood glucose level of >7.0 mmol/L in two blood samples.

Blood samples (5 mL) were drawn from the arterial sheath immediately before diagnostic angiography. The genomic DNA was extracted using a commercially available DNA isolation kit (Tiangen Biotech, Beijing, China) according to the manufacturer's protocol. The loss-of-function CYP2C19*2 variant (681G > A; rs4244285) was genotyped using a commercially available drug metabolism genotyping assay (TaqMan Validated SNP assays, C_25986767_70, Applied Biosystems, Foster City, CA, USA) on an ABI PRISM 7300 sequence detection system (Applied Biosystems).

2.4. Genotyping

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are reported as counts and percentages. Analysis of variance (ANOVA) and chi-square tests were used to test for differences between groups for continuous
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