Reviewer's report

Title: Association between genetic polymorphisms of cytochrome P450 2C19 and the risk of cerebral ischemic stroke in Chinese

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Reviewer: Jorge Capdevila

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In: “Association between genetic polymorphisms of cytochrome P450 2C19 and the risk of cerebral ischemic stroke in Chinese” Gu et al., associate two well-known functional polymorphisms in the CYP2C19 gene (G681A and G636A) with the occurrence and recurrence of cerebral ischemic stroke CIS). While polymorphism in this gene have already been linked to risks of cardiovascular and vascular events, this study adds to that ischemic cerebral stroke, a clinically important event in need of new and more effective treatment strategies. Base on case study done with a population of Chinese Ham consisting of 299 CIS patients (~59% male) of which 114 suffered from recurrent stroke, and 295 healthy volunteers (~54% males), and the authors conclude that “the G681AA genotype may be an independent risk factor for CIS”, and that the AA genotype and A allele may be related to occurrence and recurrence of CIS. While the size of the population study is limited, the high frequency of the G681A variant genotype in Chinese Ham individuals allowed them to reach acceptable levels of significance in support of their conclusions.

While this study deserves publication, several issues need to be addressed by the authors prior to acceptance:

a) Inasmuch as Figure 1 and 2 illustrate just technical details, they should be presented in the “Additional Files” section of the manuscript, and replaced by Tables 1, 2, 3 and 4. These Tables contain the experimental data needed to support the manuscript conclusions, population characteristics (Tables 1 and 2), and allele frequencies for the different groups under study (Table 3 and 4).

b) Table could be streamlined by including only those parameters that differ between the groups under study, and by replacing those that are similar by mentioning their values in the text.

c) While hypertension is predominant in the patient population (75% of CIS patients versus 25% of controls) this important co-morbidity, known to affect the risk of stroke, including cerebral stroke, is summarily mentioned. Thus, there is no mention/discussion of its potential roles played by high blood pressure as modifier or a causative agent the observed effects of the CYP2C9 A allele in CIS, nor it is taken into account its importance in evaluating the roles of CYP2C9 gene variants in CIS. Given that several roles have been reported for the CYP2C8 and CYP2C19 enzymes in the regulation of vascular reactivity, blood pressure control, and hypertension, it is of importance the address the issue of its
relevance to the CYP2C9 genetic associations studied here either as a modifier or a causative agent.

d) Minor issues: 1) mutant should be replaced by variant. 2) p values can’t be reported as 000. There must be a numeric value assigned to p. Even if is exceedingly low, it is important to know its value. 3) From the text, page 3, 1st paragraph, line 8th: “CYP2C9*7, CYP2C19*8 and so on”. The so on is unacceptable. 4) From the text, page 7th, beginning of Discussion: “CYP2C9 is composed of……………..which exits in hepatic microsomes”. CYP2C9 is expressed, among other organs, in kidney, endothelium. It only predominates in liver. 5) Same paragraph as in 4. Microsomes are only a technical definition, and have no meaning in vivo. Should use instead endoplasmic reticulum.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests