Reviewer's report

Title: Polymorphisms of the endothelial nitric oxide synthase (NOS3) gene in preeclampsia: a candidate-gene association study

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Reviewer: Carl Hubel

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Polymorphisms of the endothelial nitric oxide synthase (NOS3) gene in preeclampsia: a candidate-gene association study
Nikos Zdoukopoulos

Comments To Authors:

Zdoukopoulos and colleagues examined the association of three common variants of the NOS3 gene (4b/a, T-786C and G894T) and their haplotypes in a case-control sample of 102 patients with preeclampsia and 176 with uncomplicated pregnancy outcome. The genotype distribution in controls were in Hardy-Weinburg equilibrium, whereas genotypes were not associated with clinical status and odds ratios were not significant. Haplotypes also showed no significant association. The study was logically designed and is well presented, and will help to counter publication bias against negative/null findings.

Minor Essential Revisions

1. The Abstract indicates a “case-control sample of 102 patients with preeclampsia and 176 healthy females”. It would be better to indicate that the controls were women with a history of uncomplicated pregnancy (the genotype distribution of these controls could differ from the general population of healthy females).

2. Are all of the inclusion/exclusion criteria for cases and controls included in Methods? Please indicate whether or not all of the controls were delivered at term and whether patients with previous renal disease, diabetes, or history of metabolic disorders were excluded from the patient sample.

3. Table 1: Please indicate significant differences. Please also include maternal pre-pregnancy body mass index (BMI) if available.

4. It may be assumed that all patients were Caucasian but race status should be indicated somewhere.

Discretionary Revisions

1. It is recommended that a few sentences and reference be added to explain
WHY the “endothelial nitric oxide synthase gene (NOS3), ..... , has emerged as a logical candidate gene in the development of preeclampsia” (beyond just the association with hypertension).

2. It might be useful to mention/discuss that the linkage recently reported for eNOS possibly reflects its relationship with (essential) hypertension rather than preeclampsia, and that preeclampsia is more than just gestational hypertension.

3. Regarding the statement, “Interestingly, 13 studies [5, 18-29] have reported association for the variants NOS3 gene...” please clarify whether these represent a mixture of positive and negative findings. Please also consider adding Hillermann R e al J Hum Genet (2005) (Glu298Asp study) to this mix of references.

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

None