Genetic variants in pre-eclampsia should be interpreted with caution

Sir,

We read the article entitled ‘Genetic variants in pre-eclampsia: a meta-analysis’ by Buurma et al. (2013) with great interest. It is an important step forward in the identification of genetic variants associated with pre-eclampsia. However, there are several important issues that require clarification or further research.

First, according to the value of $I^2$, some studies included in the meta-analysis had notable heterogeneity (e.g. AGT rs699 and SERPINE1 rs1799889). Apart from the sample size, many factors (e.g. linkage disequilibrium, ethnicity and study quality) may cause the between-study heterogeneity. Rather than simply produce a combined estimate of effect, we should explore the potential methodological reasons for heterogeneity by meta-regression or sensitivity analysis (Khoury and Little, 2000). Without these data, it is not appropriate to draw conclusions about the ‘true associations’ between gene variants and pre-eclampsia.

Secondly, the potential influence of ethnicity was not clarified clearly. Even though the overall effect of AGT (rs699) on pre-eclampsia risk was not significant, subgroup analysis showed the mutation of AGT (rs699) significantly increased the risk in Caucasians but not in Asians (Ni et al., 2012). Similarly, opposite to the overall null association, we found a positive association between MTHFR (rs1801133) mutation and pre-eclampsia when restricted to Asian population, which was also demonstrated by Xia et al. (2012). We suggest exploring the inconsistencies in specific populations and reporting detailed data for meta-analysis to avoid causing confusion.

Finally, we compared the results of Buurma et al. (2013) with a similar meta-analysis (Staines-Urias et al., 2012). Including one more original study of SERPINE1 (rs1799889) than Buurma et al., Staines-Urias et al. (n = 12) came into a different conclusion (OR, 0.89; 95% CI, 0.73–1.09). Although the change in statistical significance may be due to the exclusion of large sample-size study, the results of the meta-analysis should really be interpreted with caution. In addition, few single candidate genes of pre-eclampsia have been confirmed by Genome-wide association studies (GWAS) up to date. Since pre-eclampsia is a set of multi-factorial syndromes (Steegers et al., 2010), combining GWAS with gene–environment interaction studies (Thomas, 2010) may provide a more comprehensive sight into pre-eclampsia.

References


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We would like to thank the authors for their valuable remarks.

In their letter, the authors first mention that heterogeneity is present among various studies included in the meta-analysis. Several factors may underlie such between-study heterogeneity, and indeed exploring such heterogeneity is an important goal in itself. Therefore, we considered performing meta-regression, which is commonly used to investigate whether study characteristics may explain heterogeneity of results among studies. However, meta-regression analysis may produce misleading results, particularly when based on small numbers of studies, while there are innumerable characteristics of these studies that may potentially cause heterogeneity (Higgins and Thompson, 2004). Because many of the genetic variants included in our meta-analysis were investigated in a limited number of studies, we refrained from performing meta-regression. To weaken the assumption of one underlying true effect for all studies, we performed a random effects model by default.

As mentioned by the authors, we did not separately investigate the role of ethnicity. Our meta-analysis focused on independent replication of overall effects. We think that independent replication is an essential tool to distinguish between true associations and false-positive results. When stratifying according to (ethnic) subgroups two problems arise: false positivity (studies only reporting significantly associated subgroups) and the lower power to detect true effects. For example, in the study of Ni et al. (2012), the lack of association in the African group could either mean that there is truly no association...