

LETTERS TO THE EDITOR—COMMENT

Analysis of genetic polymorphisms in preeclampsia: Relevance of haplotypes

To the Editors,

Medica et al. carried out an interesting and important meta-analysis which examined relevant studies on the possible association between preeclampsia and polymorphisms on vasoactive genes including the endothelial nitric oxide synthase (eNOS) gene [1]. They mention that meta-analysis could ensure certainty in statistical analysis and avoid contradictions. They concluded that variants in eNOS gene have a modest effect on the risk of developing preeclampsia [1]. Although meta-analysis may shed some light on inconsistent results derived from a number of different case–control studies, haplotype (or diplotype) analysis can provide much more relevant biological information. Indeed, the analysis of haplotypes (which are combinations of genetic markers within a chromosome cluster location) has been valued as a more powerful approach in genetic association studies than the analysis of single polymorphisms [2]. For example, recent studies have shown that eNOS haplotypes involving three of the most studied eNOS polymorphisms are associated with the development of hypertension [3–5]. Interestingly, single eNOS polymorphisms were not associated with hypertension in these studies. Therefore, haplotype findings would have been missed if specific eNOS genotypes alone had been considered [3–5]. The same specific eNOS haplotypes are associated with susceptibility to hypertension in subjects with different ethnic backgrounds [3–5], even though significant interethnic differences exist in the distribution of eNOS genotypes or haplotypes [6,7]. These previous findings support the notion that interactions between eNOS polymorphisms play a role in the genetic susceptibility to hypertension, but not individual eNOS polymorphisms. Such conclusion would hardly be drawn with a meta-analysis based on single polymorphism studies, as the one conducted by Medica et al. Finally, a meta-analysis of studies based on eNOS haplotypes can lead to more certainty in statistical analysis than those based on eNOS genotypes.

References

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Meta analysis: Haplotype or single polymorphism analysis.

Authors' Reply to Comment on “Genetic polymorphisms in vasoactive genes and preeclampsia: A meta-analysis” [*Eur. J. Obstet. Gynecol. Reprod. Biol.* 131 (2007) 115–126]

Dear Editors,

Dr. Heitor Moreno Jr. has suggested that haplotype analysis is a more powerful approach to assess the contribution of genome variability to disease phenotypes in genetic association studies compared to the analysis of single gene polymorphisms. This suggestion was based on

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three papers by the same group (references in Comment from Dr. Moreno) which suggested an association between eNOS haplotypes and hypertension in White and Black patients, as well as patients with Type 2 diabetes mellitus. These data should be however replicated in other studies/populations before generalization. In fact, there is evidence that both polymorphisms [1] and haplotypes [2] of the eNOS gene are associated with some functional consequences. In general, it is impossible to predict in advance whether a single nucleotide polymorphism (SNP) or haplotype approach will be more powerful for a given gene–disease pair. Namely, the relative power of using either approach depends on the evolutionary history of the population and the genetic architecture of the candidate gene variants in that population [3]. Thus, if there is a single-functional genetic variant associated with a given disease, association analysis of that variant would be the most powerful approach. On the other hand, if a single functional mutation occurred in one haplotype and if most individuals who carry that haplotype also carry the mutation, then haplotype analysis would be a more powerful approach. In reality, situations are rarely close to both extremes, therefore a combination of approaches might be advisable.

It is evident that meta-analyses of single gene variants are more feasible, as the necessary data (genotype frequencies) are already provided in the relevant papers. Haplotype meta-analysis on the other hand depends on the availability of the individual genotypes of patients included in the studies which are generally not reported in the literature.

In conclusion, as there are pros and cons to both the single polymorphism and haplotype approaches, it would be useful to use both approaches in combination.

References

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Comment on “TVT and TVT-Obturator: Comparison of two operative procedures” *Eur. J. Obstet. Gynecol. Reprod. Biol.* 131 (2007) 87–90

Dear Editors,

I read Manahem Neuman's article titled “TVT and TVT-Obturator: comparison of two operative procedures” [1], no doubt an excellent paper that adds value to the existing and ever expanding knowledge on transobturator procedures.

Routine cystoscopy during transobturator procedures is carried out by approximately 31.45% of surgeons [2]. But anatomical dissections for both inside-out and outside-in methods clearly show that routine cystoscopy may not be necessary, although there are different schools of thought regarding this issue.

In the discussion, the author mentions that “bladder perforation was previously reported in relation to an ‘outside-in’ transobturator designed mid-urethral procedure (TOT), but never an ‘inside-out’ transobturator procedure”. I would like to refer to a paper by Hermiu et al. [3], which describes the first ever case of bladder perforation after the TVT-Obturator sling procedure.

Also, the author mentions that he assumed that no bladder perforation occurred in the TVT-Obturator group, as no signs suggesting bladder perforation (such as urinary leakage through surgical abdominal or vaginal cuts) were recorded. Bladder perforation could be asymptomatic as illustrated by Minaglia et al. [4] who identified cases of bladder perforation (clinically unsuspected) on routine cystoscopy following transobturator outside-in procedures. Bladder injury may present as worsening irritable bladder symptoms (personal observations, unpublished) after transobturator procedures.

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