Letter to the Editor

Polymorphisms and Haplotypes in Candidate Genes Related to Angiogenesis and Endothelial Dysfunction in Preeclampsia

Marcelo Rizzatti Luizon,1 Ana Carolina Taveiros Palei,2 and Valeria Cristina Sandrim3

1 Department of Pharmacology, Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Avenida Bandeirantes, 3900, 14049-900 Ribeirao Preto, SP, Brazil
2 Department of Pharmacology, Faculty of Medical Sciences, State University of Campinas, 13081-971 Campinas, SP, Brazil
3 Núcleo de Pós-Graduação e Pesquisa, Santa Casa de Belo Horizonte, Rua Domingos Vieira 590, 30150-240 Belo Horizonte, MG, Brazil

Correspondence should be addressed to Valeria Cristina Sandrim, valsandrim@yahoo.com.br

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Valenzuela and colleagues have recently reviewed some polymorphisms in important candidate genes involved in different pathogenic mechanisms related to preeclampsia (PE) and concluded that various studies in different populations have identified maternal polymorphisms associated with PE. However, we would like to contribute to some studies regarding candidate genes related to angiogenesis and endothelial dysfunction in PE performed in the Brazilian population. Specifically, genotypes and haplotypes formed by polymorphisms of VEGF, eNOS and MMP-9, along with an example of the interaction among these genes in the prediction of PE. Our suggestions may provide additional information with clinical relevance to PE susceptibility.

Valenzuela et al. [1] have recently published an interesting Review Article in a special issue of Journal of Pregnancy discussing some polymorphisms in important candidate genes involved in preeclampsia (PE). They have concluded that various studies in different populations have identified maternal polymorphisms associated with PE. However, some important references from studies performed in the Brazilian population were not cited, more specifically regarding the mentioned candidate genes related to vascular and endothelial function.

For example, our group has recently demonstrated a main effect of vascular endothelial growth factor (VEGF) genotypes and haplotypes involving three clinically relevant single nucleotide polymorphisms (SNPs) localized in the promoter region of VEGF; −2578C/A (rs699947), −1154G/A (rs1570360), and −634G/C (rs2010963) in the development of PE, but not with gestational hypertension (GH) [2]. When white and nonwhite pregnant women were considered together, no significant differences were found in the distributions of VEGF genotypes or haplotypes (P > 0.05). However, significant differences were found in genotypes distributions for two VEGF polymorphisms (−2578C/A and −634G/C; both P < 0.05) between the healthy pregnant (HP) and the PE groups when only white subjects were considered in the analysis [2]. Importantly, the haplotype including the alleles −2578C, −1154G, and −634C, which is associated with higher VEGF gene expression elsewhere [3], was less common in the PE group compared with the HP group (P = 0.0047 [2]). Moreover, we have previously reported marked interethnic differences in the distribution of these VEGF genotypes and haplotypes [4]. These differences could explain why we have found significant associations between VEGF genotypes and one VEGF haplotype with preeclampsia when only white women were considered in the analysis [2].

Regarding the endothelial nitric oxide synthase (eNOS), our group had previously examined the association of three clinically relevant polymorphisms in the promoter region (−786T/C, rs2070744), in intron 4 (a variable number of tandem repeats, VNTR) and in exon 7 (Glu298Asp, rs1799983) of eNOS with PE and GH [5]. No differences were observed in the frequencies of genotypes and alleles of the three polymorphisms among PE, GH, and HP groups (all P > 0.05). However, the haplotype “T Glu a” was more common in HP than in GH or PE (20 versus 6 and 6%, resp.;
complemented by evaluation of interaction between genes. We have recently provided an example of epistasis in PE considering the MMP-9 and VEGF polymorphisms [10]. The results from single locus analysis showed significant differences in the distribution of genotypes and alleles for the VEGF −634G/C polymorphism when PE was compared to HP and for the MMP-9 −1562C/T polymorphism when GH was compared to HP, respectively (all \( P < 0.05 \)). These results are in agreement with our previous findings [2, 9]. However, we have observed a significant interaction between MMP-9 and VEGF genes associated with the PE group compared to HP [10]. The interaction between MMP-9 and VEGF polymorphisms associated with the PE group is obscured when specific genotypes of these single genes are considered, thus highlighting the importance of gene-gene interactions as major determinants to complex diseases, including PE [11].

In conclusion, we consider that the present may contribute to the interesting review article of Valenzuela et al. [1]. The findings and suggestions from our studies on candidate genes to PE may contribute with additional information of clinical relevance to PE susceptibility.

Conflict of Interests

The authors declare no conflict of interests.

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