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Letter to the Editors-in-Chief

Haplotype analysis can provide improved clinical information than single genotype analysis

Kim et al. [1] have recently published a very interesting article evaluating the association between three eNOS polymorphisms (the T-786C polymorphism in the promoter region, the 4b4a variable number of tandem repeats in the intron 4, and the G894T in the exon 7) and coronary artery disease (CAD) in Koreans. They found that these polymorphisms are not independent risk factors to the development of CAD in Koreans. However, T-786C and 4b/4a are associated with CAD when the analysis was adjusted for various cardiovascular risk factors (hypertension, smoking, age, gender and diabetes mellitus).

At present, it has been widely acknowledged that haplotype analysis in association studies can provide much more useful information than the information derived from single polymorphisms analysis [2,3]. For example, we have recently reported that eNOS haplotypes involving the three polymorphisms studied by Kim et al. [1] are associated with the development of hypertension [4–6]. These findings are obscured when specific eNOS genotypes alone are considered [4–6]. Of note, we found that specific eNOS haplotypes, but not genotypes, are associated with susceptibility to hypertension [4–6]. Importantly, we found eNOS haplotypes are associated with susceptibility to hypertension in both black and white subjects [5], even though huge interethnic differences exist in the distribution of eNOS genotypes or haplotypes [7,8]. These data support the idea that the interaction of multiple genetic markers within a haplotype is a major determinant of disease susceptibility than are individual markers. Therefore, it would be very interesting if Kim et al. could carry out a haplotype analysis with their recently reported data [1]. To do that, Kim et al. could use freely available software programs that estimate haplotypes frequencies such as EH (The Estimating Haplotype) software program (ftp://linkage.rockefeller.edu/ott/eh.htm) and PHASE (htt://www.stat.washigton.edu/stephens). This suggestion could provide additional information with clinical relevance to CAD, especially throwing some light into much controversy usually found in current literature regarding association studies.

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Valeria Cristina Sandrim*
Jose Eduardo Tanus-Santos
Department of Pharmacology — Faculty of Medicine of Ribeirao Preto — University of Sao Paulo, Av. Bandeirantes, 3900, 14049-900, Ribeirao Preto, SP, Brazil
E-mail address: valsandrim@yahoo.com.br.
*Corresponding author. Tel.: +55 16 3602 3163; fax: +55 16 3633 2301.

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