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LETTER TO THE EDITOR

Matrix metalloproteinase (MMP)-2 and MMP-9 polymorphisms and haplotypes as disease biomarkers

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Abstract
Chaudhary and colleagues observed associations of matrix metalloproteinase (*MMP*)-*2* (-1306C/T) and *MMP-9* (-1562C/T) promoter polymorphisms with head and neck squamous cell carcinoma (HNSCC), but not with oral submucous fibrosis (OSMF) in an Indian population. We suggest that they could carry out a haplotype analysis with their data on *MMP-2* genotypes (-1306C/T and -168G/T) and that they consider genotyping the microsatellite -90 $(CA)_{14-24}$ in the *MMP-9* promoter region in order to perform haplotype analysis in combination with their data on *MMP-9* (-1562C/T) polymorphism. These suggestions could provide additional information with clinical relevance to cancer susceptibility.

Keywords: Cancer, cardiovascular diseases, genetic polymorphisms, haplotypes, matrix metalloproteinase 2 gene, matrix metalloproteinase 9 gene

Dear Editor,

Chaudhary and colleagues (Chaudhary et al. 2011) have published an interesting article in the November 2011 issue of *Biomarkers*. The authors have explored the association of three functional single nucleotide polymorphisms (SNPs) in the promoter region of matrix metalloproteinase (*MMP)-2* (-1306C/T and -168G/T) and *MMP-9* (-1562C/T) genes with oral submucous fibrosis (OSMF) and head and neck squamous cell carcinoma (HNSCC). The SNPs were genotyped by PCR-RFLP in a total of 1260 individuals, of which 412 OSMF, 422 HNSCC and 426 were controls. They have observed associations of the T alleles of *MMP-2* (-1306C/T) and *MMP-9* (-1562C/T) polymorphisms with HNSCC ($p<0.00$ and $p<0.01$, respectively), but not with OSMF and showed significant association with increasing progression of clinico-pathological grading. They have concluded that SNPs in the *MMP-2* and *MMP-9* promoter region may be associated with susceptibility to HNSCC but not OSMF (Chaudhary et al. 2011).

We would like to mention a statistical analysis that should have been taken into consideration by the authors. It has been previously acknowledged that haplotype analysis can provide much more useful information than the one derived from single polymorphisms analysis in association studies (Crawford and Nickerson, 2005, Sandrim & Tanus-Santos, 2007). For example, our group and others have recently found an effect of haplotypes formed by two functional SNPs in the *MMP-2* promoter region (-1306C/T, rs243865 and -735C/T, rs2285053) with left ventricular remodeling in hypertensive patients (Lacchini et al. 2011), in the susceptibility to esophageal squamous cell carcinoma (Yu et al. 2004), lung cancer (Zhou et al. 2005), and nasopharyngeal carcinoma (Zhou et al. 2007).

Considering the *MMP-9* gene, our group has recently examined the association of three functional polymorphisms; -1562C/T (rs3918242) and a microsatellite -90 $(CA)_{14-24}$ (rs2234681) in the promoter region, and the Q279R in exon 6 (rs17576), as well as the haplotypes formed by them, with the degree of disability of multiple sclerosis (Fernandes et al. 2009), with hypertension and with left ventricular remodeling in hypertensive patients

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(Lacchini et al. 2010a), and with preeclampsia and gestational hypertension (Palei et al. 2010). Taken together, these studies on *MMP-2* and *MMP-9* polymorphisms mentioned above suggest that haplotype analysis (the combination of alleles of polymorphisms within a gene) may lead to much better information (Crawford and Nickerson, 2005, Luizon & Sandrim, 2011).

Previous studies showed that *MMP-9* gene polymorphisms affect the circulating levels of MMP-9 in patients, as well as the prognosis (Blankenberg et al. 2003, Demacq et al. 2009). In fact, MMP-9 level is a biomarker that may help to predict mortality in patients with cardiovascular diseases (Blankenberg et al. 2003). Interestingly, we found that *MMP-9* genotypes and haplotypes affect MMP-9 levels in obese children and adolescents, and suggested that genetic factors may modify relevant pathogenetic mechanisms involved in the development of cardiovascular complications associated with obesity in childhood (Belo et al. 2012).

Moreover, we have previously reported marked interethnic differences in the distribution of *MMP-2* -1306C/T and the three *MMP-9* genotypes mentioned above (-1562C/T, -90 $(CA)_{14–24}$, and Q279R) when considering black and white Brazilians (Lacchini et al. 2010b). The alleles more often found in blacks are associated with higher expression of MMP-2 and MMP-9 and are clinically associated with cancer and cardiovascular diseases (Lacchini et al. 2010b). We have also investigated the effects of *MMP-9* gene polymorphisms and haplotypes on the circulating MMP-9 levels in healthy subjects (Demacq et al. 2006, Demacq et al. 2008, Metzger et al. 2011) and the effects of the *MMP-2* -1306C/T polymorphism on the plasma MMP-2 concentrations (Metzger et al. 2011). The *MMP-2* 1306C/T polymorphism had no effects on the plasma MMP-2 levels in black subjects (Metzger et al. 2011). Interestingly, while we found no significant differences in previous studies in white subjects (Demacq et al. 2006, Demacq et al. 2008), we have recently reported that *MMP-9* -90 $(CA)_{14–24}$ genotype and *MMP-9* haplotypes modify MMP-9 levels in black subjects (Metzger et al. 2011). Although it is possible that this difference may also reflect interactions of *MMP-9* haplotypes with environmental or other genetic factors not determined in this study, the results may offer biochemical evidence implicating MMP-9 in the pathogenesis of cardiovascular diseases in blacks (Metzger et al. 2011).

Therefore, we suggest that Chaudhary and colleagues could carry out a haplotype analysis with their recently data on MMP-2 genotypes (Chaudhary et al. 2011). In addition, we suggest that they consider genotyping the microsatellite -90 $(CA)_{14–24}$ in the MMP-9 promoter region in order to perform haplotype analysis in combination with their data on *MMP-9* (-1562C/T) polymorphism (Chaudhary et al. 2011). These suggestions could provide additional information with clinical relevance to cancer susceptibility.

Declaration of interest

This study was funded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-Brazil) and the Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP-Brazil). The authors declare no conflict of interest

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