Editorial Comment

Are Promoter Polymorphisms of Interleukin 6 Ready to Be Applied in Genetic Markers of Cardiovascular Diseases?

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Inflammation has been regarded as a major factor in the development of cardiovascular diseases. Genetic variations and environmental factors evoking inflammatory responses have been assessed independently, but few reports have examined the interaction between them. A study by Saijo *et al*. published in this issue of *Hypertension Research* showed a positive correlation between the interleukin (IL) 6 −634C>G polymorphism and serum C-reactive protein (CRP) level in nonsmokers, with G allele carriers showing higher serum CRP levels as allelic doses increased, while this trend was not observed in current smokers (*1*). Although there is convincing evidence that a smoking habit induces chronic inflammation (*2*, *3*), it is still controversial whether or not the IL6 −634C>G polymorphism is associated with inflammation.

The IL6 promoter encodes several single nucleotide polymorphisms (SNPs), which have been assessed in correlation with many clinical features. The G>C at −174 (rs1800795) is a common SNP in Caucasians, and several investigations into the correlation with inflammatory diseases have been undertaken (*4*). Although both alleles have been reported as risk factors for cardiovascular diseases (*5*, *6*), it appears that more reports show the C-allele is relevant to higher IL6 production. A meta-analysis by Sie *et al*. failed to show a significant association between the genotype and coronary heart disease, though their Rotterdam cohort study revealed that the −174C allele was associated with higher CRP in 5,924 participants (*7*). These studies suggest that the IL6 −174C carriers are prone to enhancing inflammatory responses.

Because the major allele of −634C>G SNP (rs1800796) in Japanese (C: 0.86) is rare in Caucasians (0.044), genetic study of it in Caucasians is difficult; most reports have involved Asian ethnic groups. Almost all Asian studies have shown the minor allele (G) as the risk allele (*8*), but Caucasian studies oppositely showed their minor allele (C) as the risk allele (*9*).

If the *in vitro* experimental results were compatible with the genetic results, the estimated SNP function might become robust. The promoter assay using reporter constructs showed that the activity of the −174G construct exceeded the C construct activity in HeLa cells at baseline and after stimulation by IL1 (*4*). The −174G>C SNP is localized in the promoter sequence near the binding motifs of CCAAT/enhancer binding protein β (C/EBPb) and cAMP responsive element binding protein (CRE) transcription factors, which exist 70 bp upstream from the nuclear factor κB (NFκB) binding motif. NFκB is the signal transducer activated under Toll like receptor (TLR), IL1R, and T and B cell receptor signaling pathways. Thus it is plausible that the −174G>C SNP modulates IL6 transcription efficiency and inflammation magnitude. However, the *in vitro* function of −174G>C SNP was distinct from the function estimated from genetic analysis in arteriosclerotic diseases; in the former, the G allele had higher transcription activity (*4*). The IL6 promoter assay was carried out by using HeLa cells, a cervical cancer cell line, which is not the predominant cell type producing IL6. Endothelial cells rather than epithelial cells are considered the major producer. Furthermore, there is a possibility that the SNP's function in the acute response *in vitro* may be distinct from that for chronic response *in vivo*. Further sophisticated experiments

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are required to ensure that the risk allele is a higher expresser of IL6.

The interaction between −634C>G SNP and smoking habit is the most intriguing point in Saijo's paper (*1*). Jerrard-Dunne *et al*. reported that the carriers of haplotype encoding −174C, −634G, and −639A showed higher serum IL6 than other haplotype carriers in both nonsmokers and smokers (*10*). Those authors also found correlations with common carotid artery intima-medial thickness (IMT). Similar trends were observed in IL1 haplotype (IL1RA VNTR2 and IL1B −31T) and CD14 −159T>C SNP. Furthermore, they showed additive effects of gene loading with these inflammatory risk haplotypes and genotypes on the IL6 level and carotid IMT. While genetic epidemiology is expensive and time-consuming work, it is also both simple and irreplaceable by any other experiments. Further genetic studies are required before the genetic markers can be applied to personalized medicine.

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