Absence of a NPR-A Gene Functional Deletion Allele in a Postmyocardial Infarction Cohort From New Zealand

To the Editor:

Nakayama et al. described an interesting polymorphism in the NPR-A gene in a Japanese population. An 8-nucleotide deletion in the 5'-untranslated region (UTR) of the gene was found to be associated with essential hypertension and left ventricular hypertrophy in a study of 200 hypertensive (HT) and 200 normotensive (NT) subjects. The polymorphism occurred at a frequency of 4% in the HT patients and in a single NT subject (0.5%) who was subsequently found to have left ventricular hypertrophy. Carriers of the functional deletion (D) allele had higher plasma BNP levels, a strong marker of cardiac stress, than those with the wild-type allele. Expression of NPR-A from the D allele was reduced compared with the wild-type allele and it is suggested that the deletion interferes with binding of regulatory factors to the 5'-UTR of the gene.

We screened 498 patients from the Christchurch Post-Myocardial Infarction (PMI) Study who had acute myocardial infarction for the NPR-A D allele. DNA samples were amplified using the polymerase chain reaction primers hNPR-Af 5'-agcggcctagcctgg-gac3' and hNPR-Ar 5'-cagtcaccgctacgtctcaggt3' and the wild-type (T) and D amplimers (216 and 208 bp, respectively) were resolved on 3% agarose, 0.5 TBE gels and visualized using ethidium bromide and a Bio-Rad Fluor-S imaging system (Hercules, Calif). Patient DNA samples with (n=3) and without (n=3) the functional deletion from the Japanese study were used as controls. The New Zealand patients were 75% male, with a mean age of 62.4 (+0.5) years, 15.0% had a history of previous myocardial infarction, 52.0% had or were being treated for hypertension, 60.4% were past or present smokers, 11.4% had diabetes, 1.6% had congestive heart failure, 52.7% were being treated with β-blockers, and 31.7% were being treated with an angiotensin-converting enzyme inhibitor; 83.3% were of European ethnicity, 3.8% Maori, 1.2% other (Indian, Middle Eastern, Pacific Islanders), and 11.7% not stated.

None of the 498 New Zealand patients carried the NPR-A D allele. However, patient DNA samples with the functional deletion mutation from the original Japanese study were positive in our assay, indicating that any positive samples in our New Zealand sample population would have been detected had they been present. The upper 95% confidence limit for the prevalence of carriers of the D allele is 0.60% in this PMI patient cohort.

These findings suggest that this functional deletion polymorphism is rare outside Japanese populations. This conclusion is supported by the report of Knowles et al. who studied the structure of the entire NPR-A gene from 34 unrelated individuals of black, white, and unknown ethnicities, finding 10 polymorphic sites in noncoding regions of the gene, but not the 5'-UTR 8 bp ID polymorphism.

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