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The Molecualr Genetic Studies on Coronary Artery Disease (CAD) by Genetic Markers and Mutation Screening

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Coronary artery disease (CAD) is a multifactorial disease caused by gentic and environmental factors and there are many genetic factors associated with CAD. In view of the clinical importance of haptoglobin (Hp), apolipoproteinB (apoB) and low density lipoprotein (LDL) receptor as major risk factor for CAD, we investigated the polymorphims for haptoglobin and apoB, and performed mutation screeing for large rearrangements of LDL receptor gene by long-distance PCR. First, the distribution of Hp phenotypes did not show any significant differences between the healthy controls and the patients with cardiovascular disease. In the control group, however, the subgroup of $\geq$ 50-year-olds had a significantly higher Hp*1 allele frequency than the subgroup < 50 years ($p<0.005$). This was not seen in the patient group. Hp phenotypes were associated with levels of high-density lipoprotein cholesterol in the hypertensive group. This results indicate that Hp polymorphism, at least in the Korean population, dose not predispose to occurrence of CAD. Second, we investigated the two polymorphisms (signal peptide and *Xba*I) of the apoB gene. The inertion allele (*Ins*) frequency of signal peptide polymorphism was significantly higher in case than the controls ($p<0.05$). Signal peptide polymorphism was also associated with levels of plasma cholesterol, triglyceride and LDL cholesterol. However, XbaI polymorphism was not associated with plasma lipid levels. Therefore, our results suggest that signal peptide polymorphism of the apoB gene might be one of the factors in explaining an association in Korean CAD patients. Finally, we performed mutation screening for LDL receptor gene. For rapid and reliable detection of large rearrangements in the LDL receptor gene, we established a screening method based on long-distance PCR as an alternative to Southern blot hybridization. Two different deletion mutations, FH6 (same type as FH3 and FH311) and FH32, were detected in four families by long-distance PCR. Detailed restriction mapping and sequence analysis showed that FH6 was a 5.71-kb deletion extending from intron 8 to intron 12 and that FH32 was a 2-kb deletion extending from intron

6 to intron 7. Sequence analysis for the breakpoints of all deletions detected in Korean FH patinets showed that only left arms of the Alu repetitive sequences were involved in the deletion event. These results suggest that *Ins/Del* polymorphism of apoB gene and two large deletion of LDL receptor gene are independent risk factors in the pathogenesis of CAD.