Abstract: P708
Identification of 26 novel loci that confer susceptibility to early-onset coronary artery disease in a Japanese population

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Background: Early-onset coronary artery disease (CAD) has a strong genetic component. Although genome-wide association studies have identified various genes and loci significantly associated with CAD mainly in European ancestry populations, genetic variants that contribute to susceptibility to this condition in Japanese individuals remain to be identified definitively.

Purpose: The purpose of the study was to identify genetic variants that confer susceptibility to early-onset CAD in Japanese. We have now performed exome-wide association studies (EWASs) in subjects with early-onset CAD and controls.

Methods: A total of 7256 individuals aged ≤65 years was enrolled in the study. The EWAS was conducted with 1482 subjects with CAD and 5774 controls. Genotyping of single nucleotide polymorphisms (SNPs) was performed with Illumina Human Exome-12 DNA Analysis BeadChip or Infinium Exome-24 BeadChip arrays. The relation of allele frequencies for 31,465 SNPs that passed quality control to CAD was examined with Fisher's exact test. To compensate for multiple comparisons of allele frequencies with CAD, we applied a false discovery rate (FDR) of <0.05 for statistical significance of association.

Results: The relation of allele frequencies for 31,465 SNPs to CAD with the use of Fisher's exact test showed that 170 SNPs were significantly (FDR <0.05) associated with CAD. Multivariable logistic regression analysis with adjustment for age, sex, and the prevalence of hypertension, diabetes mellitus, and dyslipidemia revealed that 162 SNPs were significantly (P<0.05) related to CAD. A stepwise forward selection procedure was performed to examine the effects of genotypes for the 162 SNPs on CAD. The 54 SNPs were significant (P<0.05) and independent [coefficient of determination (R²), 0.0008 to 0.0297] determinants of CAD. These SNPs together accounted for 15.5% of the cause of CAD. After examination of results from previous genome-wide association studies and linkage disequilibrium of the identified SNPs, we newly identified 21 genes (RNF2, YEATS2, USP45, ITGB8, TNS3, FAM170B-AS1, PRKG1, BTRC, MKI67, STIM1, OR52E4, KIAA1551, MON2, PLUT, LINC00354, TRPM1, ADAT1, KRT27, LIPE, GFY, EIF3L) and five chromosomal regions (2p13, 4q31.2, 5q12, 13q34, 20q13.2) that were significantly associated with CAD. Gene ontology analysis showed that various biological functions were predicted in the 18 genes identified in the present study. The network analysis revealed that the 18 genes had potential direct or indirect interactions with the 30 genes previously shown to be associated with CAD or with the 228 genes identified in previous genome-wide association studies of CAD.

Conclusion: We have newly identified 26 loci that confer susceptibility to CAD. Determination of genotypes for the SNPs at these loci may prove informative for assessment of the genetic risk for CAD in Japanese.
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