Identification of six novel susceptibility loci for dyslipidemia by longitudinal exome-wide association studies in Japanese

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Background: The circulating concentrations of triglycerides, high density lipoprotein (HDL)-cholesterol, and low density lipoprotein (LDL)-cholesterol have a substantial genetic component. Although previous genome-wide association studies identified various genes and loci related to plasma lipid levels, those studies were conducted in a cross-sectional manner.

Purpose: The purpose of the study was to identify genetic variants that confer susceptibility to hypertriglyceridemia, hypo-HDL-cholesterolemia, and hyper-LDL-cholesterolemia in Japanese. We have now performed longitudinal exome-wide association studies (EWASs) to identify novel loci for dyslipidemia by examining temporal changes in serum lipid profiles.

Methods: Longitudinal EWASs (mean follow-up period, 5 years) for hypertriglyceridemia (2056 case, 3966 controls), hypo-HDL-cholesterolemia (698 cases, 5324 controls), and hyper-LDL-cholesterolemia (2769 cases, 3251 controls) were performed with Illumina Human Exome arrays. The relation of genotypes of 24,691 single nucleotide polymorphisms (SNPs) that passed quality control to dyslipidemia-related traits was examined with the generalized estimating equation (GEE). To compensate for multiple comparisons of genotypes with each of the three conditions, we applied Bonferroni's correction for statistical significance of association. Replication studies with cross-sectional data were performed for hypertriglyceridemia (2685 cases, 4703 controls), hypo-HDL-cholesterolemia (1947 cases, 6146 controls), and hyper-LDL-cholesterolemia (1719 cases, 5833 controls).

Results: Longitudinal EWASs revealed that 30 SNPs were significantly ($P<2.03 \times 10–6$ by GEE) associated with hypertriglyceridemia, 46 SNPs with hypo-HDL-cholesterolemia, and 25 SNPs with hyper-LDL-cholesterolemia. After examination of the relation of identified SNPs to serum lipid profiles, linkage disequilibrium, and results of the previous genome-wide association studies, we newly identified rs74416240 of TCHP, rs925368 of GIT2, rs7969300 of ATXN2, and rs12231744 of NAA25 as a susceptibility loci for hypo-HDL-cholesterolemia; and rs34902660 of SLC17A3 and rs1042127 of CDSN for hyper-LDL-cholesterolemia. These SNPs were not in linkage disequilibrium with those previously reported to be associated with dyslipidemia, indicating independent effects of the SNPs identified in the present study on serum concentrations of HDL-cholesterol or LDL-cholesterol in Japanese. According to allele frequency data from the 1000 Genomes project database, five of the six identified SNPs were monomorphic or rare variants in European populations. In the replication study, all six SNPs were associated with dyslipidemia-related phenotypes.

Conclusion: We have thus identified six novel loci that confer susceptibility to hypo-HDL-cholesterolemia or hyper-LDL-cholesterolemia. Determination of genotypes for these SNPs at these loci may prove informative for assessment of the genetic risk for dyslipidemia in Japanese.

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