Abstract: **P4470**

**Identification of four genes as novel susceptibility loci for early-onset type 2 diabetes mellitus, metabolic syndrome, or hyperuricemia in Japanese**

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Background: Given that early-onset type 2 diabetes mellitus (T2DM), metabolic syndrome, and hyperuricemia have been shown to have strong genetic components, statistical power of a genetic association study may be increased by focusing on early-onset subjects with these conditions. Although genome-wide association studies have identified various genes and loci significantly associated with T2DM, metabolic syndrome, and hyperuricemia, genetic variants that contribute to predisposition to these conditions 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 T2DM, metabolic syndrome, or hyperuricemia in Japanese. We have now performed exome-wide association studies (EWASs) for early-onset subjects with T2DM, metabolic syndrome, or hyperuricemia and corresponding controls.

Methods: A total of 8102 individuals aged ≥65 years was enrolled in the study. The EWAS for T2DM was performed with 7407 subjects (1696 cases, 5711 controls), that for metabolic syndrome with 4215 subjects (2296 cases, 1919 controls), and that for hyperuricemia with 7919 subjects (1365 cases, 6554 controls). Single nucleotide polymorphisms (SNPs) were genotyped with Illumina Human Exome-12 DNA Analysis BeadChip or Infinium Exome-24 BeadChip arrays. The relation of allele frequencies for 31,210, 31,521, or 31,142 SNPs that passed quality control to T2DM, metabolic syndrome, or hyperuricemia, respectively, was examined with Fisher’s exact test. To compensate for multiple comparisons of genotypes with T2DM, metabolic syndrome, or hyperuricemia, we applied Bonferroni’s correction for statistical significance of association.

Results: The EWAS of allele frequencies revealed that four, six, or nine SNPs were significantly associated with T2DM ($P < 1.60 \times 10^{-6}$), metabolic syndrome ($P < 1.59 \times 10^{-6}$), or hyperuricemia ($P < 1.61 \times 10^{-6}$), respectively. Multivariable logistic regression analysis with adjustment for age and sex revealed that three, six, or nine SNPs were significantly related to T2DM ($P < 0.0031$), metabolic syndrome ($P < 0.0021$), or hyperuricemia ($P < 0.0014$). After examination of the association of identified SNPs to T2DM-, metabolic syndrome-, or hyperuricemia-related traits, linkage disequilibrium of the SNPs, and results of previous genome-wide association studies, we have newly identified ZNF860 and OR4F6 as susceptibility loci for T2DM, OR52E4 and OR4F6 for metabolic syndrome, and HERPUD2 for hyperuricemia. Conclusion: Given that OR4F6 was significantly associated with both T2DM and metabolic syndrome, we thus newly identified four...
genes (ZNF860, OR4F6, OR52E4, HERPUD2) that confer susceptibility to early-onset T2DM, metabolic syndrome, or hyperuricemia. Determination of genotypes for the SNPs in these genes may prove informative for assessment of the genetic risk for T2DM, metabolic syndrome, or hyperuricemia in Japanese.