# Identification of two genes as novel susceptibility loci for type 2 diabetes mellitus in Japanese

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**Background:** The heritability of Type 2 diabetes mellitus (T2DM) has been estimated to be 50% to 60%. Although genome-wide association studies identified >120 loci that confer susceptibility to T2DM, these studies were commonly conducted in a cross-sectional manner.

**Purpose:** The purpose of the study was to identify genetic variants that confer susceptibility to T2DM in Japanese. We have now performed longitudinal exome-wide association studies (EWASs) to identify novel loci for T2DM by examining temporal changes in fasting plasma glucose (FPG) level, blood hemoglobin A1c (HbA1c) content, and the prevalence of T2DM.

**Methods:** Longitudinal EWASs (mean follow-up period, 5 years) were performed with Illumina Human Exome-12 v1.2 DNA Analysis BeadChip or Infinium Exome-24 v1.0 BeadChip arrays and with 6,022 Japanese (755 subjects with T2DM, 5267 controls). The relation of genotypes of 24,579 SNPs that passed quality control to FPG level, blood HbA1c content, or the prevalence of T2DM was examined with the generalized estimating equation (GEE). To compensate for multiple comparisons of genotypes with each of the three parameters, we applied Bonferroni's correction for statistical significance of association.

**Results:** Longitudinal EWASs (GEE with adjustment for age, sex, body mass index, and smoking) revealed that rs6414624 of EVC ($P<2.0\times10^{-16}$ for T2DM, $P=9.1\times10^{-11}$ for FPG), rs78338345 of GGA3 ($P<2.0\times10^{-16}$ for T2DM, $P=4.3\times10^{-9}$ for FPG), rs10490775 of PTPRG ($P<2.0\times10^{-16}$ for T2DM, $P=3.3\times10^{-7}$ for FPG), and rs61739510 of GLT6D1 ($P<2.0\times10^{-16}$ for T2DM, $P=5.8\times10^{-7}$ for FPG) were significantly associated with the prevalence of T2DM and FPG levels; and rs11558471 in SLC30A8 with FPG level ($P=1.8\times10^{-8}$) and blood HbA1c content ($P=1.2\times10^{-7}$). After examination of the relation of identified SNPs to FPG level and blood HbA1c content, linkage disequilibrium of the SNPs, and results of the previous genome-wide association studies, we identified rs6414624 of EVC and rs78338345 of GGA3 as novel susceptibility loci for T2DM. In the identified SNPs (rs6414624 and rs7833834), FPG level, blood HbA1c content, and the prevalence of T2DM were significantly lower in homozygotes with the minor alleles than in homozygotes with the major alleles or heterozygotes. These results suggest that the minor alleles of rs6414624 and rs78338345 are protective against T2DM in Japanese. According to allele frequency data from the 1000 Genomes Project database, the minor G allele of rs78338345 of GGA3 is specifically distributed in East Asia. This suggests that the minor allele frequency may have increased in East Asian populations after the split of East Asian and non-East Asian populations.

**Conclusion:** We have newly identified EVC and GGA3 as susceptibility loci for T2DM in Japanese. Determination of genotypes for these SNPs at these loci may prove informative for assessment of the genetic risk for T2DM in Japanese.