論文の内容の要旨

論文題目　Identification of 28 novel susceptibility loci for type 2 diabetes in the Japanese population

（日本人における 28 の新規２型糖尿病感受性領域の同定）

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Type 2 diabetes (T2D) is a chronic metabolic disorder caused by multiple pathogenesis including genetic and environmental factors. Today, more than 400 million patients have T2D on the globe, and its rising prevalence is an important health issue in many countries, including Japan. Genetic association studies have identified more than 150 susceptibility loci for T2D. These loci were mainly identified in European studies. However, epidemiology of T2D of Japanese is different from that of Europeans; Japanese are more susceptible to T2D than Europeans at the same level of waist circumference or body mass index (BMI). This difference in epidemiology suggests that different pathogenesis may exist in the development of T2D in these populations.

For the purpose of understanding the genetics of T2D in Japanese and identifying more susceptibility loci for T2D, I conducted the meta-analysis of the four genome-wide association studies (36,614 cases and 155,150 controls). Of the 163 established loci, lead variants at 138 loci had the statistics in the current association study. Ninety-six (70%) of these established loci were replicated ($P < 0.05$ with consistent direction of effect).

In the meta-analysis, eighty-eight loci were significantly associated with T2D ($P < 5 \times 10^{-8}$), of which 28 were novel. Sixty-eight of the 88 lead variants (77%) were common (MAF ≥ 0.05) in Japanese and Europeans. In addition, I found strong positive correlation (Pearson's $r^2 = 0.87$, $P = 1.35 \times 10\text{-}22$) and directional consistency (94.2%, sign test $P = 3.11 \times 10\text{-}15$) of the effect sizes of the T2D associated

variants in Japanese and Europeans. I conducted stepwise conditional analysis to find multiple independent signals at a locus. I detected 27 additional signals that reached locus-wide significance ($P < 5 \times 10^{-8}$), increasing the total number of signals to 115.

To gain insights into the causal variants and genes exerting the effect at each signal, I searched for missense variants in LD with the identified T2D signals. I found 28 missense variants that were in linkage- disequilibrium (LD) with the lead variants of the T2D signals ($r^2 > 0.6$ in East Asians (EAS)). Identified missense variants in genes related to pancreatic acinar cells (*GP2* and *CPA1*) and insulin secretion (*GLP1R*) belonged to different minor allele frequencies (MAF) spectra in Japanese and Europeans ($MAF_{JPN} = 0.05 - 0.18$ v.s. $MAF_{EUR} < 0.002$).

I also searched for lead cis-eQTL variants that overlaps with T2D signals using data from GTEx database. Fifty-nine transcripts had the lead cis-eQTL variants that were in LD ($r^2 > 0.6$ in East Asians or Europeans) with T2D signals; of these, 16 transcripts were located in novel loci. *NUS1* locus was a biologically notable example. In the *NUS1* locus, the lead T2D variant (rs80196932) coincided with the lead cis-eQTL variant of *NUS1* in pancreas and was in LD with those in skeletal muscle and stomach (r^2= 1 and 0.95 in East Asians, respectively). *NUS1* plays an important role in protein glycosylation and intracellular cholesterol trafficking. It is also annotated with congenital disorder of glycosylation (OMIM ID 617082).

To evaluate the genetics shared with other traits, I calculated genetic correlation between T2D and 91 complex human traits (32 diseases and 59 quantitative traits) in Japanese, using bivariate LD score regression. I detected previously unreported positive genetic correlation (FDR $q < 0.01$) with ossification of posterior longitudinal ligament (OPLL) ($r_g = 0.26$, $P = 4.1 \times 10^{-5}$) and white blood cell count (WBC) ($r_g = 0.17$, $P = 4.6 \times 10^{-5}$); and negative correlation with bipolar disorder (BD) ($r_g = -0.22$, $P = 1.0 \times 10^{-4}$).

To gain insights into pathways underlying T2D pathogenesis, I conducted trans-ethnic molecular pathway analysis. Of the 1077 pathways, seven were significantly associated with T2D in the Japanese population (Bonferroni-corrected $P < 0.05/1077$). These included pathways involved in monogenic diabetes (maturity onset diabetes of the young (MODY)), beta cells, development, insulin secretion, and NOTCH signaling. In the pathway analysis using European T2D GWAS, pathways of MODY, development, beta cells and NOTCH were also significantly associated with T2D (FDR $q < 0.05$). On the other hand, 'regulation of insulin secretion' was not statistically significant ($P = 1.97$ x 10-2, $q = 0.293$).

NOTCH signaling is important for the development of pancreas. Inhibition of NOTCH signaling is known to lead to insulin-deficient diabetes. In the liver, inactivation of NOTCH signaling was reported to improve the insulin sensitivity in mice.

'Regulation of insulin secretion' had stronger association with T2D in Japanese than in Europeans. Epidemiological studies reported that Japanese and East Asians have lower capacity of insulin secretion than Europeans. In addition, Japanese people are more prone to T2D than Europeans at the same level of BMI or waist circumference.

Taken together, these findings give insights into the shared and distinct etiology of T2D in Japanese and Europeans.