Genome-Wide Association Studies Identify Two Novel Susceptibility Loci to Diabetic Retinopathy in Japanese Patients with Type 2 Diabetes

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Several reports have shown familial aggregations of diabetic retinopathy (DR) or advanced DR among patients with type 1 or type 2 diabetes, suggesting genetic susceptibility contributes to the development and/or progression of DR. However, the genes involved in the susceptibility to DR are still unknown. To identify novel genetic loci associated with the susceptibility to DR, we performed a meta-analysis of genome-wide association studies (GWAS) for DR in Japanese patients with type 2 diabetes registered in BioBank Japan (Study-1; 4,839 DR cases and 4,041 controls, Study-2; 693 DR cases and 1,524 controls). DR cases were patients having any stages of DR and controls were patients who did not have any sign of DR with long duration of diabetes (≥5 years) or with diabetic nephropathy. We analyzed the association with DR of ~7.5 million single nucleotide polymorphisms (SNPs) from directly genotyped data (Study-1; Omni-express exome, Study-2; Illumina 610K) and genotype imputation using MACH and minimac. We have identified 85 loci showing suggestive association with DR (p < 1 x 10^-4) through the GWAS meta-analysis. These loci were further evaluated in an independent case-control study (Study-3; 2,260 DR cases and 723 controls, BioBank Japan). After combining all the association data (Study-1, 2 and 3) by a meta-analysis, the association of two loci reached genome-wide significance level; rs12630354 on Ch3: p = 1.62 x 10^-9, Odds ratio [OR] = 1.17, 95% Confidence Interval [CI] 1.11-1.23, rs140508424 on Ch9, p = 4.19 x 10^-8, OR = 1.61, 95% CI 1.36-1.91. None of the association with advanced DR reached genome-wide significance (p > 5.0 x 10^-8) in a sub-group analysis: excluding patients with simple DR (DR cases n = 2,003, 368 and 1,260 for Study-1, Study-2 and Study-3, respectively). In conclusion, we have identified two novel loci contributing to DR susceptibility, although further replication studies are required to validate the association of these loci with DR.