[課程―２]

審査の結果の要旨

氏名　ビシュワ ラジ サプコタ
Bishwa Raj SAPKOTA

In this study, a genome-wide association study was performed in a Japanese population recruited from three observational population-based cohorts to identify genetic variation that is associated with knee osteoarthritis. A total of 2329 samples were analyzed in this study including 340 samples in the discovery set and 1989 samples in the replication sets located in three distinct areas of Japan. Genotyping of the discovery sample sets were performed using Affymetrix® Genome-Wide Human SNP Array 6.0. A total of 307 individuals (125 cases and 182 controls) and 462055 SNPs remain for further analysis in the discovery sample sets after all the stringent quality control procedures. Finally, top 94 promising SNPs were selected for replication stages. These most promising variants were evaluated in an independent replication sample sets of 500 cases with severe radiographic knee osteoarthritis and 1489 controls recruited from three distinct cohorts located in three different areas in Japan. All the cases and controls evaluated in this study were of Japanese ancestry.

A strong signal for a variant at 3' untranslated region of a gene located at 19q13 was identified with genome-wide significance level (combined p-value = 1.94×10^{-8}, odds ratio (OR) = 1.76 with 95% confidence interval (CI) = 1.45-2.15) that was associated with knee osteoarthritis in the Japanese population. In further regional imputation analysis to fine-map the association signal around ±2000 kb region using 1000-genome database, the genotyped SNP showed stronger evidence of association than any other imputed SNPs. In the follow-up of functional implication of the associated variant, altered gene expression of the associated

gene by the genetic variants and surrogate markers that are in linkage disequilibrium (LD) around the 100kb of the associated SNP was evaluated in the Japanese HapMap individuals. In this analysis, the associated region of 19q13 showed highest expression than any other SNPs in LD obtained from imputed data with reference to HapMap individuals. In an analysis of whole mRNA expression data from GENe Expression VARiation (GENEVAR) database in HapMap individuals, this variant was significantly associated both in Japanese HapMap individuals (p value = 0.006) and in all HapMap populations (p value = 0.043). Moreover, this variant has *cis* effect in an analysis of expression Quantitative Trait Locus effect (eQTL) (q-value = 1×10^{-20}) in public database. Similarly, searching for eQTL data in Multiple Tissue Human Expression Resource (MuTHER), transcript levels measured in lymphoblastoid cell lines for the associated gene showed significant different with the associated SNP genotypes. The knee osteoarthritis associated variant showed the highest significant association in the region. Taken together, a novel genetic variant associated with knee osteoarthritis was identified with genome-wide significance level for the Japanese population. This finding provides the first demonstration of the relevance of the identified locus to individuals for the Japanese population. This result provides the new biological insights in the genetic association for knee osteoarthritis.

Considering the overall theme of the thesis, its contents, and novel finding of the associated variant for knee osteoarthritis in the Japanese population with the relevance functional significance of the finding, it is an important contribution in the genetics of knee osteoarthritis field. After critical reviewing of the submitted contents and through discussions after presentation, we the examination committee determined the entire thesis is worthy of acceptance for the degree of Doctor of Philosophy.