博士論文 (要約)

Genome-wide association study and fine-mapping of risk loci in idiopathic membranous nephropathy in Japanese

（日本人特発性膜性腎症を対象としたゲノムワイド関連解析および高密度遺伝子多型マッピング）

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Idiopathic membranous nephropathy (IMN) is an autoimmune kidney disease. Genome-wide association study (GWAS) in European has identified the strong associations of single nucleotide polymorphisms (SNPs) in *PLA2R1* and *HLA-DQA1* and they were widely replicated in many populations. In Japanese, a previous fine-mapping study detected SNPs in *PLA2R1* and *HLA-DRB1*15:01-DQB1*06:02* haplotype in IMN. However, there were many significant associations of similar degree in both regions due to strong linkage disequilibrium (LD) among variants, and the primary variants in these loci still need to be determined.

We conducted GWAS in 98 Japanese IMN and 413 controls and replicated in an independent sample set of 130 IMN cases and 288 controls. GWAS did not detect any new associated locus with IMN but it provided a high-resolution genotype data for fine mapping of *PLA2R1* region. Imputation of *PLA2R1* region is done using 2,048 sequenced Japanese samples from the Tohoku Medical Megabank Organization (ToMMo), and the most significant SNPs were replicated in a separate sample set of 130 IMN and 288 controls. A two-SNP haplotype containing a non-coding and missense SNPs was more strongly associated than the individual SNPs (OR = 2.68; P = 3.76×10^{-15}). In *HLA* region, the relative predispositional effect test identified additional risk alleles in both *DRB1* and *DQB1*. We collapsed the risk alleles in each of *DRB1* and *DQB1* into single risk alleles in which *DRB1* is more strongly associated than *DQB1* and reciprocal conditioning showed more residual significance for *DRB1* collapsed risk (conditional OR = 2.08; P = 1.3×10^{-4}) than *DQB1* collapsed risk (conditional OR = 1.63; P = 0.0051) implying that *DRB1* is more likely to be the primary association. The haplotype of a non-coding and coding SNPs suggests the role of both regulatory and structural changes. The non-coding SNP is found to be a strong expression quantitative trait locus for *PLA2R1* gene expression levels in the GTEx database, and the missense SNP is predicted to alter affinity of peptide binding with the protein coded by *DRB1*15:01* by the IEDB database.

These results indicate that both expression and structural changes in PLA2R1 protein are important for the disease pathogenesis and *HLA-DRB1* alleles are the primary associations with IMN in *HLA* region.