［課程－２］

審査の結果の要旨

氏名　**クン ゾー ラット**

In order to examine the genetic susceptibility factors associated with idiopathic membranous nephropathy (IMN) in the Japanese population comprehensively and to fine-map the known associated regions for the evaluation of primary causal variants, genome-wide association study (GWAS) and *HLA* analysis was performed in two independent sample sets of Japanese IMN and controls. The present study included three parts:

Part 1: The GWAS of IMN using 104 IMN cases and 419 healthy controls genotyped by Japonica whole genome genotyping array. The single nucleotide polymorphisms (SNPs) with p-value less than 10^{-5} from two loci (*PLA2R1*, *FAM170A-PRR16*) were replicated in an independent sample set of 130 IMN and 288 controls using TaqMan genotyping assays. The SNPs from known loci of *PLA2R1* were significantly replicated and passed genome-wide significance in the combined analysis while the SNP in *FAM170A-PRR16* was not replicated.

Part 2: It was previously reported that *HLA-DRB1*15:01* and *-DQB1*06:02* are strongly associated with IMN in Japanese population. However, these two alleles are in very high LD and it is still unclear which one is the primary association. In the present study, using relative predispositional effects (RPE) tests, new alleles in both *DRB1* (*DRB1*14:54* and *DRB1*11:01*) and *DQB1* (*DQB1*05:02* and *DQB1*03:01*) genes were detected. By collapsing all associated *DRB1* and *DQB1* alleles in each gene and reciprocally conditioning these collapsed alleles, *DRB1* collapsed allele was found to have more residual significance than it's *DQB1* counterpart, suggesting that *DRB1* alleles are more likely to be the primary associations with IMN in *HLA* region.

Part 3: Top SNPs in PLA2R1 region that were reported to be associated with IMN in European GWAS were replicated in several populations as markers of IMN. In the present study, the *PLA2R1* region was comprehensively fine-mapped using

Japanese-specific genotyping array and imputation using over 2000 sequenced Japanese samples as reference. The strongest risk association in the region was the haplotype of an intronic (rs4664308) and missense (rs35771982) SNPs. The intronic SNP is strongly associated with *PLA2R1* gene expression levels according to the Genotype-Tissue Expression database (GTEx). The missense SNP is located in the domain that is part of the major epitope recognized by anti-PLA2R antibodies and was also predicted to bind more strongly to HLA-DRB1*15:01 protein according to Immune Epitope Database (IEDB). These results suggest that changes in both structure and expression levels of PLA2R protein is important for IMN pathogenesis.

The GWAS in the present study could not detect new loci associated with IMN. This is probably because of the relatively low sample size of the GWAS and the strong associations of already reported loci (*PLA2R1* & *HLA*). However, using high-resolution genotype data and robust statistical tests, this study could fine-map the known loci and pinpoint the most likely primary causal associations in each of these loci as well as the functional roles of these variants. Based on the significant contribution to the genetics of nephrotic syndrome, the thesis is considered to justify the conferment of degree.