

審査の結果の要旨

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In order to identify the genetic associations of *PLA2R1* and *HLA* with Japanese Idiopathic Membranous Nephropathy (IMN) patients, and to investigate the interaction effect of *PLA2R1* and *HLA*, high-density association mapping covering the whole region of *PLA2R1* and *HLA* regions was performed using two independent sample sets. The present study included three parts as follow:

1. In the fine mapping study of *PLA2R1* gene, fifteen selected SNPs were genotyped using the discovery sample set by using TaqMan SNP Genotyping Assay. Seven SNPs were found to be significantly associated with IMN. Five SNPs out of seven were successfully replicated using the replication sample set.
2. In the *HLA* study of IMN, *HLA* typing of *HLA* class I and class II genes were performed using the discovery sample set, and significant associations of *HLA-DRB1*15:01* and *DQB1*06:02* were observed with IMN after multiple testing. Both *HLA-DRB1*15:01* and *DQB1*06:02* were successfully replicated and showed stronger association with IMN in the replication sample set. The results of *HLA-DRB1-DQB1* haplotype association analysis identified *DRB1*15:01-DQB1*06:02* haplotype to be the most susceptible haplotype in Japanese IMN patients.
3. In the study of the genetic interaction between *HLA* and *PLA2R1*, positive interaction or more than additive effect with IMN was identified between *HLA DRB1*15:01-DQB1*06:02* haplotype and *PLA2R1* risk variants.

The present study provides evidence of *PLA2R1* and *HLA* associations with IMN in Japanese population by high-density mapping approach. This is the first study to investigate the interaction effects between *HLA* haplotype and *PLA2R1* variants supporting the importance of interaction effect of *HLA* and *PLA2R1* in the development of IMN.