Genome-wide association study revealed multiple associated loci with IgG4-related disease.

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Objectives:

IgG4-related disease (IgG4RD) is an emerging concept of an autoimmune disease entity including autoimmune pancreatitis, IgG4-related sialadenitis and IgG-related kidney disease. Comprehensive genetic landscape of IgG4RD is unknown. Genome-wide association study and sequencing would provide novel insight of pathophysiology of IgG4RD. Here, we conducted a genome-wide association study of IgG4RD to detect susceptibility loci.

Methods:

We conducted a two-staged genome-wide association study comprising a total of 850 cases and 2,082 controls by genotyping 2,310,564 single nucleotide polymorphism (SNP) markers. Allele frequencies were compared between cases and controls by logistic regression analysis and followed by meta-analysis with use of inverse-variance method. Comprehensive analysis in the HLA region using imputation of amino acid residues of classical HLA alleles with use of SNP2HLA program in combination with direct sequencing was also performed. We also analyzed the associations between clinical manifestations and correlates especially genetic components.

Results:

We identified FCGR2B and the HLA region as susceptibility loci to IgG4RD (p≤1.2x10^{-11}). We also found evidence that the HLA region contained at least two independent associations in HLA-DRB1 and HLA-A regions. The amino acid position 11 in the HLA-DRB1 peptide-binding groove, the strongest susceptibility position to other autoimmune diseases, was strongly associated with IgG4RD (p=1.3x10^{-22}). The susceptibility SNP in FCGR2B was in linkage disequilibrium with a functional missense variant of FCGR2B and showed an association with the decreased gene expression (p=2.1x10^{-18}). The SNP and age at diagnosis were independently associated with recurrence of IgG4RD (p≤0.013).

Conclusions:

A total of three susceptibility markers to IgG4RD were identified. FCGR2B may play critical roles in developing and the progression of IgG4RD. HLA-DRB1 amino acid position 11 is important for IgG4RD.