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 ($p \leq 1.2 \times 10^{-11}$). 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 ($p = 1.3 \times 10^{-22}$). 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 ($p = 2.1 \times 10^{-18}$). The SNP and age at diagnosis were independently associated with recurrence of IgG4RD ($p \leq 0.013$).

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.