Genome-wide association studies across autoimmune and allergic diseases identify shared and distinct genetic component

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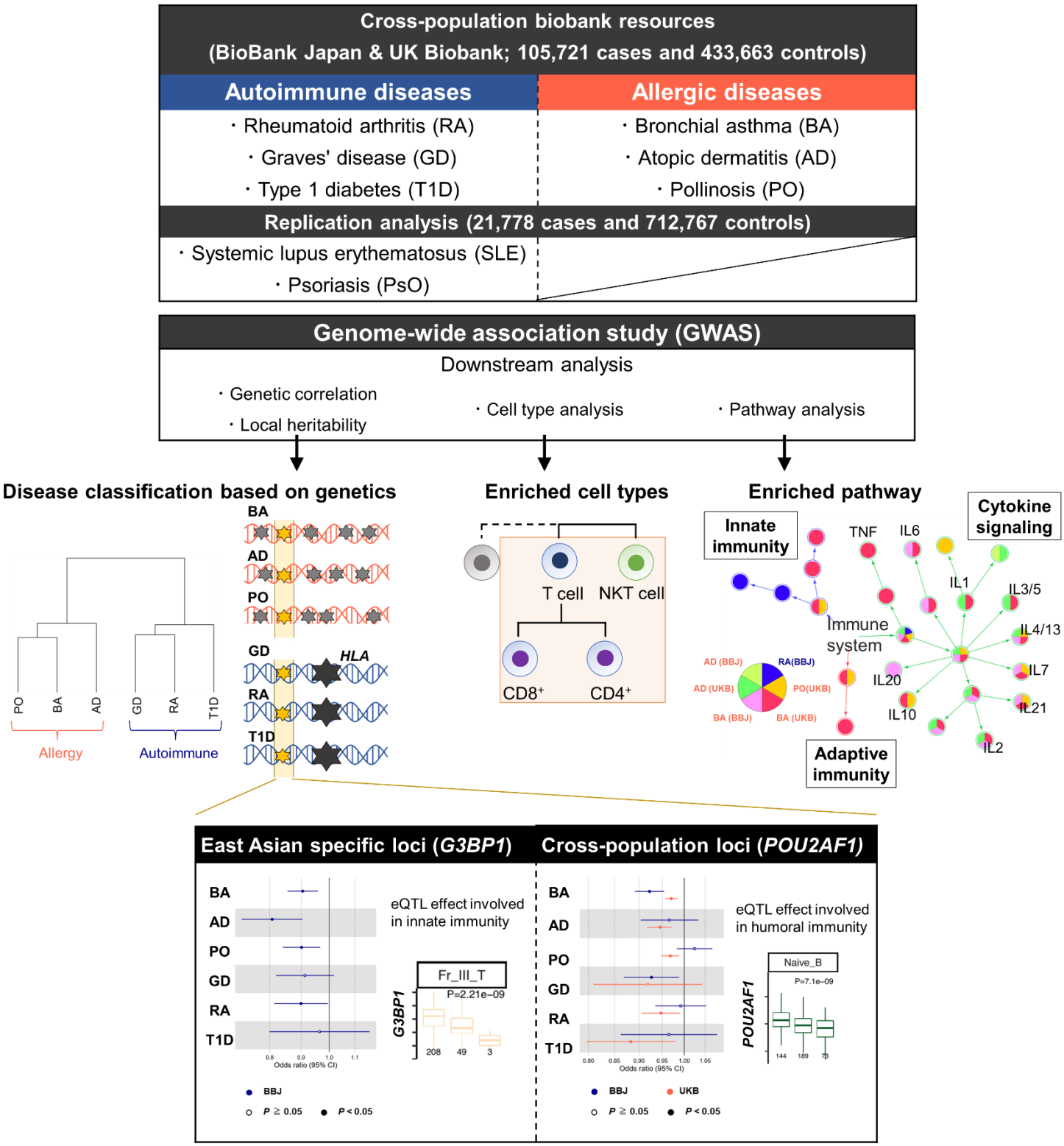
Autoimmune and allergic diseases are outcomes of the immune system dysregulation. While they are regarded as pathogenetically distinct conditions, several allergic diseases have been reported to be associated with the long-term risks of developing autoimmune diseases. This observation suggests shared genetic components across autoimmune and allergic diseases. We performed a multi-trait genome-wide association study (GWAS) meta-analysis of six immune-related diseases: rheumatoid arthritis, Graves' disease, type 1 diabetes for autoimmune diseases, and asthma, atopic dermatitis, and pollinosis for allergic diseases. By integrating large-scale biobank resources (Biobank Japan and UK biobank), our study included 105,721 cases and 433,663 controls. Autoimmune and allergic diseases were classified based on genetic backgrounds. The difference was derived from the fact that in autoimmune diseases the genetic risk was concentrated in the *HLA* gene region, whereas in allergic diseases the genetic risk was distributed in cytokine genes. Multi-trait GWAS meta-analysis newly identified four loci shared between the autoimmune and allergic diseases. Of these, the genetic effect was East Asian specific in *G3BP1* loci and consistent among ancestral populations in *POU2AF1* loci. *G3BP1* is involved in type I interferon, and *POU2AF1* is involved in antibody production in B cells. We indicated that the identified variants could attenuate disease risk by decreasing the expression levels of the respective gene. Our analysis should contribute to the elucidation of the complicated etiology in autoimmune and allergic diseases, and the shared risk genes are expected to become potential multi-target drug targets as key genes that regulate the immune system.


Cross-population biobank resources
(BioBank Japan & UK Biobank; 105,721 cases and 433,663 controls)
Autoimmune diseases
・Rheumatoid arthritis (RA)
・Graves' disease (GD)
・Type 1 diabetes (T1D)
Allergic diseases
・Bronchial asthma (BA)
・Atopic dermatitis (AD)
・Pollinosis (PO)
Replication analysis (21,778 cases and 712,767 controls)
・Systemic lupus erythematosus (SLE)
・Psoriasis (PsO)
Genome-wide association study (GWAS)
Downstream analysis
・Genetic correlation
・Local heritability
・Cell type analysis
・Pathway analysis
Disease classification based on genetics
Enriched cell types
Enriched pathway
PO
BA
AD
GD
RA
T1D
Allergy
Autoimmune
HLA
T cell
NKT cell
CD8+
CD4+
Innate immunity
Cytokine signaling
TNF
IL6
IL1
IL3/5
IL4/13
IL7
IL21
IL2
IL10
IL20
Immune system
Adaptive immunity
AD (BBJ)
RA(BBJ)
AD (UKB)
PO(UKB)
BA (BBJ)
BA (UKB)
East Asian specific loci (G3BP1)
Cross-population loci (POU2AF1)
eQTL effect involved in innate immunity
eQTL effect involved in humoral immunity
G3BP1
Fr_III_T
P=2.21e-09
208
49
3
POU2AF1
Naive_B
P=7.1e-09
144
189
Odds ratio (95% CI)
BBJ
UKB
P ≥ 0.05
P < 0.05