Transcriptome-wide Analysis of Psoriasis and Ulcerative colitis for Potential Genetic Marker

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Abstract

Psoriasis is a chronic inflammatory skin disease characterized with cutaneous eruptions and pruritus. As it has been revealed that immune abnormalities are the major etiological feature of psoriasis, associations with other autoimmune diseases have been raised. In order to analyze the genetic and transcriptomic correlation with ulcerative colitis (UC), one of the autoimmune diseases with high comorbidity with psoriasis, we conducted transcriptome-wide association study (TWAS). As a result of conducting TWAS analysis on 5 panels which are relevant for both psoriasis and UC, a total of 13 genes (*PUS10*, *C6orf3*, *IRF5*, *TMED1*, *UBE2L3*, *KIAA1919*, *ALDH2*, *C16orf75*, *IKZF3*, *GSDMB*, *ORMDL3*, *REL*, *CCDC116*) were significantly associated in both psoriasis and UC (false discovery rate < 0.05). After finding common genes, network analysis was performed for co-expression and protein-protein interactions (PPI) between genes, and the results showed that the genes play an important role. These findings may contribute to reveal the underlying genetic mechanisms of comorbidity between psoriasis and UC.

Workflow

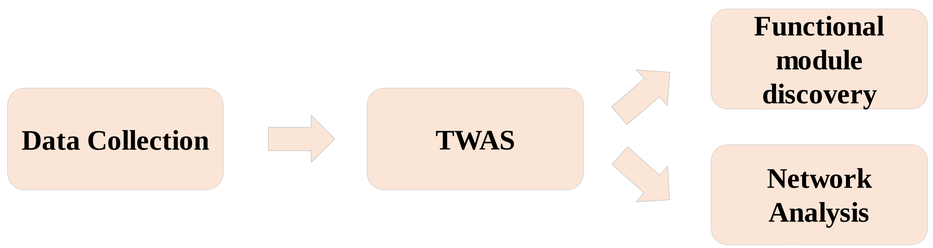

Figure 1. Workflow of overall study. GWAS summary statistics data on psoriasis were collected from GWAS atlas (GCST90014456). Then, transcriptome-wide analysis was conducted using a computational tool, FUSION (Gusev et al.). The results of TWAS for ulcerative colitis were retrieved from TWAS hub (http://twas-hub.org/traits/UC2017/). We compared the analysis results for 5 panels (Whole_Blood, NTR_Blood, YFS_Blood, Lower_leg, Suprapubic) and found 13 commonly detected genes (FDR < 0.05). In order to classify the characteristics of genes that passed the criteria, we conducted functional module discovery with HumanBase web tool and Network Analysis using NetworkAnalyst web interface.

Common Gene List

Gene	Panel	Chromosome	RSID	TWAS.Z	FDR	Disease
ALDH2	Lower_leg	12	rs11066188	3.15	0.049086	UC
	NTR_Blood	12	rs3184504	-3.9065	0.021909	Psoriasis
C16orf75	NTR_Blood	16	rs415595	-3.201042	0.046411	UC
	NTR_Blood	16	rs4451969	-3.6112	0.046069	Psoriasis
C6orf3	Lower_leg	6	rs13190932	-5.174942	5.18E-05	UC
	Whole_Blood	6	rs13190932	-3.854086	0.005252	UC
	Lower_leg	6	rs13203885	-4.62506	0.00296	Psoriasis
	Suprapubic	6	rs13203885	-4.50252	0.004914	Psoriasis
	Whole_Blood	6	rs13203885	-4.36104	0.005403	Psoriasis
CCDC116	Suprapubic	22	rs131665	-3.878594	0.006615	UC
	Lower_leg	22	rs131665	-3.773975	0.00887	UC
	Lower_leg	22	rs4821124	-4.41755	0.006205	Psoriasis
	Suprapubic	22	rs4821124	-4.10127	0.018783	Psoriasis
GSDMB	Whole_Blood	17	rs2872507	-7.604954	2.84E-11	UC
	NTR_Blood	17	rs2872507	-7.025646	1.71E-09	UC
	YFS_Blood	17	rs2872507	-6.8042	1.18E-08	UC
	NTR_Blood	17	rs10852936	-3.78237	0.028758	Psoriasis
	YFS_Blood	17	rs10852936	-3.85719	0.029103	Psoriasis
IKZF3	NTR_Blood	17	rs2872507	6.872805	2.52E-09	UC
	NTR_Blood	17	rs10852936	3.561	0.046069	Psoriasis
IRF5	Lower_leg	7	rs4728142	6.36	1.88E-07	UC
	Whole_Blood	7	rs4728142	5.69	2.99E-06	UC
	YFS_Blood	7	rs4728142	-3.93	0.007424	UC
	Suprapubic	7	rs4728142	5.52271	4.88E-05	Psoriasis
	Lower_leg	7	rs4728142	5.42688	0.000125	Psoriasis
	Whole_Blood	7	rs4728142	5.05658	0.000626	Psoriasis
KIAA1919	NTR_Blood	6	rs13190932	5.777949	1.82E-06	UC
	Suprapubic	6	rs13196377	3.584923	0.015055	UC
	NTR_Blood	6	rs13203885	4.0249	0.017186	Psoriasis
ORMDL3	NTR_Blood	17	rs2872507	-6.888317	2.52E-09	UC
	Whole_Blood	17	rs2872507	-6.90861	3.25E-09	UC
	YFS_Blood	17	rs2872507	-6.68286	2.16E-08	UC
	Lower_leg	17	rs2872507	-4.567984	0.000559	UC
	NTR_Blood	17	rs10852936	-4.10319	0.016361	Psoriasis
	YFS_Blood	17	rs10852936	-3.97166	0.020938	Psoriasis
PUS10	YFS_Blood	2	rs7608910	3.87	0.009154	UC
	Whole_Blood	2	rs842636	-4.40474	0.00518	Psoriasis
REL	YFS_Blood	2	rs7608910	3.99	0.006103	UC
	YFS_Blood	2	rs842636	-4.99835	0.000821	Psoriasis
TMED1	YFS_Blood	19	rs12720356	-3.35	0.03755	UC
	Whole_Blood	19	rs2304256	5.97174	1.38E-05	Psoriasis
UBE2L3	YFS_Blood	22	rs131665	4.423182	0.001362	UC
	Whole_Blood	22	rs131665	3.259625	0.031423	UC
	YFS_Blood	22	rs4821124	4.5333	0.003016	Psoriasis
	Lower_leg	22	rs4821124	4.253	0.010804	Psoriasis
	Whole_Blood	22	rs4821124	4.176743	0.011572	Psoriasis

Table 1. Thirteen genes were commonly found in psoriasis and ulcerative colitis by TWAS (FDR < 0.05).

Functional Module

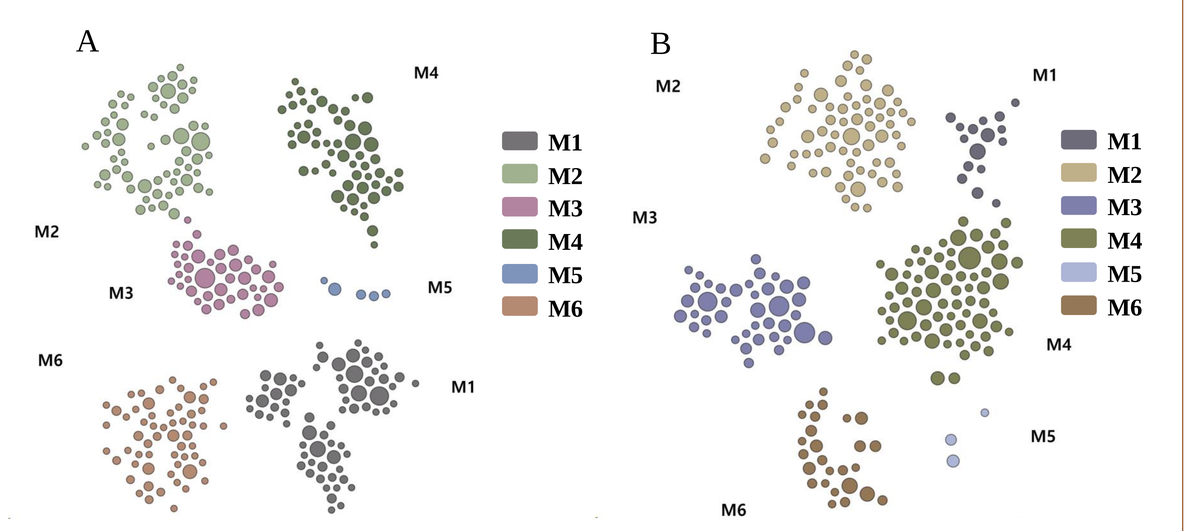

Figure 2. Functional module of TWAS genes. 404 genes that passed the criteria in psoriasis of ulcerative colitis were used for analysis. Tissue-specific modules of TWAS genes in (A) blood tissue and (B) skin tissue. At a blood-specific tissue, 6 modules were clustered, of which M1 containing the most genes is the genes involved in immune response-activating cell surface receptor signaling pathway. At a skin-specific tissue, 6 modules were also found out, of which M4 covering the most genes is the genes related with interferon-beta production.

Network Analysis

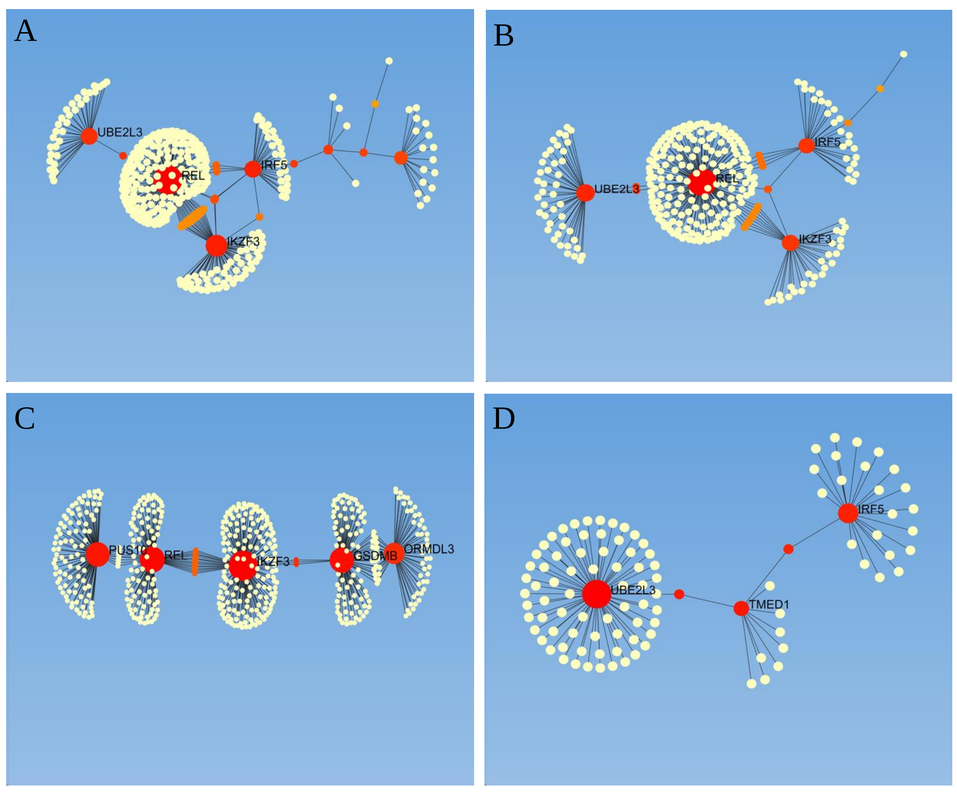

Figure 3. Results of network analysis using 404 genes that have passed the criteria. PPI network of the genes in (A) blood-specific tissue and (B) skin-specific tissue. In both PPI, *REL*, *IRF5*, *UBE2L3*, *IKZF3* play the role of hub genes. (C) and (D) represent co-expression in blood-specific tissue. Similarly, it can be seen that *PUS10*, *REL*, *IKZF3*, *GSDMB*, *ORMDL3*, *UBE2L3*, *TMED1* and *IRF5* belonging to the common genes are co-expressed with many other genes.

Conclusion

As a result of TWAS, a total of 404 genes showed significant result in psoriasis and ulcerative colitis, of which 13 genes were commonly found in both disease. The genes were grouped into modules with functions associated with the 2 diseases, and it was confirmed that common genes played an important role in the PPI and co-expression networks.

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