Transcriptome profiling and autoimmunity-related serological markers identify TP53 and C3aR as drug targets in neuropsychiatric SLE

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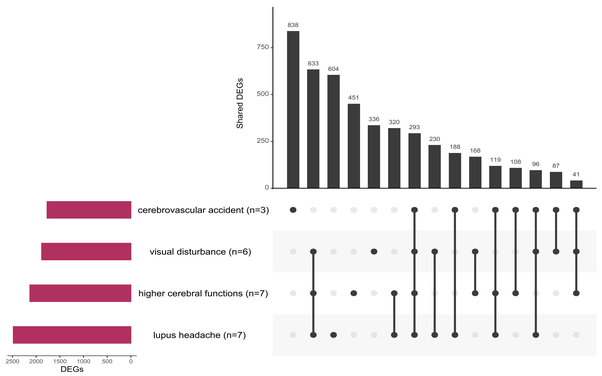
Conclusions

Integrative omics analysis revealed potentiality for BTK and C3aR modulation in CNS lupus.

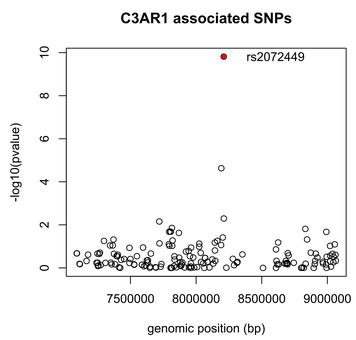
	Healthy controls	Active/ past CNS lupus	Active CNS lupus	Past CNS lupus	Non-NP inactive* SLE	Active/ past CNS AID†	Active CNS AID†	Past CNS AID†	Non-NP AID†	P value
	N=497	N=58	N=26	N=17	N=94	N=54	N=11	N=43	N=765	
Age (y, mean ± SD)	47.1±13.0	45.7±13.6	45.5±14.6	49.7±13.7	48.7±15.0	56.7±15.4	52.6±12.2	57.7±16.1	57.5±13.2	**<0.001**
Female sex (%)	393 (79.1)	53 (91.4)	25 (96.2)	16 (94.1)	89 (94.7)	42 (77.8)	11 (100.0)	31 (72.1)	657 (85.9)	**<0.001**
Disease duration (y, mean ± SD)	N/A	18.0±10.5	15.1±9.9	24.2±10.1	14.0±9.5	9.5±9.1	10.5±10.0	9.3±9.0	10.7±9.0	**<0.001**
SLEDAI-2K score (median [IQR])	N/A	9.0 (1.3–14.0)	12.0 (10.0–17.0)	0.0 (0.0–4.0)	0.0 (0.0–2.0)	N/A	N/A	N/A	N/A	**<0.001**
Anti-dsDNA (+, %)	0 (0.0)	10 (22.7)	3 (15.8)	3 (23.1)	25 (36.2)	1 (2.8)	0 (0.0)	1 (3.3)	14 (2.4)	**<0.001**
Low C3c (%)	70 (21.9)	14 (31.8)	7 (36.8)	3 (23.1)	33 (47.8)	6 (16.7)	0 (0.0)	6 (20.0)	122 (20.7)	**<0.001**
Low C4 (%)	32 (10.0)	13 (29.5)	7 (36.8)	3 (23.1)	21 (30.4)	7 (19.4)	1 (16.7)	6 (20.0)	76 (12.9)	**<0.001**

Characteristics of patients with autoimmune diseases and healthy controls in the PRECISESADS study population.

* Defined as clinical SLEDAI-2K=0; † Mixed connective tissue disease, primary antiphospholipid syndrome, primary Sjögren's syndrome, rheumatoid arthritis and systemic sclerosis.

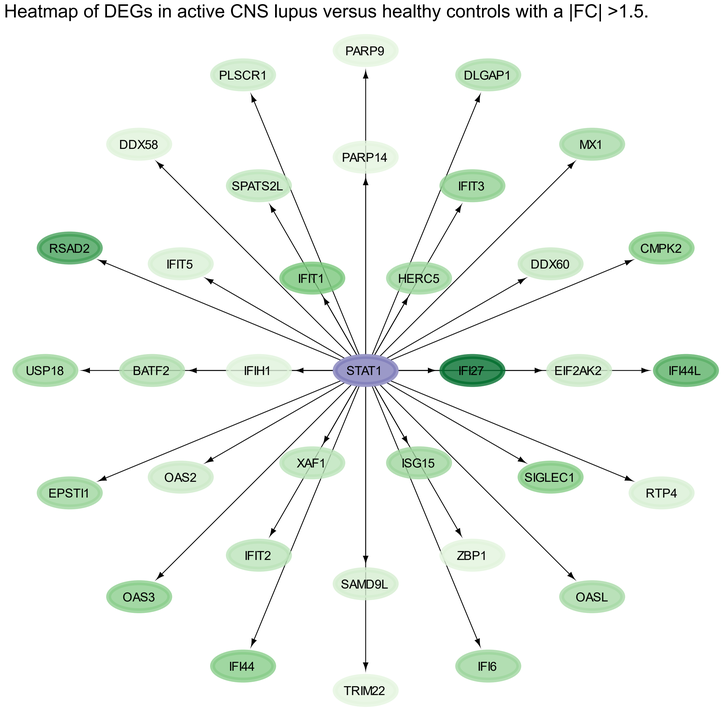


DEGs in CNS lupus patient subgroups versus healthy controls.



Cis-eQTLs associated with C3AR1 in patients with active/past CNS lupus.

Heatmap of DEGs in active CNS lupus versus healthy controls with a |FC| >1.5.



Top signalling molecule network of upregulated DEGs in active CNS lupus versus healthy controls.

Background and aims

The management of neuropsychiatric systemic lupus erythematosus is poorly optimised and specific treatment is lacking. The aim of this study was to investigate expression quantitative trait loci (eQTLs), the transcriptome, and autoimmunity-related cytokines and autoantibodies in patients with CNS lupus to gain insights into underlying mechanisms and identify drug targets.

Methods

We analysed differentially expressed genes (DEGs), pathways and their druggability in active CNS lupus (n=26) versus healthy controls (n=497), and eQTLs in active or past CNS lupus (n=53), based on validated DEGs in SLE (n=350) versus healthy controls (n=497), in whole blood collected within the frame of the PRECISESADS consortium. Genome-wide RNA-sequencing and genotyping was previously performed by Illumina assays, and cytokines were analysed using a Luminex assay and ELISA [1].

Results

Among 5631 significant and validated DEGs in active CNS patients compared with healthy controls, 1922 DEGs were found in 21 and 176 significant KEGG and Reactome pathways, respectively. The pathways included 29 of 59 DEGs with a |fold change| >1.5, 6 genes from 14 significant cis-eQTLs and 10 genes from 22 trans-eQTLs, and 2 genes from 8 cytokines that differed significantly between active CNS lupus and healthy controls. Among 496 drugs, the Bruton tyrosine kinase (BTK) inhibitor ibrutinib with ability to interfere with tumour protein P53 (TP53) activity and a complement C3a receptor (C3aR) antagonist were of particular interest.

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