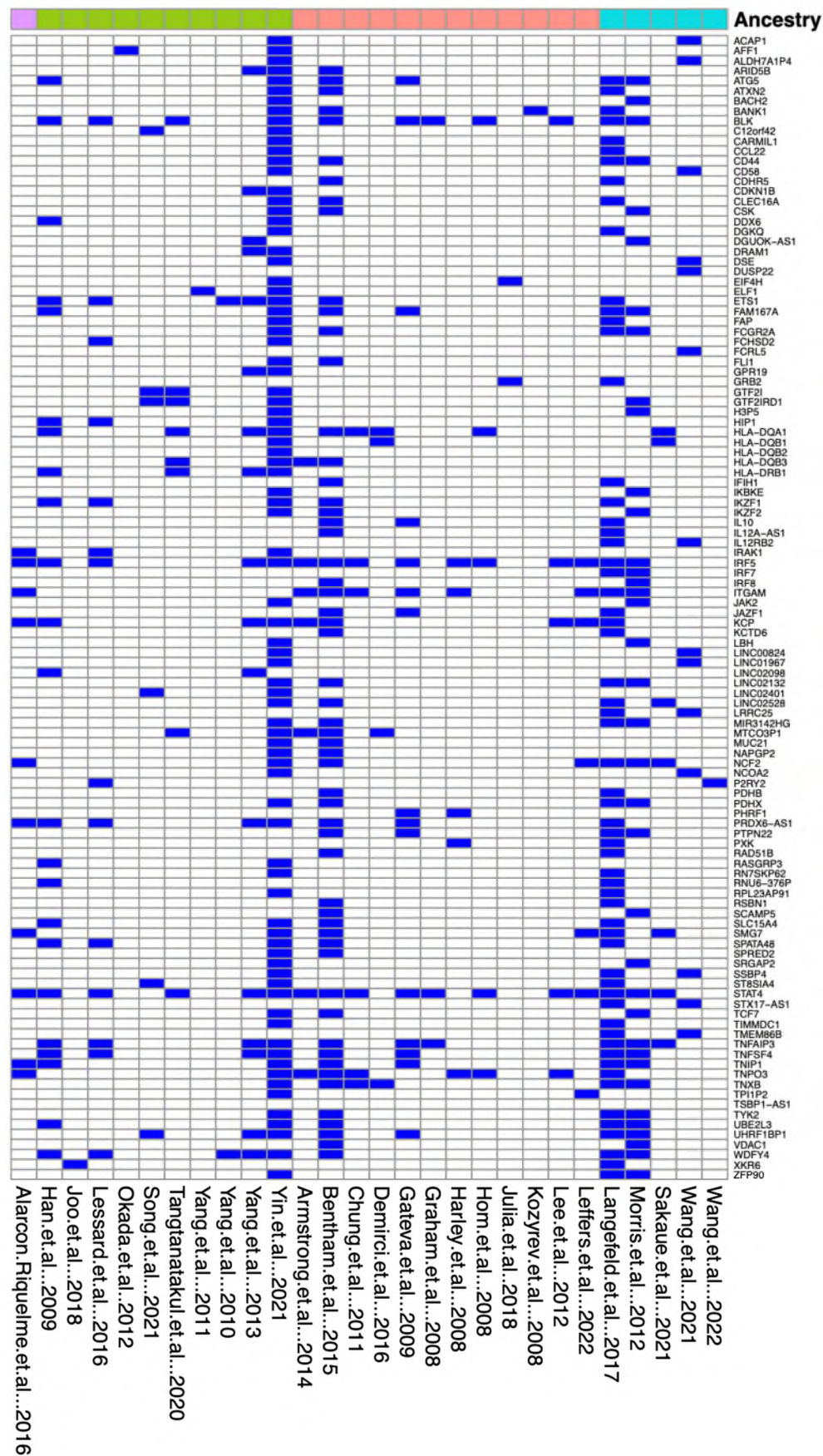


Genetics of SLE: mechanistic insights from monogenic disease and disease-associated variants

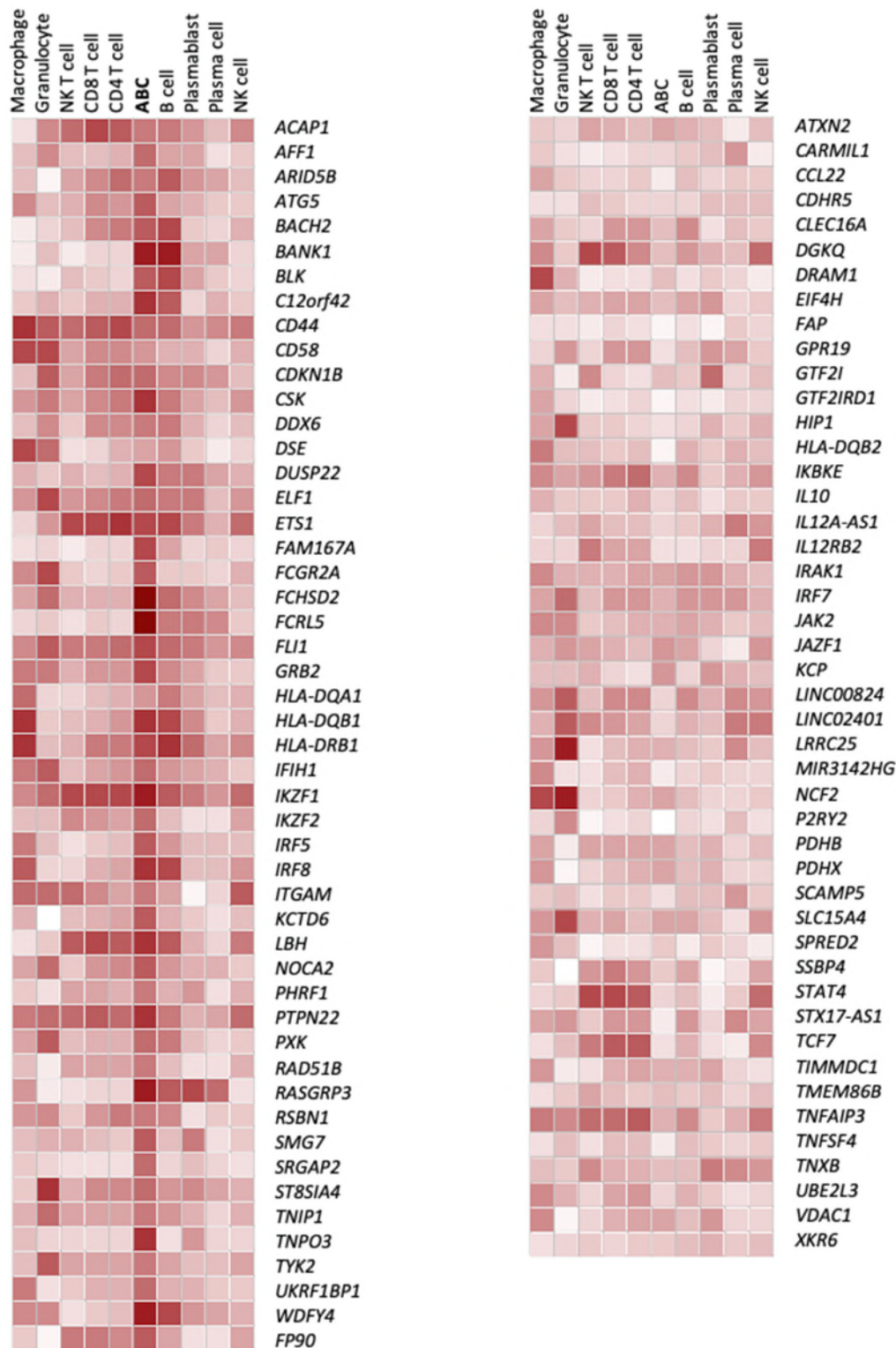
In the format provided by the
authors and unedited

Supplementary figure 1. Mapped common variants identified by SLE GWAS



The figure illustrates selected common variants that have been identified in ≥ 2 genome-wide association studies (GWAS) studies of systemic lupus erythematosus (SLE) ¹⁻²⁸. Genes associated with significant single-nucleotide polymorphisms (SNPs) (that is, with a genome-wide significance $< 5 \times 10^{-8}$) in the summary data from the GWAS catalog, are listed by ancestry. This figure excludes studies exploring shared susceptibility, or specific aspects of SLE, such as response to treatment. A filled-in box denotes that gene has been mapped by that GWAS.

Supplementary figure 2- Expression of SLE-associated genes across immune cell subsets



The heatmap illustrates the Log2-transformed expression of genes associated with significant single-nucleotide polymorphism (SNPs) in ≥ 2 or more systemic lupus erythematosus (SLE) genome-wide association studies (GWAS) (Supplementary figure 1) in 10 key immune cells. These immune cell subsets include age-associated B cells (ABCs), which have been defined as CD19⁺CD27⁻CD21⁻CD10⁻ B cells. The heatmap was

created using the online transcriptome database GENEVESTIGATOR® (Affymetrix Human Genome U133 Plus 2.0 Array) and a compendium-wide analysis using conditional search of cell types. Hierarchical clustering performed by cell type.

References

- 1 Alarcon-Riquelme, M. E. *et al.* Genome-Wide Association Study in an Amerindian Ancestry Population Reveals Novel Systemic Lupus Erythematosus Risk Loci and the Role of European Admixture. *Arthritis Rheumatol* **68**, 932-943 (2016). <https://doi.org:10.1002/art.39504>
- 2 Han, J. W. *et al.* Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. *Nat Genet* **41**, 1234-1237 (2009). <https://doi.org:10.1038/ng.472>
- 3 Joo, Y. B. *et al.* Publisher Correction: Genetic variants in systemic lupus erythematosus susceptibility loci, XKR6 and GLT1D1 are associated with childhood-onset SLE in a Korean cohort. *Sci Rep* **8**, 11713 (2018). <https://doi.org:10.1038/s41598-018-30082-9>
- 4 Lessard, C. J. *et al.* Identification of a Systemic Lupus Erythematosus Risk Locus Spanning ATG16L2, FCHSD2, and P2RY2 in Koreans. *Arthritis Rheumatol* **68**, 1197-1209 (2016). <https://doi.org:10.1002/art.39548>
- 5 Okada, Y. *et al.* A genome-wide association study identified AFF1 as a susceptibility locus for systemic lupus erythematosus in Japanese. *PLoS Genet* **8**, e1002455 (2012). <https://doi.org:10.1371/journal.pgen.1002455>
- 6 Song, Q. *et al.* Genome-wide association study on Northern Chinese identifies KLF2, DOT1L and STAB2 associated with systemic lupus erythematosus. *Rheumatology (Oxford)* **60**, 4407-4417 (2021). <https://doi.org:10.1093/rheumatology/keab016>
- 7 Tangtanatakul, P. *et al.* Meta-analysis of genome-wide association study identifies FBN2 as a novel locus associated with systemic lupus erythematosus in Thai population. *Arthritis Res Ther* **22**, 185 (2020). <https://doi.org:10.1186/s13075-020-02276-y>
- 8 Yang, J. *et al.* ELF1 is associated with systemic lupus erythematosus in Asian populations. *Hum Mol Genet* **20**, 601-607 (2011). <https://doi.org:10.1093/hmg/ddq474>
- 9 Yang, W. *et al.* Genome-wide association study in Asian populations identifies variants in ETS1 and WDFY4 associated with systemic lupus erythematosus. *PLoS Genet* **6**, e1000841 (2010). <https://doi.org:10.1371/journal.pgen.1000841>
- 10 Yang, W. *et al.* Meta-analysis followed by replication identifies loci in or near CDKN1B, TET3, CD80, DRAM1, and ARID5B as associated with systemic lupus erythematosus in Asians. *Am J Hum Genet* **92**, 41-51 (2013). <https://doi.org:10.1016/j.ajhg.2012.11.018>
- 11 Yin, X. *et al.* Meta-analysis of 208370 East Asians identifies 113 susceptibility loci for systemic lupus erythematosus. *Ann Rheum Dis* **80**, 632-640 (2021). <https://doi.org:10.1136/annrheumdis-2020-219209>
- 12 Armstrong, D. L. *et al.* GWAS identifies novel SLE susceptibility genes and explains the association of the HLA region. *Genes Immun* **15**, 347-354 (2014). <https://doi.org:10.1038/gene.2014.23>
- 13 Bentham, J. *et al.* Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. *Nat Genet* **47**, 1457-1464 (2015). <https://doi.org:10.1038/ng.3434>
- 14 Chung, S. A. *et al.* Differential genetic associations for systemic lupus erythematosus based on anti-dsDNA autoantibody production. *PLoS Genet* **7**, e1001323 (2011). <https://doi.org:10.1371/journal.pgen.1001323>
- 15 Demirci, F. Y. *et al.* Identification of a New Susceptibility Locus for Systemic Lupus Erythematosus on Chromosome 12 in Individuals of European Ancestry. *Arthritis Rheumatol* **68**, 174-183 (2016). <https://doi.org:10.1002/art.39403>

- 16 Gateva, V. *et al.* A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. *Nat Genet* **41**, 1228-1233 (2009). <https://doi.org:10.1038/ng.468>
- 17 Graham, R. R. *et al.* Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. *Nat Genet* **40**, 1059-1061 (2008). <https://doi.org:10.1038/ng.200>
- 18 International Consortium for Systemic Lupus Erythematosus, G. *et al.* Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PTK, KIAA1542 and other loci. *Nat Genet* **40**, 204-210 (2008). <https://doi.org:10.1038/ng.81>
- 19 Hom, G. *et al.* Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. *N Engl J Med* **358**, 900-909 (2008). <https://doi.org:10.1056/NEJMoa0707865>
- 20 Julia, A. *et al.* Genome-wide association study meta-analysis identifies five new loci for systemic lupus erythematosus. *Arthritis Res Ther* **20**, 100 (2018). <https://doi.org:10.1186/s13075-018-1604-1>
- 21 Kozyrev, S. V. *et al.* Functional variants in the B-cell gene BANK1 are associated with systemic lupus erythematosus. *Nat Genet* **40**, 211-216 (2008). <https://doi.org:10.1038/ng.79>
- 22 Lee, Y. H., Bae, S. C., Choi, S. J., Ji, J. D. & Song, G. G. Genome-wide pathway analysis of genome-wide association studies on systemic lupus erythematosus and rheumatoid arthritis. *Mol Biol Rep* **39**, 10627-10635 (2012). <https://doi.org:10.1007/s11033-012-1952-x>
- 23 Leffers, H. C. B. *et al.* Established risk loci for systemic lupus erythematosus at NCF2, STAT4, TNPO3, IRF5 and ITGAM associate with distinct clinical manifestations: A Danish genome-wide association study. *Joint Bone Spine* **89**, 105357 (2022). <https://doi.org:10.1016/j.jbspin.2022.105357>
- 24 Langefeld, C. D. *et al.* Transancestral mapping and genetic load in systemic lupus erythematosus. *Nat Commun* **8**, 16021 (2017). <https://doi.org:10.1038/ncomms16021>
- 25 Morris, D. L. *et al.* Genome-wide association meta-analysis in Chinese and European individuals identifies ten new loci associated with systemic lupus erythematosus. *Nat Genet* **48**, 940-946 (2016). <https://doi.org:10.1038/ng.3603>
- 26 Sakaue, S. *et al.* A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet* **53**, 1415-1424 (2021). <https://doi.org:10.1038/s41588-021-00931-x>
- 27 Wang, Y. F. *et al.* Identification of 38 novel loci for systemic lupus erythematosus and genetic heterogeneity between ancestral groups. *Nat Commun* **12**, 772 (2021). <https://doi.org:10.1038/s41467-021-21049-y>
- 28 Wang, Y. F. *et al.* Identification of Shared and Asian-Specific Loci for Systemic Lupus Erythematosus and Evidence for Roles of Type III Interferon Signaling and Lysosomal Function in the Disease: A Multi-Ancestral Genome-Wide Association Study. *Arthritis Rheumatol* **74**, 840-848 (2022). <https://doi.org:10.1002/art.42021>