nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	FlowJo v10, FACSDiva, CRISPRpick tool, QuantStudio 3 Real-Time PCR.
Data analysis	trim_galore v0.6.6, FastQC v0.11.9, Salmon v1.5.1, R v4.1.2, tximport 1.22.0, DESeq2 v1.34, edgeR v3.36, WGCNA v1.72, clusterProfiler v4.2.2, STAR v2.7.9a, QTLtools v1.3.1, Cell Ranger v6.1.1, Seurat v4.1.1, demuxmix v1.6.0, demuxlet "first release", Harmony v1.2.0, nfcore/atacseq v2.0, DESeq2 v1.34, HOMER v4.11, LDSC v1.0.1, SuSiE v0.12.35, PLINK v1.9, STAR v2.7.9a, regtools v0.5.1, leafcutter v.0.2.9, fgsea v1.20.0, leafviz v0.1.0. All code available at: <https://github.com/gutierrez-arcelus-lab/bcellactivation>

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The raw sequencing data generated in this study are available in dbGaP under accession code phs004221.v1.p1 [https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs004221.v1.p1]. The data include raw RNA-seq, CITE-seq, and ATAC-seq sequence reads (FASTQ/BAM) from 27 donors. Because these are individual-level human genomic sequencing data that represent potentially identifying information, and in accordance with the study protocols and the written informed consent provided by participants, they are under controlled access. Access is overseen by the NIAMS Data Access Committee and can be requested through the dbGaP Authorized Access portal, requiring endorsement by an institutional Signing Official and a signed Data Use Certification; use is restricted to health/medical/biomedical research (HMB). Requests are typically reviewed within a few weeks. Approved access is granted for a period of one (1) year, with the option to renew access.
All processed data, including count matrices and differential expression/accessibility summary statistics, have been deposited in Zenodo [https://zenodo.org/uploads/15595470]. We made processed data publicly available via an interactive website that can be easily queried for visualization of gene expression, single cell profiles, chromatin accessibility, and splicing events [https://mgalab.shinyapps.io/bcellactivation/].
Publicly available data used in this study include: Reference genome and transcript annotations, GENCODE v38 [https://www.gencodegenes.org/human/release_38.html], and GENCODE v42 [https://www.gencodegenes.org/human/release_42.html]; ENCODE blacklist regions (hg38) [https://www.encodeproject.org/files/ENCFF356LFX/]; Open Targets Platform (Locus-to-Gene predictions) [https://platform.opentargets.org]; Nakano et al. 2022, Cell (Supplementary Table S2) [https://doi.org/10.1016/j.cell.2022.07.021]; LDSC reference files including pre-processed GWAS summary statistics, LD scores, and SNP lists, and baseline model (Zenodo) [https://zenodo.org/records/10515792]; GWAS summary statistics from Langefeld et al. 2017, GWAS Catalog [https://www.ebi.ac.uk/gwas/studies/GCST007400]; Enhancer-to-Gene (E2G) predictions, E2G Browser [https://e2g.stanford.edu/]; MSigDB C5 (GO) gene sets, v2022.1.Hs [https://www.gsea-msigdb.org/gsea/msigdb].
All data are included in the Supplementary Information or available from the authors, as are unique reagents used in this Article. The raw numbers for charts and graphs are available in the Source Data file whenever possible. Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	All 27 donors were self-reported females given that donors were recruited as part of lupus research studies, and lupus is 9 times more common in females than males. Sex was obtained from the biobank records; gender was not collected.
Reporting on race, ethnicity, or other socially relevant groupings	All recruited donors were of race 'White'.
Population characteristics	All recruited donors were healthy adults (20–60 years old).
Recruitment	All donors were recruited as part of lupus research studies through the Joint Biology Consortium Recruitment Core (Mass General Brigham) and the Boston Children's Hospital Biorepository of Adult Healthy Controls.
Ethics oversight	The Mass General Brigham and Boston Children's Hospital Institutional Review Boards gave ethical approval for this study.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes were determined in order to ensure sufficient statistical power for differential expression analysis and to make it feasible to profile a large number of conditions across different data modalities. See main text and figures for samples size for each assay.
Data exclusions	RNA-seq samples that yielded less than 2 million reads were excluded from all analysis.

Replication	All our experiments include biological replicates, and a subset of samples have technical replicates. We employed alternative analytical methods to ensure the robustness of our findings. See main text and methods for details.
Randomization	Low input RNA-seq was performed in one plate, with samples across donors and experimental conditions randomized within the plate. For scRNA-seq, experiments were performed in two batches, with donors randomized across batches, but for a given donor all experimental conditions were pooled in the same run. Similar design was applied for normal input RNA-seq.
Blinding	Investigators were blind to any individual characteristic.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Antibody Fluorophore Clone Company Cat#
Anti-CD69 APC/Cyanine7 (clone FN50) Biolegend Cat#310914
Anti-IgD BV605 (clone IA6-2) Biolegend Cat#348231
Anti-CD27 PE/Cyanine7 (clone O323) Biolegend Cat#302837
Anti-CD19 PE (clone HIB19) Biolegend Cat#302207
Anti-CD185 (CXCR5) PerCP/Cyanine5.5 (clone J252D4) Biolegend Cat#356909
Anti-CD86 APC (clone IT2.2) Biolegend Cat#305411
Anti-IgG AF700 (clone G18-145) BDBioscience Cat#561296
Anti-Tbet BV421 (clone 4B10) Biolegend Cat#644815
Anti-CD21 APC/Cyanine7 (clone Bu32) Biolegend Cat#354927
Anti-CD11c PE (clone B-ly6) BDBioscience Cat#560999
Anti-CD19 BV786 (clone SJ25-C1) BDBioscience Cat#563326
Anti-CD27 PE/Cyanine7 (clone M-T271) Biolegend Cat#356411
Anti-CD19 PE (clone 4G7) Biolegend Cat#392505
Anti-CD38 FITC (clone HB-7) Biolegend Cat#356609
Anti-CD3 AF488 (clone HIT3a) Biolegend Cat#300320
Anti-CD45 r718 (clone HI30) BDBioscience cat#566962
Anti-CD3 BV786 (clone UCHT1) BDBioscience Cat#565491
Anti-IgD FITC (clone IA6-2) BDBioscience Cat#562023
Anti-CD27 BV605 (clone L128) BDBioscience Cat#562656
Anti-CD21 PeCy7 (clone B-ly4) BDBioscience Cat#561374
Zombie NIR Biolegend "Cat#423105 "
7AAD L/D marker staining solution Invitrogen Cat#00-6993-50
eFluor 506 Fix Viability Dye Invitrogen Cat#65-0866-14

Validation

Validation is described on the company website for each product

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Lymphoblastoid B cell line, GM12878, was obtained from the Coriell Institute for Medical Research
Authentication	The cell line used was not authenticated
Mycoplasma contamination	All the cell lines were tested negative for Mycoplasma
Commonly misidentified lines (See ICLAC register)	N/A

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	100ml of whole blood were isolated using cell preparation tubes containing EDTA
Instrument	BD LSRFortessa X-20
Software	Data were analyzed using FlowJo software version 10.10.0 (BD Biosciences)
Cell population abundance	Purity was determined for all samples, timepoints and conditions, when enough material was available
Gating strategy	For low-input RNA-seq and scRNA-seq+CITE-seq, all samples were sorted based on the following gating strategy: 1) Lymphocytes based on FSC-A/SSC-A; 2) Singlets based on FSC-A/FSC-H; 3) Live cells based on 7AAD negative; 4) CD19+ cells

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.