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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	CyTOF FCS files of acquired events were normalized and concatenated with Fluidigm acquisition software. Flow cytomoetry was acquired with FACSDiva software (BD Bioscience). Luminex data was acquired with Milliplex Analyst software using a 5P regression algorithm.
Data analysis	Autoantibody analysis was done in R (v4.0.4) using the following packages: limma microarray analysis suite (v3.46.0), UpSetR (v1.4.0)59 and ggvennDiagram (https://github.com/gaospecial/ggVennDiagram) (v1.2.1) packages. Heatmaps were generated using the ComplexHeatmap (v2.7.4), HPAanalyze (v1.8.1). CyTOF analysis was performed in Cytobank. Flow cytometry analysis was performed with FlowJo. BCR sequencing analysis was performed usign the immunoSEQ Analyzer toolset. Graphpad Prism 9 and Microsoft Excel 16.57 were also used for data analysis.

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 data that support the findings of this study are available in the article and supplementary materials

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	The study cohort was comprised of both sexes as shown in Supplemental Tables 1 and 2. Sexes were included whenever possible. There were no significant differences between genders for any of the reported findings.
Population characteristics	N/A
Recruitment	"Individuals with DS" participants with a diagnosis of Down syndrome were recruited, via their referring physicians or via the NIH's DS-Connect ® national registry (dsconnect.nih.gov).
Ethics oversight	Mount Sinai Health System (MSHS) (IRB-18-00638/ STUDY-18-00627 and IRB-20-03276), Boston Children's Hospital (04-09-113R), National Institute of Allergy and Infectious Disease (NIAID, NIH) (05-I-0213), Rockefeller University (JCA-0700 and XFK-0815), the French Ethics Committee "Comité de Protection des Personnes," the French National Agency for Medicine and Health Product Safety, and the "Institut National de la Santé et de la Recherche Médicale" (protocols # C10-13 and C10-14).

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	DS (n=23) and HC (n=21)
Data exclusions	N/A
Replication	Experiments were repeated with a minimum of n=2 in each condition
Randomization	Individuals were randomly allocated within HC and DS groups
Blinding	Blinding was not performed in our study

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

Methods

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

Antibodies

Antibodies used

Cd111-GranzymeB, Cd112-IgA, In113-CD57, In115-CD11c, Cd116-IgD, I127-127I, Ce140-140Ce, Pr141-Ki67, Nd142-CD19, Nd143-CD45RA, Nd144-CD103, Nd145-CD4, Nd146-CD8, Sm147-pSTAT5, 150Nd-pSTAT5, Nd148-CD16, Sm149-CD127 Sm149-pSTAT6, Nd150-CD1c, Eu151-CD123, Sm152-CD66b, Eu153-pSTAT1, Sm154-ICOS, Gd155-CD27, Gd156-p38, 158Gd-pSTAT3, Tb159-pMAPKAP2, Gd160-CD14, Dy161-CD56, Dy162-TCRgd, Dy162-CD169, Dy163-CD172a_b, Dy164-CD69, Ho165-CD64, Ho165-STAT3, Er166-CD25, Er167-pERK1_2, Er168-CD3, Tm169-CD71, Tm169-STAT1, Er170-CD38, Yb171-CD95, Yb171-CD141, Yb172-CD39, Yb173-Tbet, Yb174-HLADR, Lu175-pS6, Yb176-CD54, Pr141-IFNg, Nd144-CD141, 171Yb-CD141, Sm147-IL_1b, Sm149-IL_1RA, Eu153-TNFa, Gd156-IL_6, Gd158-IL_2, Tb159-GM_CSF, Dy164-IL_17A, Ho165-CCL4, Er166-IL_10, Tm169-IFNa2b, Yb173-IL_8, Lu175-IL_29, Yb176-CXCL10.
CD19 APC-Cy7 (SJ25C1), CD27 FITC (M-T271), CD38 APC (HIT2), CD38 PE-Cy7 (HIT2), CD11c PE (B LY6), IgD BV421 (IA6), CD21 APC (Bu32), anti-phospho-STAT1-PE (1:25, BD) , anti-human 9G4 IgG APC (generously provided by Jocelyn Farmer).
Tofacitinib (500nM, ApexBio), Tocilizumab (50ug/mL, Selleckchem), anti-IFNAR2 (2.5ug/mL PBL Assay Science), anti-IFN-a (0.2ug/mL, PBL 31110–1), and IFN-b (0.2ug/mL, PBL 31401-1), anti-IL10 (5ug/mL, Biolegend), anti-IL-10R (5ug/mL, Biolegend), nti-IFNGR2 (2ug/mL, Thermofisher PA5-47938), Adalimumab (2ug/mL, Selleckchem).

Validation

N/A

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration

N/A

Study protocol

Mount Sinai Health System (MSHS) (IRB-18-00638/ STUDY-18-00627 and IRB-20-03276), Boston Children's Hospital (04-09-113R), National Institute of Allergy and Infectious Disease (NIAID, NIH) (05-I-0213), Rockefeller University (JCA-0700 and XFK-0815), the French Ethics Committee "Comité de Protection des Personnes," the French National Agency for Medicine and Health Product Safety, and the "Institut National de la Santé et de la Recherche Médicale" (protocols # C10-13 and C10-14).

Data collection

N/A

Outcomes

N/A

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

CYTOF: Frozen stabilized blood samples were thawed according to the manufacturer's recommended protocol, then washed with barcode permeabilization buffer (Fluidigm). Samples were uniquely barcoded with Cell-ID 20-Plex Pd Barcoding Kit (Fluidigm) and pooled together. For previously unstained samples, cells were then incubated with an antibody cocktail for surface markers to identify major immune populations, followed by methanol permeabilization, heparin-block and stain with a cocktail of antibodies against intracellular targets, including markers of phosphorylation and signaling. After washing, cells were then incubated in freshly diluted 2.4% formaldehyde containing 125nM Ir Intercalator (Fluidigm), 0.02% saponin and 30 nM OsO4 (ACROS Organics) for 30 min at room temperature. Samples were then washed and acquired immediately.
Flow: For extracellular markers, cells were immunostained with antibodies in 0.5% BSA in PBS for 1 hour, washed 3x in 0.5% BSA in PBS for 1 hour and acquired immediately.

Instrument	CyTOF: Helios mass cytometer (Fluidigm) with a modified wide-bore injector (Fluidigm). Flow: BD LSR Fortessa II
Software	CyTOF: Fluidigm acquisition software Flow: BD FACSDiva software
Cell population abundance	See figures
Gating strategy	Major populations were The gated populations were manually gated based on the previously described gating scheme (Geanon, D. et al. A Streamlined CyTOF Workflow To Facilitate Standardized Multi-Site Immune Profiling of COVID-19 Patients. medRxiv (2020)). B cell populations were gated according to gating in Supplemental Figure 4B.

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