

Reporting Summary

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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
<input type="checkbox"/>	<input checked="" type="checkbox"/> The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement
<input type="checkbox"/>	<input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
<input type="checkbox"/>	<input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/> A description of all covariates tested
<input type="checkbox"/>	<input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
<input type="checkbox"/>	<input checked="" type="checkbox"/> 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)
<input type="checkbox"/>	<input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
<input checked="" type="checkbox"/>	<input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
<input type="checkbox"/>	<input checked="" type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), 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	No software was used
Data analysis	Cellranger V7.0.0 10x Genomics https://support.10xgenomics.com/single-cell-gene-expression/software/pipelines/latest/installation Seurat V4.3.0 Hao et al https://github.com/satijalab/seurat/releases/tag/v4.3.0 Harmony V1.2.0 Korsunsky et al https://cran.r-project.org/web/packages/harmony/ Cellranger ARC V2.0.0 10x Genomics https://www.10xgenomics.com/support/cn/software/cell-ranger-arc/latest/release-notes/reference-release-notes Signac V1.13.0 Stuart, Tim, et al. https://github.com/stuart-lab/signac/releases Python V3.10.9 Python Software Foundation https://www.python.org/ Gseapy V1.1.4 Fang et al., 2022 https://gseapy.readthedocs.io/en/latest/introduction.html GSEA_scRNA https://github.com/gulkhan007/GSEA_scRNA R V4.5.0 R Core https://www.r-project.org/

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](#)

Lead contact

Any information and reagent request will be provided by the lead contact, Lionel Blanc (lblanc@northwell.edu).

Materials availability

All unique materials will be available upon request to the lead contact.

Data availability

All sequencing datasets have been deposited to NCBI Gene Expression Omnibus under accession codes GSE304205 and GSE302344. Any additional information with regards to the datasets is available from the lead contact upon request.

Code availability

There is no original code generated in this study.

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

Sex and gender information were collected from patients through an extensive 14-page questionnaire, following the protocol established by the Diamond Blackfan Anemia Registry (01.10.088G).

Reporting on race, ethnicity, or other socially relevant groupings

Information such as race or ethnicity was collected but not used to categorize patients. Diamond-Blackfan anemia is a rare genetic disease that affects individuals across all ethnicities and social groups, making such classification irrelevant for the purposes of this study.

Population characteristics

Patients present characteristics of DBA with mutations in a ribosomal protein gene.

Recruitment

Patients were recruited through the DBAR following protocol 01.10.088G

Ethics oversight

IRB at Northwell health

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](https://www.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

All measurements were taken from distinct samples, with a minimum of 3 biological replicates. No statistical method was used to predetermine sample size. These were based on our previous experience and published literature on similar models to ensure the robustness of the observed phenotypes.

Data exclusions

No data got excluded.

Replication

All experiments were repeated at least twice using independent samples and were compared with the initial results to confirm the reproducibility of the findings. All replication attempts were successful.

Randomization

Randomization was not applicable to the characterization of the DBA mouse model, as most observations were made directly on genetically modified animals without any experimental treatment of the organism or cells.

Mutant mice exhibited a strong and readily identifiable phenotype, making blinded analysis impractical. Blinding was therefore not applied for the characterization of this model. In addition, for experiments requiring large amounts of material, samples were pooled when necessary.

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		Methods	
n/a	Involved in the study	n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies	<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines	<input type="checkbox"/>	<input checked="" type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology	<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms		
<input type="checkbox"/>	<input checked="" type="checkbox"/> Clinical data		
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern		
<input checked="" type="checkbox"/>	<input type="checkbox"/> Plants		

Antibodies

Antibodies used	Antibodies
	CD4-BV605 Biolegend Cat# 100451 CD8a-BV6-5 Biolegend Cat# 100744 Ter119-BV605 Biolegend Cat# 116239 CD45R/B220-BV605 Biolegend Cat# 103224 Ly-6G/Ly-6C-BV605 Biolegend Cat# 108440 C-Kit-APC-eFluor780 eBioscience Cat# 47-1171-82 Sca-1-BV711 Thermo Scientific Cat# 11-5981-82 CD48-AlexaFlour 700 Biolegend Cat# 103426 CD150-BV-785 Biolegend Cat# 115937 CD34-PE BD Cat# 551387 CD34-FITC BD Cat# 553733 CD16/32-PerCP-Cy5.5 (Thermo Scientific #45-0161 CD71-PE eBioscience Cat# 12-0711-83 CD44-APC Biolegend Cat# 100412 Ter119-FITC BD Cat# 557915 CD45R-APC-Cy7 BD Cat# 552094 CD11b-APC-Cy7 BD Bioscience Cat# 557657 Ly6G/Ly6C-APC-Cy7 BD Bioscience Cat# 557661 Annexin V-FITC Biolegend Cat# 640945 GAPDH-HRP CST Cat# 8884 P53 CST Cat# 2524 Rps19 Bethyl Labs Cat# A304-002A Rpl5 Abcam Cat# ab86863 AML1 CST Cat# 4334 S6 CST Cat# 2217 pS6 CST Cat# 4858 4EBP1 CST Cat# 9644 p4EBP1 CST Cat# 2855 p21 BD Cat# 556431 eEF2 CST Cat# 2332 peEF2 CST Cat# 2331 eIF2a CST Cat# 5324 peIF2a CST Cat# 3398 UBA52 Abcam Cat# 109227 Actin-B CST Cat# 4970 eIF5a BD Bioscience Cat# 611976 Hypusine Creative Biolab Cat# PABL-202 PABP1 CST Cat# 4992 eIF4E CST Cat# 2067 eIF4G CST Cat# 2469 eIF4H CST Cat# 3469

AML CST Cat# 8529

Validation

Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals

We used C57BL/6 mouse strain. Majority of the experiments were performed on the embryos between stage E13.5 and E15.5. Follow up of the mice survival was done up to 60 days.

Wild animals

The study did not involve wild animals

Reporting on sex

Embryos were analyzed independently of their sex. No difference was noted in male or female embryos.

Field-collected samples

The study did not involve samples collected from the field.

Ethics oversight

The study was approved by the Feinstein Institutes IACUC, protocol #2022-019

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

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

Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.

Study protocol

Note where the full trial protocol can be accessed OR if not available, explain why.

Data collection

Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.

Outcomes

Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.

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, mosaicism, 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

Fetal livers were collected from embryos and mechanically dissociated into single-cell suspensions. Fetal liver cells were then either analyzed directly by flow cytometry or treated with drugs prior to downstream measurements.

Instrument	LSRFortessa cytometer (BD Biosciences).
Software	Data were collected using BD FACSDiva™ Software and analyse on FlowJo™ v10 Software.
Cell population abundance	Cells were not sorted by flow cytometry
Gating strategy	Cells were first gated based on size and granularity using FSC/SSC parameters. Doublets were excluded by FSC-A/FSC-H gating to retain single cells only. Live cells were selected using a viability marker, and lineage-positive cells were excluded using a cocktail of lineage-specific antibodies. The population of interest were then identified using specific antibodies as described in Figure 2.

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