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	Not applicable.
Data analysis	Data analysis was completed during each patient's initial diagnostic evaluation using the clinically validated pipeline which was also previously published in our group's research article in Nat Commun 9, 3962 (2018). https://doi.org/10.1038/s41467-018-06485-7.

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

All sequencing data are available through St. Jude Cloud Genomics Platform (https://platform.stjude.cloud/data/samples). Regarding sample ID, 'SJxxxxxx' used in the manuscript is equivalent to 'SJAMLxxxxxx' in St. Jude Cloud Genomics Platform.

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	Only biological attribute (sex) was relevant to the study and reported in the manuscript.
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable.
Population characteristics	The study cohort included 154 patients, and the median age at diagnosis was 11 years old (1 week – 22 years). Samples from the first available time point were analyzed, comprising 13 treatment-related AML (tAML), 27 relapsed AML cases of which the initial diagnosis and treatment were conducted outside St. Jude Children's Research Hospital (SJCRH), and 114 cases with de novo AML. Regarding tAML cases, past diagnosis was presented in the Supplementary Table S1.
Recruitment	Participants were not specifically recruited or selected for this study. A total of 154 pediatric and adolescent patients with AML, admitted to St. Jude Children's Research Hospital (SJCRH) (n=136) and/or enrolled in SJCRH-sponsored clinical trials (n=18), were included in the study cohort between 2016 and 2021. Informed consent was obtained from all patients for clinical genomics and research.
Ethics oversight	This study was reviewed and approved by the Institutional Review Board (IRB) at St. Jude Children's Research Hospital.

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	154 patients. A total of 154 pediatric and adolescent patients with AML, admitted to St. Jude Children's Research Hospital (SJCRH) (n=136) and/or enrolled in SJCRH-sponsored clinical trials (n=18), were included in the study cohort between 2016 and 2021. Informed consent was obtained from all patients for clinical genomics and research. The sample from the first available time point of each patient were used for the study.
Data exclusions	Not applicable.
Replication	In this study, findings are considered to be replicated if same results were obtained across different sequencing and/or testing platforms.
Randomization	Not applicable.
Blinding	Not applicable.

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

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	COLO 829 (CRL-1974, ATCC, USA) and COLO 829BL (CRL-1980, ATCC, USA)
Authentication	Commercially available cell lines from ATCC.
Mycoplasma contamination	No.
Commonly misidentified lines (See ICLAC register)	Not applicable.

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	Not applicable.
Study protocol	Not applicable.
Data collection	A total of 154 pediatric and adolescent patients with AML, admitted to St. Jude Children's Research Hospital (SJCRH) (n=136) and/or enrolled in SJCRH-sponsored clinical trials (n=18), were included in the study cohort between 2016 and 2021. Informed consent was obtained from all patients for clinical genomics and research. All clinical data were collected from electronic medical records of patients.
Outcomes	Not applicable.

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.