

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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ 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 Sequencing data were collected using Illumina sequencers. Digital droplet PCR were performed using Bio-Rad QX200 Droplet Digital PCR System.

Data analysis NGS data analysis pipeline for QBDA variant calling is available from Github (<https://github.com/wrj915/QBDA>). Alignment was performed using the Bowtie2 software. Digital droplet PCR data were analyzed using Bio-Rad QuantaSoft Software v1.4

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 main data supporting the results in this study are available within the paper and its Supplementary Information. Source data are provided with this paper. Raw sequencing data for QBDA AML panel can be found at <https://doi.org/10.6084/m9.figshare.15117642.v1> and <https://doi.org/10.6084/m9.figshare.15102276.v1>

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	No sample size calculation was carried out during experiment design. Clinical sample size was determined by availability.
Data exclusions	No sample was excluded.
Replication	The analytical performance of AML panel was assessed with negative reference sample in five replicates, and was assessed with positive reference sample in triplicates. There was only 1 false negative out of the 3 positive reference sample attempts, corresponding to $1-1/(22*3) = 98.5\%$ technical sensitivity. We observed only 1 false positive mutation call out of the 5 negative sample libraries. Therefore, the technical specificity of AML panel can be calculated as $1-1/(382*5) = 99.95\%$.
Randomization	Not relevant. Samples were obtained from the Leukemia Sample Bank at the MD Anderson Cancer Center based on availability.
Blinding	The clinical information for the clinical samples such as duration of remission and MRD results from multicolor flow cytometry in AML samples and treatment information for melanoma patients were blinded to researchers performing QBDA until the experiments and data analysis were complete.

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	Population characteristics including age, gender, diagnosis and treatment categories are summarized in Supplementary Data 3. All five AML patients have NPM1 mutation detected at diagnosis.
Recruitment	Samples were obtained from the Leukemia Sample Bank at the MD Anderson Cancer Center. These samples were obtained after consent provided by patients treated at MD Anderson. They were chosen randomly based on NPM1 mutational status and availability of sequential samples to allow genomic longitudinal analysis.
Ethics oversight	All procedures performed in studies involving human participants were approved by Institutional Review Board at MD Anderson, and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

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