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	Please see below
Data analysis	Softwares used for Demultiplexing and base calling: bcl2fastq2 (version 2.20.0) Software used for processing: Aligner & variant caller - DRAGEN (version 4.2.7). Software used for tertiary analysis: Emedgene (version 36.0) Database used for tertiary analysis: gnomAD (version 4.1) ClinVar (2025-07-06) OMIM (2025-08-20) DECIPHER (version 9.30) dbSNP 155 ClinGen (2025-08-21)

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

Deidentified aggregate data supporting the findings of this study are provided in the main Article, Figures, Source Data, Extended Data and Supplementary Files. These materials include clinical, demographics, genomic, diagnostic and clinical utility data underlying the reported analyses and figures. The raw whole-genome sequencing data generated in this study can be requested from the corresponding author (Ahmad.Tayoun@dubaihealth.ae) who will respond within two weeks from receipt of the request. Requests in line with the ethics approval of the study will be considered for data sharing.

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	This is a prospective rapid whole genome sequencing (rWGS) program implemented across neonatal and pediatric intensive care units within the Dubai healthcare system, involving 100 critically ill patients of equal gender distribution (53 males and 47 females). For comparison, a retrospective group of critically ill patients (N=100) referred to genetic testing from NICU/PICU before the launch of Little Falcon were randomly selected. Therefore, gender distribution was equal in this control group (53% females and 47% males).
Reporting on race, ethnicity, or other socially relevant groupings	The study cohort comprised 100 critically ill pediatric patients enrolled in a citywide rapid whole genome sequencing (rWGS) program through neonatal and pediatric intensive care units in Dubai, United Arab Emirates. The cohort represents a multiethnic population, predominantly of Arab (61%) and Asian (36%) origin. Specifically, the majority of participants were of Middle Eastern/Arab origin, with additional representation from South Asian (India, Pakistan, Bangladesh, SriLanka, and Nepal), Southeast Asian (Philippines), African (Cameroon and Comoros), and Western (Canada and Germany) populations. For comparison, a retrospective group of critically ill patients (N=100) referred to genetic testing from NICU/PICU before the launch of Little Falcon were randomly selected. The ethic distribution in this control group was similar to that in Little Falcon (69% Arabs, 23% Asians, and 8% others).
Population characteristics	Patient population included 100 critically ill neonatal and pediatric patients (87% < 1 years of age; 47% females) selected by neonatologists, pediatric specialists and genetic counselors following predefined inclusion criteria, focusing on patients with suspected monogenic disorders where a rapid diagnosis was anticipated to inform acute clinical management (Please refer to Figure 1B and Methods for more specific details on inclusion criteria). For comparison, a retrospective group of critically ill patients (N=100; 89% < 1 years of age; 53% females) referred to genetic testing from NICU/PICU before the launch of Little Falcon were randomly selected. Clinical indications in this group were consistent with that in Little Falcon cohort (53% single system disorders and 47% multisystem diseases or multiple congenital anomalies).
Recruitment	Please see above
Ethics oversight	Mohammed Bin Rashid University institutional review board (MBRU IRB #: DAHC-MBRU-IRB-2023-008) and the Dubai Scientific Research Ethics Committee (DSREC-08/2025_17).

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	One hundred critically ill pediatric patients, meeting eligibility criteria described above and in manuscript, underwent trio rapid whole genome sequencing. This sample size provides reasonable precision to assess implementation parameters and to estimate diagnostic yield, turnaround time and clinical utility, and to characterize the genetic architecture of critically ill children in this setting. Similarily, 100 cirtically ill patients

	(matched control group) referred to standard testing, predating Little Falcon, provided reasonable precision to compare diagnostic yield, turaround time and clinical utility.
Data exclusions	No data were excluded from the analyses
Replication	Not applicable.
Randomization	Patients in the control group were randomly selected from critically ill patients who were referred for genetic testing from NICU/PICU and whose clinical presentations suggest a possible genetic etiology according to the eligibility criteria for rWGS. This selection process was otherwise blind to all other variables, including genetics and clinical outcomes.
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

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 not a clinical trial.
Study protocol	The study protocol is summarized in the methods.
Data collection	This is included in the methods of the manuscript.
Outcomes	The primary outcomes included turnaround time, diagnostic yield and clinical utility.

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.*