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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	No software was used
Data analysis	Graphpad prism, Pymol v2.3.3, IntFOLD7, MultiFOLD, PINOT server, DISOPRED3 server, MEMSAT-SVM

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

Data are available from the corresponding author upon request

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	No sex or gender based analyses were performed.
Reporting on race, ethnicity, or other socially relevant groupings	Ethic backgrounds for each kindred were provided to highlight population level frequency of variants in this gene and to highlight the enrichment of the p.T352M in the European population.
Population characteristics	Patients ranged in age from <5years to 53 years; The cohort consisted of 4 males and 1 female proband; All patients demonstrated a history of postnatal growth restriction and a complex phenotype of varying clinical features.
Recruitment	Patients were recruited through the 100KGenomes project and through referral to our centre.
Ethics oversight	The study was approved by the Health Research Authority, East of England-Cambridge East Research Ethics Committee (REC reference 17/EE/0178)

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	NA
Data exclusions	NA
Replication	NA
Randomization	NA
Blinding	NA

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

Antibodies

Antibodies used	Rabbit anti-QSOX2 antibody (ab121376, RRID:AB_11128050, dilution 1:1000), Monoclonal ANTI-FLAG® M2 antibody (Sigma Aldrich F3165, RRID:AB_259529, dilution 1:1000), Rabbit anti-Phospho-Stat5 antibody (Tyr694) (Cell Signalling Technology D47E7, RRID:AB_10544692, dilution 1:500), Rabbit anti-phospho-Stat3 antibody (Tyr705) (Cell Signalling Technology D3A7,

RRID:AB_2491009, dilution 1:500), Rabbit anti-phospho-Stat1 antibody (Tyr701) (Cell Signalling Technology Clone 58D6, RRID:AB_561284, dilution 1:500), Rabbit anti-Tom20 antibody (Cell Signalling Technology D8T4N, RRID:AB_2687663, dilution 1:200), Rabbit anti-phospho-DRP1 (Ser616) (Cell Signalling Technology D9A1, RRID:AB_11178659, dilution 1:200), Rabbit anti-GAPDH antibody (ab9485, RRID:AB_307275, dilution 1:10,000), Mouse anti-Actin beta monoclonal antibody (ab6276, RRID:AB_2223210, dilution 1:10,000), Mouse anti-Histone Deacetylase 1 antibody (Santa-Cruz biotechnology sc-81598, RRID:AB_2118083, dilution 1:1000), Rabbit anti-GFP antibody (ab290, RRID:AB_303395, dilution 1:1000), Fluorescent probe - MitoTracker™ Red (M22425, Thermo Fisher Scientific), Rat anti-Human phospho-STAT5a/b Y694/Y699 (R&D Systems Clone MAB4190, dilution 1:300), Mouse anti-alpha Tubulin antibody DM1A (ab7291, RRID:AB_2241126, dilution 1:1000), Total OXPHOS Rodent WB Antibody Cocktail (ab110413, RRID:AB_2629281, dilution 1:500), Rabbit anti-Phospho-Akt (Ser473) antibody (Cell Signalling Technology D9E, RRID:AB_2315049, dilution 1:750), Rabbit anti-Akt (pan) antibody (Cell Signalling Technology C67E7, RRID:AB_915783, dilution 1:1000), Rabbit anti-MAP Kinase (ERK-1, ERK-2) antibody (Sigma Aldrich M5670, RRID:AB_477216, dilution 1:1000), Monoclonal anti-MAP Kinase, Activated (Diphosphorylated ERK-1&2) antibody (Sigma Aldrich M9692, RRID:AB_260729, dilution 1:1000), Goat anti-Rat IgG (H+L) Highly Cross-Adsorbed Secondary Antibody Alexa Fluor Plus 488 (A48262 RRID:AB_2896330, dilution 1:500), Goat anti-mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody Alexa Fluor Plus 488 (A32723, RRID:AB_2633275, dilution 1:500), Goat anti-Rabbit IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor Plus 647 (A32733, RRID:AB_2633282, dilution 1:500), IRDye® 800CW Goat anti-Mouse IgG (RRID:AB_10793856, dilution 1:5000), IRDye® 800CW Goat anti-Rabbit IgG (RRID:AB_10796098, dilution 1:5000), IRDye® 680RD Goat anti-Mouse IgG (RRID:AB_2651128, dilution 1:5000), IRDye® 680RD Goat anti-Rabbit IgG (RRID:AB_2721181, dilution 1:5000), Tetramethylrhodamine, ethyl ester (TMRE, ab113852).

Validation

All antibodies were validated by suppliers and in-house to ensure reproducibility.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Fibroblasts were obtained from patient and control skin biopsies, HEK-GHR cells were obtained from Professor Richard Ross
Authentication	These cell lines were not authenticated
Mycoplasma contamination	Cell lines tested negative for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	NA

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.*