

## 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

NMR: Bruker Topspin 3.1  
Western Blot: LICOR Odyssey 2.1  
Plate reader: TECAN SparkControl 2.1  
LC-MS: Waters MassLynx 4.2  
Fluorescence scanner: GE Typhoon FLA 9000

Data analysis

GraphPad Prism 9.0  
Mestronova 14.1.2  
ImageJ 2.3.0  
MaxQuant 2.0.3.1  
CCP4i2 1.0.2 (including iMosflm 7.4.0, Aimless 0.7.4 and Phaser 2.8.3 modules)  
Coot 0.9.6  
Phenix 1.19.2

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](#)

Atomic coordinates and structure factors for the reported crystal structures have been deposited with the Protein Data Bank (PDB), with the following accession numbers: K-Ras(G12S)•GDP – 7TLK; K-Ras(G12S)•GDP•1 – 7TLE; K-Ras(G12S)•GDP•5 – 7TLG. Uncropped, unprocessed gel images are provided as Source Data files accompanying this paper.

## 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://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

Data exclusions

Replication

Randomization

Blinding

## 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                                     |
|-------------------------------------|---|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies            |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Human research participants      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern     |

### Methods

- | n/a                                 | Involved in the study                           |
|-------------------------------------|---|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Antibodies

Antibodies used

P-ERK [T202/Y204] Cell Signaling Technology 9101, Polyclonal  
 Total ERK Cell Signaling Technology 4695, Clone 137F5  
 Pan-Ras Abcam 108602, Clone EPR3255  
 Ras(G12S) NewEast Bio 26186, Clone# Not Available  
 GAPDH Proteintech 60004-1-Ig, Clone 1E6D9  
 goat anti-rabbit IgG-IRDye 800, LI-COR, 926-32211, Clone# Not Available  
 goat anti-mouse IgG-IRDye 680, LI-COR, 926-68070, Clone# Not Available

## Validation

The validation of the Ras(G12S) antibody is included in the Supplementary Information. All other commercial antibodies have been validated by the manufacturers (see website links below)  
 P-AKT [S473]: <https://www.cellsignal.com/products/primary-antibodies/phospho-akt-ser473-d9e-xp-rabbit-mab/4060>  
 P-AKT [T308]: <https://www.cellsignal.com/products/primary-antibodies/phospho-akt-thr308-244f9-rabbit-mab/4056>  
 AKT: <https://www.cellsignal.com/products/primary-antibodies/akt-pan-40d4-mouse-mab/2920>  
 P-ERK [T202/Y204]: <https://www.cellsignal.com/products/primary-antibodies/phospho-p44-42-mapk-erk1-2-thr202-tyr204-antibody/9101>  
 Total ERK: <https://www.cellsignal.com/products/primary-antibodies/p44-42-mapk-erk1-2-137f5-rabbit-mab/4695>  
 Pan-Ras: <https://www.abcam.com/ras-antibody-epr3255-ab108602.html>  
 GAPDH: <https://www.ptglab.com/products/GAPDH-Antibody-60004-1-Ig.htm>  
 Goat anti-rabbit IgG-IRDye 800: <https://www.licor.com/documents/rfm2hw40wf33p06f3ndjrcorwi5usbft>  
 Goat anti-mouse IgG-IRDye 680: <https://www.licor.com/documents/7boh1sfzugcc22fh0um00cvz8ocizf>

## Eukaryotic cell lines

### Policy information about [cell lines](#)

## Cell line source(s)

A549: UCSF Cell Culture Facility  
 HKA1: Japanese Collection of Research Biosources Cell Bank (JCRB)  
 KMS20: Japanese Collection of Research Biosources Cell Bank (JCRB)  
 LS123: American Type Culture Collection (ATCC)  
 H358: American Type Culture Collection (ATCC)  
 A375: American Type Culture Collection (ATCC)  
 SW1990: American Type Culture Collection (ATCC)  
 Ba/F3: German Collection of Microorganisms and Cell Cultures GmbH (DSMZ)  
 EcoPack 293: Clonetech

## Authentication

Cell lines from JRCB, DSMZ and ATCC were STR profiled by the manufacturer.  
 A549 cells were STR profiled by the UCSF Cell Culture Facility.  
 EcoPack 293 is a commercial cell line established and maintained by the manufacturer (Clonetech) and authentication is provided by the manufacturer.

## Mycoplasma contamination

All cell lines were tested mycoplasma negative using MycoAlert™ Mycoplasma Detection Kit (Lonza).

Commonly misidentified lines  
(See [ICLAC](#) register)

None found.