

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	Crystallographic data were collected at the following European synchrotron radiation facilities: PetralIII (beamlines P13 and P14), Soleil (beamline Proxima2A), ESRF Grenoble (beamline ID23-1). SAXS data was collected at the Soleil synchrotron (beamline SWING). SEC-MALLS data were measured using a miniDAWN TREOS instrument using Astra 6.1.6 (Wyatt Technology). ITC data was collected on a MicroCal PEAQ-ITC instrument using the PEAQ-ITC data collection software (version 1.1.0.1262). BLI data was collected using an Octet Red 96 instrument with the Data collection software (version 9.0.0.14).
Data analysis	Software used to process, analyse and validate the crystallographic data was provided by the XDS-suite (multiple versions during 2018-2020), PHENIX version 1.17.1. (including phaser, phenix.autosol, phenix.hyss, Resolve, phenix.refine, and phenix.xtriage), autoBuster version 2.11.2 (Global Phasing Ltd.). Structures were built using Coot (versions 0.8.8 and 0.9) and ARP/wARP v8.0. SEC-MALLS results were analysed using Astra 6.1.6 (Wyatt Technology). BLI data analysis was performed using the Data analysis software (version 9.0.0.14). SAXS data was analyzed using programs from the RAW suite v2.1.0 and the AllosMod-FoXS web server. ITC data was analyzed using the PEAQ-ITC data analysis software (version 1.1.0.1262). Plotting and statistical analysis of cellular assay data using GraphPad prism 8/9. Structures were analyzed with Pymol version 2.0.5 and ChimeraX version 1.1. Sequence alignments were created and edited using the MAFFT, Cobalt and ESPript 3.0 web servers.

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](#)

Coordinates and structure factors for the complexes have been deposited in the Protein Data Bank (PDB) under accessions 7NWZ (ALKTG—ALKAL2), 7NX0 (LTKTG—ALKAL1—Nb3.16), 7NX1 (LTKTG), 7NX2 (unbound Fab324), 7NX3 (ALKTG-EGFL—Fab324), 7NX4 (ALKTG-EGFL).

Most common SNPs were obtained from the COSMIC database (<https://cancer.sanger.ac.uk/cosmic>) and gnomAD database (<https://gnomad.broadinstitute.org>).

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	No sample size calculation was performed. All cellular experiments were successfully reproduced in triplicate. All biophysical experiments successfully reproduced with at least two separate protein batches as indicated in the figure legends.
Data exclusions	No data were excluded from the analyses.
Replication	All cellular experiments were successfully reproduced in triplicate. All biophysical experiments successfully reproduced with at least two separate protein batches as indicated in the figure legends.
Randomization	Our structural and biophysical studies did not require randomization.
Blinding	Our study did not involve experiments where blinding was required or appropriate. None of the experiments involved human or animal models or group allocation.

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

Antibodies

Antibodies used	For Western blotting, the following antibodies were used: ALK (Purchased from Cell Signaling Technologies; catalog no.: 3633; dilution: 1:1,000), Phospho-ALK (Tyr1278) (Cell Signaling Technologies; 6941; 1:250), Phospho-ALK (Tyr1604) (Cell Signaling Technologies; 3341; 1:250), Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (Cell Signaling Technologies; 4370; 1:2,000), p44/42 MAPK(Erk1/2) (Cell Signaling Technologies; 9102; 1:1,000), β -actin (Sigma-Aldrich; A-5441; 1:2,000), GAPDH (GENETEX; GTX100118; 1:2000). VHH antibody 3.16 was obtained in this work and used for crystallization.
Validation	According to manufacturer's specifications via the corresponding websites. Cell Signaling validates all their antibodies in-house, in multiple research applications. This statement can be found at their website at https://www.cellsignal.com/about-us/cst-antibody-

performance-guarantee.

Sigma-Aldrich validates their antibodies for each recommended immunodetection application according to their standard antibody validation processes: <https://www.sigmaaldrich.com/BE/en/products/protein-biology/antibodies/enhanced-validation-ab>

Genetex validates their antibodies using 5 different methods as indicated in their 5 pillars https://www.genetex.com/MarketingMaterial/Index/five_pillars

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Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)

The HEK293S MGAT-/- cell line was obtained from Philip J. Reeves (Reeves et al. 2002 PNAS). HEK293T/S were obtained from Nico Callewaert (Lin et al. 2014 Nature Communications). Ba/F3 cells were obtained from DSMZ.

Authentication

An aliquot of each cell line was authenticated using DSMZ/Clontech DNA fingerprinting.

Mycoplasma contamination

All cell lines are frequently tested for mycoplasma contamination. Cell lines used in this study were verified to be mycoplasma negative before undertaking any experiments with them.

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

No commonly misidentified cell lines were used.