

## 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

- |                                     |                                     |                                                                                                                                                                                                                                                            |
|-------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                    |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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** Metamorph Premier ver 7.8.12.0 (Molecular Devices, LLC, USA) for image acquisition, FluorEssence ver 6.5 for fluorescence measurements, Image Lab™ Software 6.0.0 for PAGE image acquisition Section: Online methods, pCLAMP 11.0 (Molecular Devices) and Graphpad (Prism) computer software for Voltage protocols and data analysis.

**Data analysis** Origin 2018 b9.4.0.220 (OriginLab Corporation, Northampton, MA, USA) for data plotting, ImageJ/Fiji 1.52e a for image analysis.

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 raw data supporting Figures 1–6, Extended data Figures, Supplementary Figures respectively, are available for public access at Figshare.  
[https://figshare.com/articles/dataset/Figure\\_1/23713359](https://figshare.com/articles/dataset/Figure_1/23713359)

[https://figshare.com/articles/dataset/Figure\\_2/23713554](https://figshare.com/articles/dataset/Figure_2/23713554)  
[https://figshare.com/articles/dataset/Figure\\_3/23713776](https://figshare.com/articles/dataset/Figure_3/23713776)  
[https://figshare.com/articles/dataset/Figure\\_4/23713821](https://figshare.com/articles/dataset/Figure_4/23713821)  
[https://figshare.com/articles/dataset/Figure\\_5/23713833](https://figshare.com/articles/dataset/Figure_5/23713833)  
[https://figshare.com/articles/dataset/Figure\\_6/23713851](https://figshare.com/articles/dataset/Figure_6/23713851)  
[https://figshare.com/articles/dataset/Extended\\_data\\_figures/23713899](https://figshare.com/articles/dataset/Extended_data_figures/23713899)  
[https://figshare.com/articles/dataset/Supplementary\\_Figures/23713947](https://figshare.com/articles/dataset/Supplementary_Figures/23713947)

## Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

|                             |     |
|-----------------------------|-----|
| Reporting on sex and gender | N/A |
| Population characteristics  | N/A |
| Recruitment                 | N/A |
| Ethics oversight            | N/A |

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](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 statistical analysis was done to predetermine sample size. Sample size is counted by analysis software or manually. Sample size was chosen based on adequate representation of the population. Sample sizes are sufficient because distribution of population is close to normally distributed. |
| Data exclusions | No data were excluded from the analyses.                                                                                                                                                                                                                                                           |
| Replication     | We perform all experiments except 2 ions measurement (2-IM) imaging in triplicates to ensure reproducibility. 2-IM imaging was performed in duplicate to ensure reproducibility. All replications were successful.                                                                                 |
| Randomization   | Allocation was random. Cultured dishes containing various types of cells were randomized for selection in imaging experiments and biochemical assays.                                                                                                                                              |
| Blinding        | The investigators were not blinded during data acquisition and analysis.                                                                                                                                                                                                                           |

## 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"/> 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 | Rabbit anti-Kv11.1 antibody (Alomone Catalog no. APC-062, APC062AN1702)<br>Mouse monoclonal anti-58K antibody (Abcam, Catalog no. ab27043, 58K-9, GR33959595)<br>Mouse monoclonal Transferrin receptor antibody (Thermofischer, Catalog no. 13-6800, H68.4, YA366564)<br>Goat anti-rabbit secondary antibody conjugated with Alexa Fluor 647 (Life Technologies, cat. no. A21244)<br>Goat anti-Mouse secondary antibody conjugated with Alexa-488 (Life Technologies, cat. no. A11001, 1613346) |
| Validation      | Rabbit monoclonal anti-Kv11.1 antibody (Alomone Catalog no. APC-062) validation and relevant citation: Hall, A. R. et al., Front. Physiol. 9:584. (2018).<br>mouse monoclonal anti-58K antibody (Abcam Catalog no. ab27043): Yang, B. et al., J Virol. 95(8):e02101-20 (2021).<br>mouse monoclonal Transferrin receptor antibody (Thermofischer Catalog no. 13-6800): Feng, H. et al., Cell Reports 30, 3411–3423 (2020).                                                                       |

## Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cell line source(s)                                                  | Human embryonic kidney cells (HEK 293T) cells were gifts from B. Dickinson (Department of Chemistry, University of Chicago).<br>Human embryonic kidney 293 (HEK293) cell lines expressing wild-type Kv11.1 (WT) or the trafficking-deficient G601S-Kv11.1 channel proteins are from Brian P. Delisle lab (Department of Physiology, University of Kentucky College of Medicine)<br>BMDM WT and TWIK2 KO cells are from Asrar B Malik (Department of Pharmacology and Regenerative Medicine, The University of Illinois College of Medicine, Chicago, IL 60612) |
| Authentication                                                       | No further authentication was performed after receiving the cells as a gift.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Mycoplasma contamination                                             | We routinely check our cell lines for Mycoplasma contamination using Hoechst staining and all cell lines used in this study turned out to be negative for Mycoplasma contamination.                                                                                                                                                                                                                                                                                                                                                                            |
| Commonly misidentified lines<br>(See <a href="#">ICLAC</a> register) | No commonly misidentified cell lines were used in this study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |