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

Genetic data collected as described previously (Kaplanis et al., Nature 2020, https://doi.org/10.1038/s41586-020-2832-5). This software includes: Genome Analysis Toolkit (GATK); Ensembl Variant Effect Predictor (VEP); DeNovoGear; FastQC; GATK Haplotype Caller; GenotypeGVCF; BioR Toolkit. Functional (electrophysiological) data were collected using Clampex 11 and HEKA PatchMaster 2x91.

Data analysis

Functional data were analysed using commonly available software (Clampfit v11 and Origin v2019b) as described in the methods.

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 authors confirm that all relevant data are included in the article and/or its supplementary information. For some probands only AHI and nadir SpO2 values from
Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender

Population characteristics

Probands were recruited as defined by criteria specified in the original study (Kaplanis et al, Nature 2020; https://doi.org/10.1038/s41586-020-2832-5). Covariate-relevant population characteristics are N/A for this study.

Recruitment

Probands were recruited as defined by criteria specified in the original study (https://doi.org/10.1038/s41586-020-2832-5).

Ethics oversight

Ethical approval for the original study (Kaplanis et al, Nature 2020; https://doi.org/10.1038/s41586-020-2832-5) was provided by the UK Research Ethics Committee approval [10/H0305/83, granted by the Cambridge South REC, and GEN/284/12 granted by the Republic of Ireland REC].

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-list.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

No statistical methods were used to predetermine sample sizes. Required experimental sample sizes were estimated based on previous established protocols in the field. The sample sizes were adequate as the differences between experimental groups were reproducible. For all functional data the results from at least 3 independent biological replicates were compared.

Data exclusions

No exclusion criteria were pre-established. No data was excluded from the measurements shown.

Replication

All attempts to replicate the experiments were successful. Number of biological replicates (n) are illustrated in the respective figure legends or graphs.

Randomization

Not usually relevant for this type of study involving experimental analysis of small to medium-sized samples where the measured effects are large and causality is obvious.

Blinding

As we were not comparing animal or human populations with individuals assigned to groups, it was not relevant to do double blind tests.

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

| r/a | Involved in the study |
|-----|-----------------------|
| ☑  | Antigens              |
| ☑  | Eukaryotic cell lines |
| ☑  | Palaeontology and archaeology |
| ☑  | Animals and other organisms |
| ☑  | Clinical data         |
| ☑  | Dual use research of concern |

Methods

| r/a | Involved in the study |
|-----|-----------------------|
| ☑  | ChIP-seq              |
| ☑  | Flow cytometry        |
| ☑  | MRI-based neuroimaging |
**Animals and other research organisms**

Policy information about [studies involving animals](#), [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#).

| Category               | Information                                                                                                                                                                                                 |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Laboratory animals     | No live animals used directly in this study. All oocytes (1st Grade) from Xenopus laevis were purchased directly from Ecocyt Biosciences (Dortmund, Germany) for microinjection of mRNA.                               |
| Wild animals           | No wild animals used in this study.                                                                                                                                                                            |
| Reporting on sex       | Only females used for production of oocytes.                                                                                                                                                                   |
| Field-collected samples| N/A                                                                                                                                                                                                        |
| Ethics oversight       | N/A - oocytes purchased directly from Ecocyt Biosciences, Germany                                                                                                                                           |

Note that full information on the approval of the study protocol must also be provided in the manuscript.