

## Reporting Summary

Nature Research 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 Research 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 checked="" type="checkbox"/> | <input 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 checked="" type="checkbox"/> | <input 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 checked="" type="checkbox"/> | <input 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 checked="" type="checkbox"/> | <input 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 | We extracted common USP9X variants from Genome Aggregation Database (gnomAD V2.1.1) and USP9X cancer variants from Catalogue of Somatic Mutations in Cancer (COSMIC V90) database. Structural modelling was performed using PyMol software (Schrödinger).                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Data analysis   | Two-proportion z-test for enrichment of variants in the catalytic domain was conducted using <a href="http://www.sthda.com/english/wiki/two-proportions-z-test-in-r">http://www.sthda.com/english/wiki/two-proportions-z-test-in-r</a> . Variant predictions were performed using Annovar accessed via the webserver <a href="http://wannovar.wglab.org/">http://wannovar.wglab.org/</a> . 2-tailed equal variance Student's t-test were conducted with Microsoft Excel. USP9X tolerance to variation landscape was outputted using the Metadome Version 1.0.1 webserver at <a href="https://stuart.radboudumc.nl/metadome/dashboard">https://stuart.radboudumc.nl/metadome/dashboard</a> . |

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 Research [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 list of figures that have associated raw data
- A description of any restrictions on data availability

Additional data and materials from this study are available from the authors on reasonable request, subject to compliance with our obligations under human research ethics.

## 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     | Number of individual USP9X mutations analysed in this study was determined by availability of such data, i.e. the USP9X cohorts were assembled retrospectively. Number of comon and cancer variants was determined by availability of such data within the Gnomad and COSMIC data bases listed above.                                                                                              |
| Data exclusions | For comparisons of USP9X varaints against gnomAD common varinst we excluded gnomAD common varinats with allele frequeuncy > 1:100,000 as gnomAD may contain ultra rare varaints of borderline pathogenicity. For spatial/structual comparison of USP9X variants woth COSMIC variants we excluded COSMIC variants with CADD score <30 so as to focus on those with strong evidence of pathogenicity |
| Replication     | Clinical phenotype of our USP9X female cohorts was compared to other USP9X female and male cohorts.                                                                                                                                                                                                                                                                                                |
| Randomization   | Participants were grouped based on sex, and USP9X variant type.                                                                                                                                                                                                                                                                                                                                    |
| Blinding        | Blinding was not possible as numbers of participants and the variants in each cohort is are identifiable parameters.                                                                                                                                                                                                                                                                               |

## 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 checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                             |
| <input checked="" type="checkbox"/> | <input 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 type="checkbox"/>            | <input checked="" 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 type="checkbox"/>            | <input checked="" type="checkbox"/> MRI-based neuroimaging |

## Human research participants

Policy information about [studies involving human research participants](#)

|                            |                                                            |
|----------------------------|------------------------------------------------------------|
| Population characteristics | Female individuals with USP9X variants                     |
| Recruitment                | Retrospectively recruited                                  |
| Ethics oversight           | Womens and Children's Health Network, Adelaide, Australia. |

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

## Magnetic resonance imaging

### Experimental design

|                                 |                                            |
|---------------------------------|--------------------------------------------|
| Design type                     | Resting                                    |
| Design specifications           | Varaiable. Data collected Retrospectively. |
| Behavioral performance measures | N/A                                        |

## Acquisition

|                               |                                           |                                              |
|-------------------------------|-------------------------------------------|----------------------------------------------|
| Imaging type(s)               | Variable. Data collected Retrospectively. |                                              |
| Field strength                | Variable. Data collected Retrospectively. |                                              |
| Sequence & imaging parameters | Variable. Data collected Retrospectively. |                                              |
| Area of acquisition           | Variable. Data collected Retrospectively. |                                              |
| Diffusion MRI                 | <input type="checkbox"/> Used             | <input checked="" type="checkbox"/> Not used |

## Preprocessing

|                            |                                           |
|----------------------------|-------------------------------------------|
| Preprocessing software     | Variable. Data collected Retrospectively. |
| Normalization              | Variable. Data collected Retrospectively. |
| Normalization template     | Variable. Data collected Retrospectively. |
| Noise and artifact removal | Variable. Data collected Retrospectively. |
| Volume censoring           | Variable. Data collected Retrospectively. |

## Statistical modeling & inference

|                                                                           |                                                                                                                  |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Model type and settings                                                   | N/A                                                                                                              |
| Effect(s) tested                                                          | N/A                                                                                                              |
| Specify type of analysis:                                                 | <input checked="" type="checkbox"/> Whole brain <input type="checkbox"/> ROI-based <input type="checkbox"/> Both |
| Statistic type for inference<br>(See <a href="#">Eklund et al. 2016</a> ) | N/A                                                                                                              |
| Correction                                                                | N/A                                                                                                              |

## Models & analysis

|                                     |                                                                       |
|-------------------------------------|-----------------------------------------------------------------------|
| n/a                                 | Involved in the study                                                 |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Functional and/or effective connectivity     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Graph analysis                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Multivariate modeling or predictive analysis |