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Last updated by author(s): Jul 12, 2020

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	
☐	☒	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	Acqknowledge software was used for data collection (version 4.4.2)
Data analysis	ImageJ (version 2.0.0-rc-49/1.51d), and Acqknowledge software (version 4.4.2) were used, and versions added to the supplementary information. Code availability statement in manuscript: "Code for calcium imaging analysis is previously published13. Matlab (R2018b) code was used for cystometry analysis and is available at: https://github.com/PatapoutianLab/cystometry."

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

The raw data that support the findings of this study are available from the corresponding author upon reasonable request.

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 statistical test was used to pre-determine sample size. Instead, sample size was determined by animal availability and previous studies in the field, which found these sample sized sufficient to detect deficits during cystometry (Keller et al., 2018 PMID: 30104734) and histological differences in remodeling and behavior (Everaerts and Zhen, 2010, PMID: 20956320)
Data exclusions	We established exclusion criteria prior to collecting cystometry data: data from the first 30 minutes of cystometry recording was not used because bladder muscle activity has often not stabilized. Moreover, animals that displayed bladder leaking during recording were excluded from analysis, as leaking indicated a flawed seal and thus inaccurate filling responses.
Replication	FISH experiments were independently replicated 2-3 times with the same results. Cystometry recordings were performed in independent male and female cohorts, and results were replicated. To verify the reproducibility of experimental findings, we restricted the time of day that cystometry recordings were done (Zeitgeber 8-14) and we performed every experiment in a cohort of male and female mice to compare to their wildtype littermates.
Randomization	The order of recordings for different genotypes was randomized. Beyond this, assigning animals to experimental groups is not relevant to this study, as the groups are defined by genotype. Animals of different sexes were analyzed independently to remove this covariate.
Blinding	The experimenter was blind to genotype when possible for all experiments. HoxB8Cre+;Piezo2f/f knockout mice have obvious motor impairments, so it was impossible to keep the experimenter blind for these groups.

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

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Mice were kept in standard housing with 12 h light/dark cycle set with lights on from 6 AM to 6 PM, with room temperature kept around 72 degrees Fahrenheit, with humidity between 30-80 % (not controlled). Adult male and female mice were used as indicated in the text. Age-matched knockout and wildtype littermates were tested at the same age in each cohort, but ages tested ranged from 5-12 months). The HoxB8Cre;Piezof/f mouse line has been previously described11. GCaMP6f+/+ mice (B6;129S-Gt(ROSA)26Sortm95.1(CAG-GCaMP6f)Hze/J, Jackson Laboratory: Ai95, #024105) were bred to Piezo2f/f mice as described previously13,35 . Piezo2f/f mice were mated with SNSCre mice29 or UPK IICre mice (B6(129)-Tg(Upk2-cre)1Rkl/WghJ , Jackson Laboratory: #029281) to create sensory-neuron specific and urothelial specific Piezo2 knockout animals, respectively. Each of these Cre lines was also crossed with Ai9 mice (B6.Cg-Gt(ROSA)26Sortm9(CAG-tdTomato)Hze/J, Jackson Laboratory: # 07909) to assess Cre expression.
Wild animals	No wild animals were used in this study
Field-collected samples	No field collected samples were used in this study.

Ethics oversight	All experiments were performed within the protocols and guidelines approved by the Institutional Animal Care and Use Committees of The Scripps Research Institute in compliance with regulatory standards established by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Twelve patients with PIEZO2 loss-of-function mutations from 11 families (N=4 males and 8 females, ranging in age from 4 to 43) were evaluated at the National Institutes of Health (NIH) under research protocol approved by the Institutional Review Boards of National Institute of Neurological Disorders and Stroke (NINDS, protocol 12-N-0095) between April of 2015 and May of 2020. Written informed consent and/or assent (for minor patients) was obtained from each participant in the study. Genotype information can be found in Extended Data Table 1, along with past treatments and diagnoses.
Recruitment	Patients were recruited on the basis of their biparentally inherited bi-allelic homozygous or compound heterozygous nonsense variant mutations in the Piezo2 gene. Patients with PIEZO2 loss of function either found us, or were referred to our group through our network of international collaborators. The nature of this group means that we are only analyzing patients without functional Piezo2, which is the goal of the study.
Ethics oversight	Research protocol approved by the Institutional Review Boards of National Institute of Neurological Disorders and Stroke (NINDS, protocol 12-N-0095)

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	This is not a clinical trial, but approval was through: NINDS, protocol 12-N-0095
Study protocol	NINDS, protocol 12-N-0095
Data collection	Data was collected at the NIH between April of 2015 and May of 2020.
Outcomes	No outcomes measured.