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Corresponding author(s): J BRENT RICHARDS
DAVID M EVANS

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 Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Data from the UK Biobank were downloaded via their FTP protocols
Data analysis	BOLT-LMM, BOLT-REML, GCTA, FINEMAP, LDSTORE, BGENIX, R v3.4.2, Plink2, EasyStrata, METAL, Bedtools, LDSC, Trimmomatic, BWA, Hotspot2, UCSC liftOver, STAR, HTseq-count, HiC-Pro, Homer, GOTHiC, Juicer, FUMA, VEP, FastPCA, EMCluster, WikiPathways, Image Lab 5.1, GraphPad Prism, CehmoSpec v4.2.8, MESS v0.3-2

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/reviewers upon request. 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

Human genotype and phenotype data on which the results of this study were based are available upon application from the UK Biobank ("URLs"). GWAS summary

statistics for eBMD and fracture can be downloaded from the GEFOS website ("URLs"). RNA-seq and ATAC-seq data generated for human osteoblast cell lines, including re-called DHS peaks from human primary osteoblasts, can be downloaded from the Gene Expression Omnibus (accession number GSE120755). Mouse phenotype data are available online from the IMPC ("URLs") and OBCD ("URLs"). Analysis scripts available by request from the authors.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	Drawing upon data from the UK Biobank full release, we applied stringent quality control criteria to select 424,482 participants for GWAS. Participants were selected if they had high-quality quantitative heel ultrasound data or fracture data and if they were of a White British genetic ethnicity. These sample sizes were sufficient for GWAS and represent the largest sample size to-date for any musculoskeletal trait.
Data exclusions	We excluded participants if they were missing covariates pertinent to the association testing using pre-determined criteria (i.e. if the data were missing, the participants were not included in the GWAS). This is because participants lacking covariates for association testing cannot be fit properly to our mixed-model approach. We also manually filtered for obvious outliers by observing the distributions of the data and removing individuals far exceeding the tail ends of the data.
Replication	We performed fracture GWAS replication with 23andMe, Inc. We took our top findings from our fracture GWAS and all findings replicated successfully.
Randomization	Participants were recruited at various sites through the UK without any selection criteria. We do adjust for genotyping chip in our association studies, as this assignment was not random.
Blinding	Blinding is not relevant to our study as the participants represent the general population of the UK.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	DAAM2 antibody: Sigma life science, catalog #HPA051300, clone #EPR10797(B, lot #r61164, dilution: 1/200 Goat anti-rabbit igG Alexa Fluor 488: Abcam, catalog #ab150077, clone number: Non Applicable, lot #GR315933-2, dilution 1/1000.
Validation	Anti-DAAM2 antibody from Sigma life science was validated by Human Protein Atlas: "For each antibody, the observed staining in the different cell lines is assigned a validation score based on concordance with available experimental gene/protein characterization data in the UniProtKB/Swiss-Prot database. The validation scores for up to three cell lines are merged into one of the main categories; Supported, Approved, or Uncertain, to represent the overall antibody staining in all analyzed cell lines. Anti-DAAM2 antibody is Approved meaning that one/multiple location(s) with no available experimental gene/protein characterization data and/or one/multiple location(s) where experimental gene/protein characterization data is partly supporting and partly conflicting." Goat anti-rabbit IgG Alexa Fluor 488 was validated by Abcam using immunofluorescence of HeLa cells stained with Anti-alpha Tubulin antibody [DM1A] and a loading Control (ab7291).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	All the cell lines were purchased form ATCC in Feb 2017: SaOS-2 (ATCC HTB-85), MG-63 (ATCC CRL-1427), U-2 OS (ATCC HTB-96) and HOS (ATCC CRL-1543)
Authentication	Growth properties and morphology have been checked by visual observation. Species determination have been determined by COI assay and STR analysis. Mycoplasma contamination were evaluated by Hoechest DNA stain, Agar culture and PCR-based assay. All the certificate of analysis could be find on line with the lot number. SaOS-2 lot number #63360718, MG-63 lot number #63045804, U-2 OS lot number #64048673 and HOS lot number #630887044
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	1) Knockout mice were generated at the Wellcome Trust Sanger Institute for the International Mouse Phenotyping Consortium. Skeletal samples from female 16 week old C57BL/6 wild type and mutant mice in an identical genetic background were analysed. 2) For detailed phenotype analysis Daam2 mice were re-derived at the Garvan Institute, Sydney, Australia. Skeletal samples from male and female 16 week old C57BL/6 wild type and Daam2 heterozygous and homozygous mutant mice in an identical genetic background were analysed. 3) Primary cultures of bone marrow derived osteoclasts and calvarial osteoblasts were obtained from WT (n=10) and Daam2 heterozygous (n=8) and homozygous knockdown (n=20) mice for in vitro studies.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.