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

☐ 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

No software was used

Data analysis

Comparison of variants across species:

- R 3.6.1
- bedtools 2.29.2
- tabix 0.2.6
- bcftools 1.9
- vcftools 0.1.13
- plink 1.9

Variant annotation and machine learning:

- bedtools 2.30.0
- samtools 1.10
- bcftools 1.10.2
- vep release/103
- python 3.6.10
- pandas 1.1.5
- pybigwig 0.3.17
- scikit learn 0.24.2
- shap 0.39.0
- xgboost 0.26.1
- sklearn 1.4.2
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 location of all GTEx variants tested was obtained from: https://storage.googleapis.com/gtex_analysis_v8/reference/GTEX_Analysis_2017-06-05_v8_WholeGenomeSeq_838Indiv_Analysis_Freeze.lookup_table.txt.gz. Those that were significant from: https://storage.googleapis.com/gtex_analysis_v8/single_tissue_qtl_data/GTEX_Analysis_v8_eQTL.tar. The three sets of fine-mapped GTEx variants from https://storage.googleapis.com/gtex_analysis_v8/single_tissue_qtl_data/. UK biobank fine-mapped results come from table S10 here: https://static-content.springer.com/esm/art%3A10.1038%2Fs41588-020-00735-5/MediaObjects/41588_2020_735_MOESM3_ESM.xls and pathogenic ClinVar variants from here: https://ftp.ncbi.nlm.nih.gov/pub/clinvar/vcf/GRCh38/clinvar.vcf.gz. The cattle and water buffalo polymorphism data used are described here https://www.nature.com/articles/s41467-020-18550-1#data-availability. The pig polymorphism data was downloaded from here ftp://download.big.ac.cn/GVM/Sus_scrofa/SNP/detailed.vcf/, the dog polymorphisms from https://sra-pub-rgs-1.s3.amazonaws.com/SRR189892/722q990SNP.INDEL.chrAll.vcf.1 and the human data from http://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/.

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 | The entire available genetic cohorts were used in these analyses. However we explore the effect of sample size in Figure 1A, illustrating that the data used picks up the majority of expected shared variants. |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data exclusions | No data exclusions |
| Replication | Not relevant to this study as intersecting genetic variants |
| Randomization | Not relevant to this study as samples within species were not allocated to groups |
| Blinding | Not relevant to this study as samples within species were not allocated to 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.
### Methods

- Involving in the study:
  - Clinical data
  - Human research participants
  - Animals and other organisms
  - Eukaryotic cell lines
  - Archaeological and paleontological materials
  - Other research materials

- Out of the study:
  - Dual use research of concern
  - Flow cytometry
  - MRI and neuroimaging
  - ChIP-seq
  - Antibodies

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**Note:** The table above outlines the methods and materials involved in the study.