

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  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( <i>n</i> ) for each experimental group/condition, given as a discrete number and unit of measurement   |
| <input type="checkbox"/>            | <input checked="" 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 type="checkbox"/>            | <input checked="" type="checkbox"/> A description of all covariates tested   |
| <input type="checkbox"/>            | <input checked="" 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 type="checkbox"/>            | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i> ) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted<br><i>Give P values as exact values whenever suitable.</i>                     |
| <input type="checkbox"/>            | <input checked="" 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 type="checkbox"/>            | <input checked="" type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i> ), 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 do not directly collect data. We used summary statistics from published studies.   |
| Data analysis   | <p>The X-ING method is implemented in a publicly available R package (see <a href="https://github.com/ylustat/X.ING">https://github.com/ylustat/X.ING</a>). The code and data to reproduce the simulations and analyses can be found at <a href="https://github.com/ylustat/XING-Analysis">https://github.com/ylustat/XING-Analysis</a>.</p> <p>Software used for data analysis:<br/>fastQTL version 2.184,<br/>plink version 1.9,<br/>samtools version 1.12,<br/>R packages:<br/>CCA version 1.2.1,<br/>RGCCA version 2.1.2,<br/>MASS version 7.3,<br/>BPSC version 0.99.2,<br/>SingleCellExperiment version 1.20.0,<br/>dplyr version 1.0.10,<br/>tidyverse version 1.3.2,<br/>pROC version 1.18.0,<br/>Other methods used for simulations:<br/>mashr - <a href="https://github.com/stephenslab/mashr">https://github.com/stephenslab/mashr</a></p> |

metasoft - [http://genetics.cs.ucla.edu/meta\\_jemdoc/](http://genetics.cs.ucla.edu/meta_jemdoc/)MT-eQTL - [http://www.bios.unc.edu/research/genomic\\_software/Multi-Tissue-eQTL/](http://www.bios.unc.edu/research/genomic_software/Multi-Tissue-eQTL/)

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 GTEx data (v8) used in this study are available in dbGaP under accession number phs000424.v8.p2 ([https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000424.v8.p2](https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000424.v8.p2)). DNAm normalized data is available at GEO (GSE213478; <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE213478>). Summary statistics of cis-mQTLs are available at the eQTL Portal (<https://gtexportal.org/home/downloads/egtex/methylation>). The GTEx SNPs from GWAS Catalog are available at <https://www.ebi.ac.uk/gwas/>. The eQTLGen data released by eQTLGen Consortium are available at <https://www.eqtlgen.org>. The GoDMC data released by the Genetics of DNA Methylation Consortium are available at <http://www.godmc.org.uk>. The FUSION data are available through FUSION Skeletal Muscle Study portal: <https://www.ebi.ac.uk/birney-srv/FUSION/>. The DLPCF data released by LIBD are available at <https://research.libd.org/spatialLIBD/>. The CommonMind Consortium data are available via access request to the CommonMind Consortium Knowledge Portal: <http://dx.doi.org/10.7303/syn2759792>. Data to generate figures is available at <https://github.com/yilustat/XING-Analysis/tree/main/Data>.

## Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender Not applicable: data used in manuscript are from existing studies.

Reporting on race, ethnicity, or other socially relevant groupings Not applicable: data used in manuscript are from existing studies.

Population characteristics Not applicable: data used in manuscript are from existing studies.

Recruitment Not applicable: data used in manuscript are from existing studies.

Ethics oversight Not applicable: data used in manuscript are from existing studies.

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-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 The work discussed in this manuscript uses publicly available individual-level data of gene expression and DNA methylation to obtain summary-level QTL statistics. The phenotype data, covariates and genotype are processed by GTEx, therefore, we do not decide the sample size.

Data exclusions No data were excluded.

Replication We evaluated the replication rates of cis- and trans-associations identified by X-ING. The replication studies were FUSION and GoDMC for cis-associations. We reported the proportions and numbers of SNP-CpG pairs identified in GTEx that are also significant in FUSION/GoDMC with p-value less than 6e-7. We used eQTLGen and GoDMC for the replication of trans-associations. As the eQTLGen provided FDR measure, we used FDR<0.05 as the criterion of replication. In GoDMC, we used p-value less than 3e-9 as the criterion of replication.

Randomization We did not perform any randomized experiments that involves randomization. We worked directly on publicly available data.

Blinding We did not perform any experiments that involves blinding. We worked directly on publicly available data.

# 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 checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                 |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                        |

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

## Plants

Seed stocks

Not applicable.

Novel plant genotypes

Not applicable.

Authentication

Not applicable.