

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 <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 <i>Give P 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 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	<div>None</div>
Data analysis	<div>Software used for data analysis include Regenie (v.3.2.1, https://github.com/rgcgithub/regenie), SnpEff (v5.3, https://pcingola.github.io/SnpEff/), SIFT (v6.2.1, https://sift.bii.a-star.edu.sg/www/code.html), PolyPhen-2 (v2, http://genetics.bwh.harvard.edu/pph2/), Mutation Taster (GRCh38, https://www.mutationtaster.org/), TOPMed Imputation Server (release-3, https://imputation.biodatacatalyst.nhlbi.nih.gov/#!), hap-IBD (v1, https://github.com/browning-lab/hap-ibd?tab=readme-ov-file), Impute5 (v5, https://jmarchini.org/software/), RFMix (v2, https://github.com/slowkoni/rfmix), SuSiE (v0.12.10, https://stephenslab.github.io/susieR/articles/finemapping.html) Plink (v2.0, https://www.cog-genomics.org/plink/2.0/)</div>

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](#)

UKB individual-level genotypic and phenotypic data are available to approved investigators via the UK Biobank study (www.ukbiobank.ac.uk/). Additional information about registration for access to the data are available at www.ukbiobank.ac.uk/register-apply/. Data access for approved applications requires a data transfer agreement between the researcher's institution and UK Biobank, the terms of which are available on the UK Biobank website (www.ukbiobank.ac.uk/media/ezrderzw/applicant-mta.pdf). MCPS individual-level data are available to qualified noncommercial researchers by emailing mcps-access@ndph.ox.ac.uk. The data access policy is outlined at www.cts.ox.ac.uk/files/mcps-data-access-policy-v2-1-english.pdf.

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	Sex is included as a covariate in the genetic association analysis. Sex is inferred from the genetic data and was confirmed by comparing with the self reported sex. We did not use gender information for any of the analysis.
Reporting on race, ethnicity, or other socially relevant groupings	We used genetic data to identify the ancestry of the participants. Accordingly, we grouped individuals in the MCPS and UK Biobank cohorts into "Indigenous American" and "European" ancestry groups respectively.
Population characteristics	Provided in the Supplementary Table 1
Recruitment	Participant recruitment information for the respective cohorts is described in the methods section along with appropriate references.
Ethics oversight	All the study participants have provided informed consent and all the participating cohorts have received ethical approval from their respective institutional review board (IRB). The UK Biobank project has received ethical approval from the Northwest Centre for Research Ethics Committee (11/NW/0382). The work described here has been approved by the UKB (application no. 26041). The MCPS study has received ethical approval from the Mexican Ministry of Health, the Mexican National Council for Science and Technology, and the University of Oxford.

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

Life sciences study design

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

Sample size	Sample size was not calculated prior to study. All samples available after quality control were included for analysis.
Data exclusions	Certain samples and genetic variants were excluded as part of the standard quality control pipeline applicable to any genetic association study. Details can be found in the methods and the cited references.
Replication	We report gene-level replication (aggregated rare variant associations) in the UK Biobank and Biobank Japan for our primary discovery. The results replicated at least nominal level of significance ($P < 0.05$) in the replication analyses.
Randomization	Not applicable. All the genetic analyses were adjusted for appropriate covariates including age, sex, ancestry, relatedness and batch-effects related sequencing assays or phenotyping
Blinding	Not applicable for genome-wide and exome-wide association studies.

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	Involvement 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	Involvement 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