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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	This does not apply to this manuscript as the paper reports a meta-analysis and no data collection was undertaken
Data analysis	Supplementary Table 21 show the imputation and analysis software used in each of the cohorts. The code used to perform the meta-analyses will become available upon publication on GitHub.

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 code used to perform the meta-analyses will become available upon publication on GitHub. GWAS summary statistics of the Meta-analysis of UK Biobank, IHC and 23andMe data for the top 10,000 independent SNPs will be available upon publication as well as summary statistics of the Meta-analysis between UK Biobank and IHC for all the SNPs. Access to the full summary statistics from the 23andMe sample (for all SNPs) can be obtained by qualified researchers through a data transfer agreement with 23andMe. Please contact 23andMe in https://research.23andme.com/dataset-access for more information.

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	In this study, we present findings from the world's largest GWAS meta-analysis of handedness to date (N = 1,766,671), combining data from 32 cohorts from the International Handedness Consortium (IHC) (N = 125,612), 23andMe (N = 1,178,877) and UK Biobank (N = 462,182). No sample size/power calculations were undertaken.
Data exclusions	At the site level participants were excluded if phenotype, covariate and/or genotypic data were missing or if the genotypic data for an individual failed quality control. All participants were of European ancestry. There were no cohort-level exclusions from the meta-analysis and all cohorts that contributed data were included in the analyses. Prior to meta-analysis, quality control thresholds were applied to each of the GWAS results from the individual studies (r2 ≥ 0.3, MAF ≥ 0.005, PHWE ≥ 1x10-5). We also removed genetic variants for which the frequency substantially differed from one of the Haplotype Reference Consortium panels (frequency difference > 0.2). We used EasyQC 55 to identify SNPs that had allele frequencies which differed substantially from the Haplotype Reference Consortium. In total, up to 13,346,399 SNPs remained for the left-handedness meta-analysis. For the ambidexterity meta-analysis, only 23andMe and the UK Biobank were used. This meta-analysis included up to 12,493,443 SNPs.
Replication	As the frequency of left-handedness is ~10% in European populations there were no sufficiently large populations with GWAS data available to replicate these findings with sufficient power at the time of analysis. In the ST2 and ST12 we provide the results for both the meta-analysis and the cohort-level results from the UK Biobank, 23andMe and IHC analyses to allow readers to examine the replicability of findings. We used also LD-score genetic correlation analyses to assess the internal replicability of findings at the genome-wide level. The genetic correlations as estimated by bivariate LD-score regression between the results from the UK Biobank, 23andMe and IHC GWAS were high (rgUKB-23andMe = 0.88, s.e. = 0.05, rgUKB-IHC = 0.73, s.e. = 0.16, rgIHC-23andMe = 0.60, s.e. = 0.11).
Randomization	This is not applicable as the paper reports a meta-analysis of genome-wide association analyses for an observed variable with no experimental manipulation.
Blinding	This is not applicable as the paper reports a meta-analysis of genome-wide association analyses for an observed variable with no experimental manipulation.

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