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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
☐	☒ 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 for data collection.
Data analysis	All data was analyzed with open-source software available online and detailed in the Methods: PLINK (v1.9, v2.0.0), SHAPEIT4 (4.2.1), Minimac4 (v1.0.1), SAIGE (v0.45, v1.0.7), REGENIE (v3.2.4, v3.3), UCSC LiftOver, METAL (version released on 2011-03-25), RE2C (v1.0.6), FUMA (v1.6.1), DEEP*HLA, Cell Ranger (v7), STAR, CellBender (v0.1.0), Scrublet (v0.2.3), scds (v1.18.0), Scanpy (v1.9.8), scDRS (v1.0.2) and gsMap (v1.71.1)

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

GWAS summary statistics and single cell sequencing data of PBMCs are available at the National Bioscience Database Center (NBDC) Human Database with the

accession ID hum0197 (https://humandbs.biosciencedbc.jp/en/hum0197-latest). GWAS genotype data of the BBJ are available at the NBDC Human Database (research ID: hum0014 and hum0311). The GWAS summary statistics of IMSGC was obtained from https://imsgc.net/. The GWAS summary statistics of Andlauer et al. and other traits were obtained from GWAS Catalog (https://www.ebi.ac.uk/gwas/). The UK Biobank analysis was conducted via application number 47821 (https://www.ukbiobank.ac.uk/). Individual-level phenotypic and genetic data from UK Biobank can be requested from UK Biobank Access Management System (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). Individual-level phenotypic and genetic data from the All of Us Research Program can be accessed following the application to use the All of Us Researcher Workbench, a cloud-based computing platform (https://www.researchallofus.org/register/). Data from the 100,000 Genomes Project can be accessed following the application to join the Genomics England Research Network (https://www.genomicsengland.co.uk/research/academic/join-research-network). The GWAS summary statistics of FinnGen Data Freeze 11 was obtained from https://www.finngen.fi/en. The GWAS summary statistics of MVP were obtained through dbGaP (accession number phs002453). The AIDA Phase 1 Data Freeze v2 PBMC scRNA-seq data were obtained from CZ CELLxGENE (https://cellxgene.cziscience.com/collections/ced320a1-29f3-47c1-a735-513c7084d508). The MS subcortical lesion snRNA-seq and ST data were obtained from the UCSC Cell Browser (https://cells-test.gi.ucsc.edu/?ds=ms-subcortical-lesions).

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	We used the term sex as with other genomic studies. We collected clinical information, including sex, from medical records in the Japan MS/NMOSD Biobank, the University of Osaka Hospital or BBJ. In UK Biobank, All of US and Genomics England, we excluded subjects with a mismatch between inferred sex from the genotype data and self-reported gender.
Reporting on race, ethnicity, or other socially relevant groupings	We estimated ancestral populations based on principal component analysis (PCA) of the genotype data.
Population characteristics	A total of 688 MS cases and 205,199 controls from the Japan MS/NMOSD Biobank, the University of Osaka Hospital and BBJ were included in the Japanese GWAS. In the cross-population GWAS meta-analyses, 27,572 cases and 1,436,801 controls of European ancestry, 819 cases and 155,904 controls of African ancestry, and 295 cases and 45,659 controls of American ancestry were included.
Recruitment	MS cases in the Japan MS/NMOSD Biobank and the University of Osaka Hospital were diagnosed using the 2010 Revised McDonald criteria, while those in the BBJ, UK Biobank, All of Us and Genomics England were identified based on ICD-10 code (G35).
Ethics oversight	All participants provided written informed consent, approved by ethics committees of the University of Osaka and the University of Tokyo.

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	The Japanese GWAS includes 688 MS cases and 205,199 controls. The cross-population GWAS meta-analysis includes 29,374 cases and 1,843,563 controls. The scRNA-seq analysis of peripheral blood mononuclear cells includes 20 MS cases in the Japanese population.
Data exclusions	All samples for our GWAS were selected based on the quality control criteria specific to each biobank, as summarized in the Methods section. Briefly, samples were selected based on genotype call rate and PCA of the genotype data.
Replication	We conducted cross-population GWAS meta-analyses and compared the GWAS results across populations.
Randomization	Not applicable due to case-control study design.
Blinding	Not applicable due to case-control study design.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.