EXTENDED DATA FIGURE LEGENDS

Extended Data Fig. 1 | Demographic characteristics by population and center. a, Discovery population (n = 12,584). **b**, Replication population (n = 9,805). Bars represent the proportion of patients in each category. Centers are ordered as in the box plot legend (bottom right subpanel). Box plots show median, first, and third quartiles; whiskers represent the smallest and largest values within 1.5-times the interquartile range; outliers are depicted as dots. The countries corresponding to the abbreviations in the box plot legend are shown in **Supplementary Table 1**. ARMSS, age-related multiple sclerosis severity; EDSS, expanded disability status scale; Primary prog., primary progressive; yrs, years.

Extended Data Fig. 2 | Principal component analysis of the discovery and replication populations. MS cases were recruited from 13 countries for the discovery (**a**) and 8 for the replication (**b**). After removing population outliers, all remaining cases were of European ancestry. The first two principal components respectively captured the north-to-south and east-to-west gradients of European genetic structure. US and Canadian participants overlapped with those from other countries. Based on self-reported ancestry, East European and Ashkenazi Jewish individuals constituted the majority of the predominantly US subcluster located at the bottom right of the discovery population (**a**). The scree plots for our principal component analysis in the discovery (**c**) and replication (**d**) populations confirm that the first few principal components capture most of the variance attributable to the minimal population structure remaining after quality control.

Extended Data Fig. 3 | Replication of MS severity variants by center. a, Genome-wide significant lead variant rs10191329. **b**, Suggestive lead variant rs149097173. Forest plots show successful replication of the two variants with minimal heterogeneity between centers as indicated by the Cochran's Q and I^2 statistics (n = 9,805 participants). ARMSS scores are rank-based inverse-normal transformed. Error bars represent 95% CIs. ARMSS, age-related multiple sclerosis severity; CI, confidence interval.

Extended Data Fig. 4 | Association of rs149097173 with longitudinal disability outcomes. a, Adjusted mean EDSS scores over time by carrier status for rs149097173 predicted from LMM analysis. Shaded ribbons indicate the standard error of the mean over time; *P* value from LMM. **b,** Covariate-adjusted cumulative incidence of 24-week confirmed disability worsening for the same groups of individuals. **c,** Covariate-adjusted cumulative incidence of requiring a walking aid; carriers had a 2.2-year shorter median time to require a walking aid. HR and two-sided *P* values were obtained from Cox proportional hazards models using imputed allele dosage (**b–c**; Methods). Results were not significant after adjusting for multiple testing across two variants (see Fig. 3 for rs10191329 associations) and three

outcomes (P < 0.05/6), although the latter are not expected to be independent. CI, confidence interval; HR, hazard ratio.

Extended Data Fig. 5 | Tissue expression for nominated MS severity genes. Gene expression profiles were obtained from GTEx[73] (version 8). Transcripts were collapsed to the gene level and expressed in natural log-transformed transcript per million (TPM) units. *DYSF*, *ZNF638*, *DNM3* and *PIGC* are expressed in the brain. Box plots show median, first, and third quartiles; whiskers represent the smallest and largest values within 1.5-times the interquartile range; outliers are depicted as dots. Bold x-axis labels identify CNS tissues. Colors represent tissue types as defined in GTEx.

Extended Data Fig. 6 | Cell type expression profiles for nominated MS severity genes. Single-cell RNA sequencing data from 25 human tissues and peripheral blood mononuclear cells were obtained from the Human Protein Atlas[77]. Transcript expression levels were summarized per gene and reported as average normalized transcripts per million (nTPM) in 76 cell types. Asterisks mark cell type specificity for the gene, defined as at least fourfold higher expression in a cell type compared to the mean of others. We note that three of the genes show specificity for oligodendrocyte lineage cells. *PIGC* expression in brain neuronal and glial cells, missing here, is demonstrated in **Extended Data Fig. 8.** Colors represent cell type categories; bold x-axis labels identify neuronal and glial cell categories.

Extended Data Fig. 7 | Cell type expression for PIGC in brain white matter tissue. Single nuclear RNA expression from 4 progressive MS patients and 5 non-neurological controls[26] confirms PIGC expression in neuronal and glial cells including oligodendrocyte lineage cells. COPs, committed oligodendrocyte precursors; ImOLGs, immune oligodendroglia; Oligo, oligodendrocyte; OPCs, oligodendrocyte precursor cells; Vasc, vascular.

Extended Data Fig. 8 | Genetic correlations with MS severity. Shared genetic contribution obtained from cross-trait LDSC. Colors correspond to genetic correlation (r_g) estimates (blue, negative; red, positive). An asterisk indicates a correlation that is significantly different from zero, based on two-sided P values calculated using LDSC (*FDR < 0.05, **FDR < 0.01). Full results are in **Supplementary Table 17**. Aging-GIP1 was constructed using principal component analysis to capture GWASs of healthspan, father lifespan, mother lifespan, longevity, frailty, and self-rated health[85].

Extended Data Fig. 9 | Association of individual MS susceptibility variants (n = 209) with longitudinal disability outcomes. a, Distribution of P values from adjusted LMM analysis of EDSS change across all study visits. Distribution of two-sided P values from adjusted Cox proportional hazards analyses of (**b**) time to 24-week confirmed disability worsening and (**c**) time to require a walking aid. The

dashed orange line represents the Bonferroni-corrected significance threshold adjusted for the number of susceptibility variants. **d**, Venn diagram of nominal associations ($P_{unadjusted} < 0.05$) between individual MS susceptibility variants and all disability outcomes considered; no variant showed consistent association across three or more outcomes. The labels in this panel correspond to the following outcomes: ARMSS, association with ARMSS scores following rank-based inverse normal transformation; Disability worsening, time to 24-week confirmed disability worsening; Walking aid, time to require a walking aid (EDSS 6.0); EDSS rate, rate of EDSS change across all study visits.

Extended Data Fig. 10 | MS susceptibility PGS and longitudinal disability outcomes. a, Adjusted mean EDSS scores over time by PGS quartile predicted from LMM analysis. Shaded ribbons indicate the standard error of the mean over time; *P* value from LMM. **b**, Covariate-adjusted cumulative incidence of 24-week confirmed disability worsening comparing individuals in the highest versus those in the lowest quartile of MS susceptibility PGS. **c**, Covariate-adjusted cumulative incidence of requiring a walking aid for the same groups of individuals. HR and two-sided *P* values were obtained from Cox proportional hazards models using imputed allele dosage (**b–c**; Methods). Across all analyses, the MS susceptibility PGS had no influence on longitudinal outcomes.