REVIEW OPEN ACCESS

Unlocking Multiple Sclerosis Genetics

From Susceptibility to Severity

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Abstract

Multiple sclerosis (MS) is a clinically diverse and unpredictable CNS disorder. The considerable heterogeneity in disease course between people with MS is believed to reflect the varying magnitude and extent of the pathologic processes present at different stages of the disease. Genetic factors are known to contribute to the risk of developing MS and are emerging as predictors of clinical outcomes. They may also offer insights into the biological processes influencing disability. In this review, we evaluate the role of genetic factors in MS from disease susceptibility to disease severity. We consider how understanding of the genetic contribution to the risk of developing MS has evolved to recognize over 230 genetic variants that implicate peripheral immune cells at disease onset. Although MS-risk genes have shown little association with disease severity outcomes, we re-evaluate associations of the main MS-risk allele, *HLA-DRB1*1501*, with disease activity using observations from long-term longitudinal cohorts. We summarize progress identifying genetic variants associated with clinical phenotypes, including the discovery of the first genetic variant associated with age-related MS severity, rs10191329, and its pathologic associations. We assess the challenges faced by replication studies, including low statistical power, methodologic variations in disability outcomes, and the potential impact from differences in treatment and disease temporality. Reconciling these findings, in contrast to MS-risk genes, MS severity variants appear enriched in CNS tissues, suggesting at least in part distinct genetic architectures for MS risk and severity. Despite advances in our understanding of MS genetics, there remain significant gaps in our knowledge that reflect the elaborate genetic architecture underlying disease progression. Potential gains are to be made from exploring rare variants and ancestrally diverse populations, while the causality of variants may be interrogated through analyses of gene sets and recognized biological pathways. However, further work is required to improve phenotyping of disease severity beyond physical disability measures and to disentangle complex genetic interactions, which may vary with environmental factors and time. Resolving these challenges is crucial if genetic analyses are going to be able to power clinically useable predictive models and inform mechanistic targets for novel treatments in progressive MS.

Introduction

Multiple sclerosis (MS) is a chronic disabling CNS disorder associated with inflammatory demyelination and neuroaxonal loss. The etiology of MS remains unknown, but environmental, lifestyle, and genetic factors are important. MS is highly heterogeneous; people with MS have very variable disease courses, and even individuals with the same clinical phenotype have different pathologic, radiologic, and clinical features. This heterogeneity likely reflects dynamic changes in the pathologies driving disease progression, shifting from acute focal inflammatory damage to widespread chronic inflammation and neurodegenerative processes coupled with failure of compensatory pathways.[1]

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Glossary

ARMSS = age-related MS severity; **CIS** = clinically isolated syndrome; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **GWAS** = genome-wide association study; **HLA** = human leukocyte antigen; **HR** = hazard ratio; **IMSGC** = International Multiple Sclerosis Genetics Consortium; **L-ARMSS** = longitudinal ARMSS; **L-MSSS** = longitudinal MSSS; **MHC** = major histocompatibility; **MS** = multiple sclerosis; **MSSS** = MS severity scale; **OR** = odds ratio; **PIRA** = progression independent of relapse activity; **RRMS** = relapsing remitting MS; **SPMS** = secondary progressive MS.

Despite not being a genetically inherited disorder, genetic factors clearly play a role in the heterogeneity of MS, both for developing the disease and its subsequent course. The ability to interrogate the whole genome has led to the discovery of more than 230 *genetic variants* (italicized items are defined in Table 1). More recently, large-scale collaborative efforts have led to the discovery of the first genetic variant, rs10191329, associated with MS clinical severity, that is, long-term disability, at *genome-wide significance*.[2] Although less well understood, the *genetic architecture* underlying disease severity seems distinct from that governing disease susceptibility, implicating CNS pathways involved in neurodegeneration and repair instead of immunologically mediated inflammation and demyelination.[2-4]

Table 1 Glossary of Genetic Terminology

Genetic variant	A permanent alteration in the most common DNA sequence of a gene; it may be benign, pathogenic, or of unknown significance
Genome-wide significance	The threshold for statistical significance ($p < 5 \times 10^{-8}$) in genome-wide association studies, based on a Bonferroni correction for all independent single-nucleotide polymorphisms across the human genome
Genetic architecture	The genetic variants contributing to a phenotypic trait and characteristics
Linkage analysis	A method of tracing inheritance patterns within high-risk families to detect the chromosomal location of disease genes by demonstrating cosegregation of genetic markers with the disease or trait
Heritability	The proportion of variation seen in an observed phenotypic trait that is due to genetic variation
Genetic determination	When a phenotypic trait is determined purely by genetics alone, typically a single gene or sometimes a handful of genes
Complex trait	A trait that is governed by multiple genes and their interaction with environmental (nongenetic) factors, exhibiting a variety of phenotypes
Polygenicity	The occurrence of multiple genes contributing additively to influence a phenotypic trait
Polygenic risk score	Aggregation of the effects of multiple variants within an individual's genotype into an overall score relating to the relative risk of a phenotypic prediction
Somatic mutation	Postzygotic (i.e., after conception) alterations in DNA that occur from mitosis or DNA damage resulting in genetically distinct cell lineages within an individual (mosaicism)
Low-frequency variant	Rare genetic variants with low minor allele frequency (typically <1% or <5%) leading to exclusion from statistical analyses in genome-wide association studies
Minor allele frequency	The frequency at which the less common (minor) allele occurs within a population
Linkage disequilibrium	The non-random association of alleles at different loci in a given population
Common variant	Variants that are commonly seen within a population, typically with minor allele frequency ≥5%
Suggestive variant	Variants not meeting genome-wide significance may have genuine and replicable effects. Thresholds often vary but are typically $5 \times 10^{-8} < p < 5 \times 10^{-5}$
Fine-mapping	The process by which a genomic region associated with a trait from a genome-wide association study is analyzed to identify causal variants
Direct genetic effect	Genetic effect that influences a trait within the individual carrying the causal alleles
Indirect genetic effect	Genetic effect that influences a trait within the relatives of the individual carrying the causal alleles, e.g., parental effects influence traits in their children
Epigenetics	The study of how phenotypic expression can be influence by gene activity occurring without changes in the DNA sequence
Mendelian randomization	An analytical method that uses random genetic variation to assess the effect of modifiable risk factors on an outcome that would otherwise be influenced by confounding factors

In this review, we focus on how understanding of the genetic architecture of MS disease severity has evolved from that of the genetic influences on MS disease susceptibility. We explore the relevance of genetic factors to the evolution of, and interplay between, inflammatory and neurodegenerative pathologic mechanisms in MS. Challenges identifying and replicating associations with long-term MS severity are considered, given that over time, different pathologic processes may dominate and that population and methodologic factors may have significant effects. Finally, we raise potential future directions for exploration that may help to eventually unlock the clinical utility of genetic analyses in MS.

We reviewed evidence published between March 1, 2022, and March 1, 2025, using the following search term in the PubMed database: ("multiple sclerosis") AND (severity OR phenotype OR disability OR progression) AND (genetics OR genotype OR gene OR locus OR rs10191329).

Disease Susceptibility

Early family aggregation studies showed higher concordance rates in monozygotic (24%–30%) vs dizygotic twins (3%–5%)[5,6] and a more than 10-fold higher lifetime risk of MS in first degree-relatives of MS cases (3%) compared with the general population (0.1%–0.3%).[7] The first genetic locus for MS susceptibility was identified in the 1970s; the human leukocyte antigen (HLA) gene cluster within the highly polymorphic major histocompatibility (MHC) region on chromosome 6 was later refined to *HLA-DRB1*1501*, the strongest MS-risk allele.[7] However, subsequent *linkage analyses* failed to identify further risk alleles, and it became evident that the genetic architecture of MS was complex.

The emergence of microarray technology, coupled with advancing computational power, made genome-wide association studies (GWASs) assessing hundreds of thousands of genetic variants across the whole genome feasible. However, advances were only made when GWAS began to use very large sample sizes and so could identify genetic variants reaching the genome-wide significance ($p < 5 \times 10^{-8}$) necessary for the numerous allelic comparisons these studies entail.[7,8]

Heritability and Polygenicity of MS Susceptibility

Collaborative efforts by the International Multiple Sclerosis Genetics Consortium (IMSGC) led to the discovery of 233 susceptibility variants in GWAS of 47,429 MS cases and 68,374 controls.[4] They estimated the overall *heritability* of MS risk at ~19%, and their genomic map of MS susceptibility variants implicated peripheral immune responses in disease generation.[4] It is important to recall the distinction between heritability and *genetic determination*; heritability refers to the proportion of variation in the phenotypic trait attributable to genetic variation and is not causation or determination. Neither MS-risk nor MS-severity is genetically determined, as in classical Mendelian inheritance, where a rare genetic variant leads to the determination of a phenotypic trait (e.g., Huntington's disease). Instead, they are *complex traits* that are multifactorial with small additive contributions from multiple common genetic variants (*polygenicity*) and influenced by environmental factors.[8]

Individual genes are neither necessary nor sufficient to predict disease, as almost the entire population have at least 160 risk alleles,[8] which are not specific to MS but shared with many other autoimmune diseases,[9] and despite this, there is a low lifetime risk of MS (~0.2%).[8] *Polygenic risk scores* have been used to capture the cumulative genetic risk and higher scores may increase susceptibility between 5-fold and 8-fold but are not presently of sufficient predictive value for clinical utility.[10,11] The heritability of developing MS must go beyond the known additive effects of individual variants and likely includes genetic interactions between genes, with environmental factors and perhaps even stochastic events, such as *somatic mutations*.[12] Furthermore, as current MS susceptibility variants have only been validated in patients of European descent, the genetic architecture of MS-risk in non-European populations remains unclear, and as will be discussed later, there is a need to investigate ancestrally diverse populations.[13]

Disease Activity

Given the expansion of the MS susceptibility genomic map, there has been significant interest in establishing the role of MS-risk genes in the development of clinical phenotypes, disease activity, and progression.

HLA-DRB1*1501

As the main risk allele for developing MS, *HLA-DRB1*1501* has been the most extensively studied single variant and has a clear effect on decreasing age at disease onset.[14-16] Studies have suggested associations of *HLA-DRB1*1501* with increasing white matter demyelination,[17-20] accelerated atrophy,[17,20,21] and even intrathecal abnormalities,[22,23] but this has not always been the case.[24,25] Beyond this, some studies have found that *HLA-DRB1*1501* was associated with clinically observed disease activity (relapses),[19,22,26] but there have been conflicting results on whether *HLA-DRB1*1501* is associated with disease severity,[17,20,22,27-29] and studies have varied for disease duration and follow-up.

A possible explanation for these inconsistent findings with disease severity comes from the results of 2 long-term longitudinal observational studies in people followed from first clinical symptoms suggestive of MS, termed a clinically isolated syndrome (CIS). Brownlee et al.[20] assessed 107 patients over 15 years following a CIS and found *HLA-DRB1*1501* was associated with greater increases in T2 white matter lesion volume, more gadolinium enhancing lesions, and ultimately a faster rate of Expanded Disability Status Scale (EDSS) worsening but did not assess relapses. However, in

another study assessing 61 CIS patients over 30 years, *HLA-DRB1*1501* was associated with greater white matter lesion volume, faster white matter lesion accrual, and higher annualized relapse rates but was not associated with EDSS or development of secondary progressive MS (SPMS) at 30 years.[19] Both studies showed an effect of *HLA-DRB1*1501* on brain atrophy, but in the latter study, this was shown to be driven by the effect of *HLA-DRB1*1501* on white matter lesions. These findings confirm the effect of *HLA-DRB1*1501* on inflammatory disease activity and suggest that genetic influences on disease severity may evolve over time.[30,31]

Polygenic Risk Scores and Early Genome-Wide Association Studies

Polygenic risk scores, such as cumulative HLA-genetic burden[21] and non-MHC genetic risk score,[15,16] have also been associated with age at onset, implying a consistent effect of risk variants not solely driven by *HLA-DRB1*1501*. However, attempts to link polygenic risk scores of susceptibility variants to relapses, disease course, or other clinical phenotypes have proven unsuccessful.[8,16,21,32]

Furthermore, in early GWAS of MS severity, established MS-risk variants did not influence disease severity, and instead the most significant variants appeared from pathway analyses and gene ontology to be distinct from the immune processes underlying disease susceptibility.[33,34] While this suggested separate genetic architectures for disease susceptibility and disease severity, progress in identifying associations with disease severity reaching genome-wide significance was slow, although clinical associations were uncovered (Table 2).

Genome-Wide Associations With Clinical Variability

Two genetic variants have been associated with relapse risk in GWAS. The rs12988804 variant in the *LRP2* locus was first associated with increased risk of relapse (hazard ratio [HR] = 2.18, $p = 3.3 \times 10^{-8}$) in 3 pooled longitudinal cohorts with prospective clinical relapse data from 449 patients with MS[35] and subsequently replicated in a cohort of 527 relapse-onset MS patients from Belgium.[36] More recently, a *low-frequency variant* (with *minor allele frequency* of 0.02) rs11871306 within *WNT9B* predicted relapse hazard in a discovery cohort of 506 people with MS (HR = 2.08, $p = 3.37 \times 10^{-8}$) and in a replication cohort (HR = 2.53, $p = 1.01 \times 10^{-4}$; discovery + replication cohort HR = 2.15, $p = 2.1 \times 10^{-10}$).[32]

The pharmacogenetics of treatment response are of significant interest in the aim for personalized medicine, and although less extensively studied, there have been some promising GWAS.[37,41,42] Most notably, rs9828519 in *SLC9A9* was associated with increased risk of nonresponse to interferon-β (based on either clinical relapses or new T2/gadolinium-enhancing lesions) at genome-wide significance (odds ratio [OR] = 5.46, 95% CI 2.89–10.33, $p = 4.43 \times 10^{-8}$) in a cohort of Italian patients followed for 2 years and was validated in a multicentric replication cohort ($p = 7.78 \times 10^{-4}$).[37] Although this was not replicated in a subsequent GWAS, this may have been due to relative underpowering and the lack of inclusion of radiologic disease activity in the treatment response criteria.[42]

Discovery of Disease Severity Variants

The First Severity Variants Reaching Genome-Wide Significance

Recently, 2 large-scale collaborative GWAS have begun elucidating the genetic contribution to MS severity. The IMSGC conducted the largest GWAS of MS severity to date in a discovery cohort of 12,584 people with MS from 21 centers across North America, Europe, and Australia with a replication cohort of 9,805 cases from 9 European centres.[2] As with the MSBase study (see below), all participants were of European ancestry (see Future Directions), while recruitment was enriched for participants with longer disease duration, older age, and availability of longitudinal outcomes. The authors identified the rs10191329 variant near *DYSF-ZNF368* as the first genome-wide significant variant associated with cross-sectional age-related MS severity (ARMSS) ARMSS ($p = 9.7 \times 10^{-9}$ in discovery cohort). In the same study, further longitudinal analyses in 8,325 MS cases (from both discovery and replication cohorts) who had at least 3 EDSS measurements confirmed that the rs10191329 variant was associated with faster disability progression, greater risk of 24-week confirmed disability worsening, and a 3.7-year shorter time to needing a walking aid, EDSS 6.0 (Table 3).

Before this, Jokubaitis et al.[6] had applied both GWAS and machine learning approaches in 1,813 relapse-onset MS patients with ≥5 years of follow-up and at least 3 EDSS assessments, recorded in the absence of relapse, from 8 MS tertiary centers in the MSBase registry.[3] EDSS scores were converted into MS severity scale (MSSS) scores at each timepoint, and the median longitudinal ARMSS (L-ARMSS) and median longitudinal MSSS (L-MSSS) scores were calculated (Figure 1). The cohort was then stratified into severity extremes based on the top and bottom quintiles, that is, mild vs severe L-ARMSS or L-MSSS scores and recruitment enriched for these patients. Although no variants were found to reach genome-wide significance in the primary analyses, the top 2 variants (rs7289446 and rs1207401) for both L-ARMSS and L-MSSS scores were nearest to the *SEZ6L* gene ($2.73 \times 10^{-7} > p$ values $> 3.35 \times 10^{-7}$) and in *linkage disequilibrium*. In survival analyses, rs7289446 independently predicted time to irreversible EDSS 3 (adjusted HR = 0.77, $p = 0.008$) and irreversible EDDS 6 (adjusted HR = 0.72, $p = 4.85 \times 10^{-4}$). Furthermore, sex-stratification showed that genome-wide significance for rs10967273, an intergenic variant, was associated with L-MSSS in females ($p = 3.52 \times 10^{-8}$) and rs698805 intronic to *CAMKMT* was associated with L-MSSS in males ($p = 4.35 \times 10^{-8}$).[3]

Considering these results together, despite having non-overlapping variants as their top signals, enrichment analyses in both studies identified genes expressed within CNS

Table 2 Variants With Genome-Wide Associations With Clinical Variability or Disease Severity

Variant	Location Chr: position	Risk allele	Variant function	Nearest gene(s)	MS traits	Other GWAS traits	Putative biological processes
rs12988804	2: 169261301	T	Intron	*LRP2*	Increased relapse risk[35,36]	Nil	Receptor-mediated endocytosis
rs11871306	17: 46877618	C	TF binding site	*WNT9B*	Increased relapse risk[32]	Nil	Neuron differentiation Canonical WNT signaling pathway Cell fate commitment
rs9828519	3: 143425978	G	Intron	*SLC9A9*	Increased risk of nonresponse to interferon-β therapy[37]	Nil	Regulation of intracellular pH Sodium ion import across plasma membrane Potassium ion transmembrane transport
rs10967273	9: 26257387	T	Intergenic	*GARIN3P1*, *CAAP1*	Higher L-MSSS in females[3]	Nil	Regulation of cysteine-type endopeptidase Activity involved in apoptotic process Negative regulation of apoptotic signaling pathway Negative regulation of cysteine-type endopeptidase activity
rs698805	2: 44473990	G	Intron	*CAMKMT*	Lower L-MSSS in males[3]	Nil	Protein modifying enzyme
rs10191329	2: 71449869	A	Intergenic	*DYSF*, *ZNF638*	Higher ARMSS[2]	Nil	Regulation of neurotransmitter secretion Regulation of RNA splicing

Abbreviations: ARMSS = age-related multiple sclerosis severity score; Chr = chromosome; GWAS = genome wide association study; L-MSSS = median longitudinal multiple sclerosis severity score; MS = multiple sclerosis; TF = transcription factor.
Variant location, function, and associated traits as provided in NHGRI-EBI GWAS Catalog[38] and Ensembl.[39] Putative biological process obtained from gene ontology classification using PANTHER GO-slim Biological Process[40] based on nearest gene in humans only. NB: All variants listed lie in noncoding regions that do not directly alter protein function and may not necessarily influence the nearest gene.

compartments in MS severity, implicating neurodegenerative and reparative pathways.[2,3] Thus, the genetic architecture of MS severity seems distinct to that of MS susceptibility, which is driven by variants associated with the immune system.[2,3,14,34] Combined with the absence of variants of large effect size, these findings also support a polygenic contribution to MS severity, as with the genetics of MS susceptibility, driven by multiple *common variants* of modest effect size.

Pathologic Effects of rs10191329

The IMSGC study showed that, postmortem, rs10191329 risk-allele homozygosity was associated with 1.83-fold increase in brainstem lesions and 1.76-fold increase in cortical lesions[2] (Table 4). Subsequent studies have looked to both replicate disability associations and elucidate the pathologic effects of the rs10191329 variant. A recent further study of the IMSGC autopsy cohort suggests that rs10191329^{AA} homozygosity increases propensity to neurodegenerative stress and chronic inflammation[45] (Table 4). Another study showed 27.5% faster annual decrease in percentage brain volume per risk allele carried in 748 people with a CIS or early relapsing remitting MS (RRMS) followed for 3 years[46] (Table 4). More recently, rs10191329^{AA} homozygosity was associated with a range of disability outcomes in 2 MS cohorts; one prospective cohort followed for 6.2 years from MS diagnosis and another retrospective cohort with median 12.1 years follow-up.[43] Rs10191329 was associated with higher serum neurofilament levels (Table 4) and subsequently with higher EDSS and disability accrual in the prospective cohort, and with higher EDSS, faster disability progression, and greater risk of SPMS in the retrospective cohort[43] (Table 3). However, it should be noted that the cohorts in both these studies[43,46] had overlapping participants with the IMSGC study.

Challenges in Replicating Severity Variants

While discovery cohorts in GWAS are subject to *genome-wide significance* thresholds ($p < 5 \times 10^{-8}$), replication efforts typically assess a vastly smaller number of variants and hence will have lower Bonferroni-corrected *p*-value thresholds. Despite this, replicating the associations of rs10191329 with disease severity outcomes in independent cohorts has proven difficult (Table 5). Explanations for the limited success in replication studies may include methodologic variations, statistical power, and environmental factors.

Disability Outcomes

Most studies of MS severity use ARMSS or MSSS scores for assessment of EDSS-measured disability in comparison with patients with similar age and disease duration (±2 years), respectively. These scores offer greater power to detect EDSS

Table 3 Observed Associations of rs10191329 With MS Severity Outcomes

Study	Cohort	Variable	Outcome	Main findings
Harroud et al. 2023[2]	GWAS: discovery cohort of 12,584 MS cases (mean disease duration 18.2 y) replication cohort of 9,805 MS cases (mean disease duration 15.8 y)	rs10191329^{A} risk allele dosage	Cross-sectional ARMSS	0.071 (0.047–0.094) greater ARMSS score with (discovery cohort; $p = 9.7 \times 10^{-9}$, replication cohort $p = 0.021$, combined $p = 3.6 \times 10^{-9}$)
	8,325 MS cases (5,565 from discovery cohort and 2,760 from replication cohort) with EDSS at 3 or more visits; spanning up to 13.9 y of follow-up from first study visit (mean 5.2 y)	rs10191329^{A} risk allele dosage	Longitudinal EDSS progression	Faster EDSS progression $p = 0.002$ Greater risk of 24-wk confirmed disability worsening: HR = 1.1 (1.02–1.18, $p = 7.9 \times 10^{-3}$)
		rs10191329^{AA} homozygosity		3.7-y shorter median time to EDSS 6.0 (need for walking aid): HR = 1.22 (1.09–1.38, $p = 9.3 \times 10^{-4}$)
Protopapa et al., 2024[43] NB: overlap with IMSGC study (22.5%)	Prospective cohort of 658 patients with MS followed from diagnosis (median 6.2 y)	rs10191329^{AA} homozygosity	Cross-sectional rank EDSS Disability accrual (%)	Greater rank EDSS vs rs10191329^{AC} heterozygotes ($p = 0.009$) and rs10191329^{CC} non-carriers ($p = 0.005$) Greater percentage experiencing disability accrual between visits ($p < 0.001$)
	Retrospective cohort of 82 patients with MS followed for median 12.1 y over median 4 visits	rs10191329^{AA} homozygosity	Cross-sectional rank EDSS	Higher rank EDSS scores than rs10191329^{CC} ($p = 0.04$) 5–10 y after diagnosis. Higher rank EDSS score vs both rs10191329^{AC} heterozygotes ($p = 0.012$) and rs10191329^{CC} non-carriers ($p < 0.001$) >10 y after diagnosis
			Longitudinal EDSS progression	Interaction term of rs10191329^{AA} with time associated with faster disability accumulation ($p < 0.001$) Faster time to EDSS 4.5 (unaided walking ability 300 m), HR = 5.43 (1.88–15.63), $p = 0.002$
			SPMS conversion	Greater risk of SPMS progression, HR = 19.32 (3.28–113.71), $p = 0.001$

Abbreviations: ARMSS = age-related multiple sclerosis severity; EDSS = expanded disability status scale; GWAS = genome-wide association study; HR = hazard ratio; IMSGC = International Multiple Sclerosis Genetics Consortium; MS = multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
95% CIs provided where available in the original study.

differences between 2 groups compared with EDSS, but as with EDSS, individual scores remain subject to fluctuation over time and limit predictive ability.[44,49] Although studies may use the same score for disease severity, differences in their longitudinal interpretation may also influence replication attempts. For example, the use of the median point in a longitudinal series (i.e., L-ARMSS or L-MSSS in the MSBase studies) may not capture the ultimate severity phenotype as well as a cross-sectional, end point measure of disability (Figure 1). Alternatively, as disease severity may vary over time, survival analyses, such as time to EDSS progression, may be used. While such measures capture how quickly disability is acquired, they do not inherently distinguish worsening due to relapse from progression independent of relapse activity (PIRA).[50]

Statistical Power and Modelling

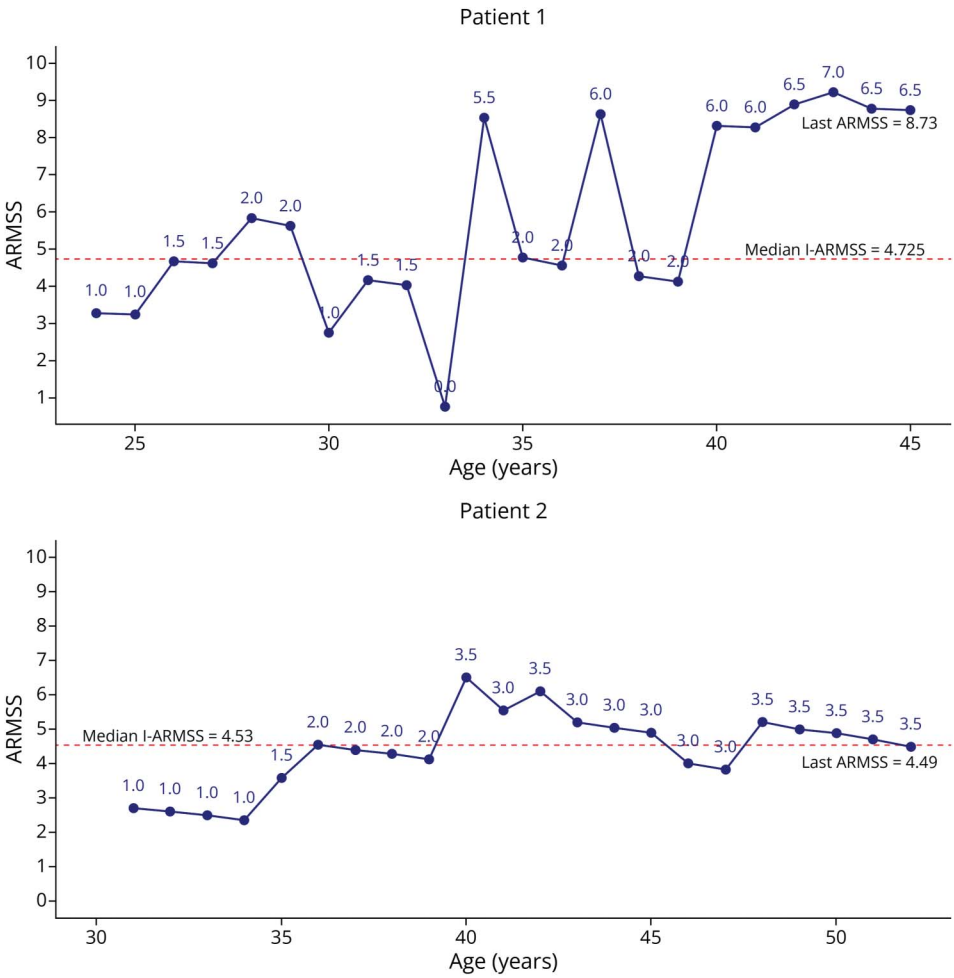
Replication studies thus far have been underpowered due to the small effect size of rs10191329, its low minor allele frequency (limiting homozygous carriers of the severity allele), and much smaller sample sizes than the IMSGC study. MSBase, the next largest study, calculated their power to detect an association between rs10191329 and binary severity outcomes (comparing "mild" vs "severe" quintiles) of L-ARMSS and L-MSSS at 83.8% and 84.8%, respectively, but was underpowered when considering these outcomes as continuous variables (41.8% and 61.4%) and tested median rather than end point severity[47] (Figure 1). This is further compounded by the winner's curse, where effect sizes in replication studies are often smaller in magnitude than that of the discovery cohort.[51]

Furthermore, the covariates included in statistical models, and demographics of the cohort, have the increasing potential to be more influential on findings in smaller, and so less-powered, studies. For example, in their main analyses, Kreft et al. observed that rs10191329 was associated with an effect in the opposite direction compared with the IMSGC study ($\beta = -0.06$ vs $+0.089$ in IMSGC), that is, a reduction in ARMSS rather than an increase. However, when they limited their cohort to 277 participants fulfilling inclusion criteria for the IMSGC study and matched covariates within the models, the directionality of effect inverted and was in keeping with the IMSGC study with larger effect size ($\beta = 0.70$), albeit not statistically significant ($p = 0.072$).[48] By contrast, the IMSGC were able to replicate their signals across different models during sensitivity analyses, due to their larger sample size and greater statistical power.

Environmental Factors, Including Treatment and Disease Temporality

Disease progression and severity in MS is a *complex trait* governed by the small cumulative effects of many genes and interaction with environmental factors, that is, any nongenetic

Figure 1 Median vs End Point Multiple Sclerosis Severity Measures



Longitudinal assessments of age-related multiple sclerosis severity (ARMSS) in 2 hypothetical patients* with different disease course. Dots indicate the ARMSS scores, with corresponding EDSS shown in labels above. Patient 1 exhibits large fluctuations in disability early in their disease course due to relapse activity before appearing to transition toward secondary progressive multiple sclerosis. Patient 2 has fewer relapses and shows indolent disability progression but overall develops less disability, as highlighted by a much lower last ARMSS. The dashed line highlights the median longitudinal ARMSS (L-ARMSS) scores, which are similar for both patients despite differing disease trajectories. Using L-ARMSS may be beneficial in reducing the effects of disability fluctuations associated with relapse activity and recovery, particularly in cohorts of shorter disease duration. However, in cohorts with lengthy follow-up, end point disability (last ARMSS) may better capture the ultimate long-term disability. *Based on example given by Manouchechrinia et al.[44]

influences on phenotype. Observation of certain genetic effects therefore may be contingent on the presence of the correct environmental conditions, which may vary between cohorts, over time or disease stage.[52] Differences in these environmental or temporal factors may contribute to varying genetic signals between different cohorts and hinder replication efforts.

Gasperi et al.[46] found no association of rs10191329 with baseline EDSS, or yearly change in EDSS, likely because their participants were much earlier in their disease course (exclusively CIS or RRMS) and had milder disability (median EDSS 1.0). Although 32% of their discovery cohort, and 87% of their replication cohort, overlapped with the IMSGC study, the IMSGC discovery cohort was enriched for older and more disabled participants, the majority (90.3%) having accrued disability despite having received disease modifying therapy. By contrast, both the South Wales MS registry[48] (26.9%) and London 30-year CIS cohorts[19] (13.7%) were largely untreated yet included a higher proportion of lower EDSS scores, capturing slower and less aggressive MS disability progression. This may reconcile why these studies were able to replicate associations of *suggestive variants* of MS severity (rs73091975, rs7289446 and rs868824) from the MSBase study (where use of median L-ARMSS may also bring forward the disability timepoint assessed) but could not replicate the IMSGC findings.[3,31,47,48]

Similarly, the smaller effect size of rs10191329 on ARMSS observed in the nonenriched IMSCG replication cohort compared with the discovery cohort (β = +0.044 vs +0.089, n = 9,805 vs n = 15,584 MS cases) was attributed to lower age (mean 47.2 years vs 51.7 years) and shorter disease duration (mean disease duration 15.8 years vs 18.2 years) (Table 3). However, the replication cohort was also less heterogeneous than the discovery cohort with >80% of participants from 2 centers (61.8% from Sweden and 21.6% from Munich, Germany) and hence potentially more prone to influence from environmental factors. For example, a greater proportion of patients in the replication cohort than in the discovery cohort were on higher-efficacy disease-modifying therapy (DMT); of those with DMT data, 30.7% of replication cohort were on

Table 4 Observed Pathologic Associations of rs10191329

Study	Cohort	Variable	Outcome	Main findings
Harroud et al., 2023[2]	Autopsy cohort consisting of 4,652 tissue blocks from 290 individuals with MS (mean disease duration 31.2 y)	rs10191329^{AA} homozygosity	Brainstem lesion counts Cortical lesion rate	1.83-fold (1.09–3.06, p = 0.023) more brainstem lesions 1.76-fold (1.15–2.69, p = 0.001) more cortical lesions
Engelenburg et al., 2025[45]	Nested case-control study comparing 6 rs10191329^{AA} carriers (mean disease duration 21.3 y) to 12 matched rs10191329^{CC} carriers from within IMSGC autopsy cohort	rs10191329^{AA} homozygosity	Foamy microglia pathology Lymphocytic infiltration Neuro-axonal damage	2.42-fold more lesions with foamy microglia (p = 0.04) and 1.35-fold fewer lesions with ramified microglia (p = 0.01) More CD79$^+$ B cells within normal-appearing white matter (p < 0.001) and more CD3$^+$ T cells in mixed lesions (p = 0.03) Higher frequency of amyloid precursor protein in normal appearing white matter (p < 0.001) and mixed lesions (p = 0.01) as well as lower cortical layer 2 neuronal density (p = 0.002)
Gasperi et al., 2023[46]	Discovery cohort 748 patients with CIS and RRMS and replication cohort of 360 patients (median scan interval 3 y) NB: overlap of cohorts with IMSGC discovery cohort (32% discovery cohort, 87% replication cohort)	rs10191329^{A} risk allele dosage	Yearly change in percentage brain volume	27.5% (15.0%–42.5%) faster decrease in annual brain volume loss, $p = 6.5 \times 10^{-5}$
Protopapa et al., 2024[43] NB: overlap with IMSGC study (22.5%)	Prospective cohort of 658 patients with MS followed from diagnosis (median 6.2 y)	rs10191329^{AA} homozygosity	Serum neurofilament levels at first follow-up (median 4.3 y)	rs10191329^{AA} associated with higher serum neurofilament levels (median 7.8 pg/mL, p = 0.005) compared with rs10191329^{AC} heterozygotes (median 5.8 pg/mL) and rs10191329^{CC} noncarriers (median 6.1 pg/mL)
		rs10191329 status	Serum neurofilament percentile (age-adjusted and BMI-adjusted) at first follow-up (median 4.3 y)	rs10191329 status independently predicted serum neurofilament percentile in analysis of covariance model (p = 0.039)

Abbreviations: BMI = body mass index; CIS = clinically isolated syndrome; IMSGC = International Multiple Sclerosis Genetics Consortium; MS = multiple sclerosis; RRMS = relapsing remitting multiple sclerosis.
95% CIs provided where available in the original study.

Natalizumab vs 13.2% in discovery cohort. As the replication cohort and discovery cohort had similar overall disability (EDSS; 3.36 vs 3.54 and ARMSS; 4.57 vs 4.23, respectively), these findings taken together suggest that the replication cohort may have acquired disability through more inflammatory activity and hence been treated more aggressively or alternatively acquired disability because they responded less well to treatment with DMT. Despite this, the association of rs10191329 with ARMSS in IMSGC replication cohort was significant (p = 0.021), although this would not have been the case had the sample size been smaller.

Future Directions

Unravelling the genetic contribution to MS severity has several potential clinical gains; phenotypic predictors could help stratify clinical trials and guide management, while insights into pathogenic pathways could provide new targets for drug development, particularly in progressive MS. However, achieving such clinical translation is currently limited by methodologic constraints and requires not only the identification of novel MS severity variants but further work to establish causality, disentangle complex genetic interactions, and explore ethnically diverse populations.

"Looking Beneath the Surface" of Disease Severity

Disability in MS may be acquired from relapse-associated worsening or result from PIRA.[50] Genetic studies have yet to make this distinction when interrogating single nucleotide variants, but neither of these clinical descriptors can be assumed to accurately reflect specific underlying pathobiological mechanisms driving disease progression.[53] Identifying associations between genetic variants and advanced MRI biomarkers may be helpful here, given that novel MRI measures are increasingly specifically able to capture elements of the complex disease processes driving disease progression.[54] For example, genetic associations with cortical lesions in particular seem to correlate with disease severity and progression.[2,19] However, we still do not know which advanced MRI biomarkers hold the greatest clinical relevance.

Although most advanced MRI biomarkers are not feasible at the large collaborative scale required for GWAS, brain atrophy and white matter lesion measures are more straightforward and may help provide temporal clarity to the predominant disease stage when genetic associations with disease severity are assessed. Recalling the associations of *HLA-DRB1*1501* with disease severity in 2 long-term longitudinal CIS cohorts,[19,20] longitudinal assessment of MRI biomarkers of

Table 5 Negative Replication Attempts of rs10191329 With Disease Severity

Study	Cohort	Variable	Outcome	Results	Main findings
Campagna et al., 2024[47]	1,813 relapse-onset MS patients from MSBASE register (median disease duration 18.1 y)	rs10191329^{A} risk allele dosage	Median L-ARMSS (mild [n = 447] vs severe [n = 464])	OR = 1.04, p = 0.80	No association with median longitudinal ARMSS or MSSS scores (whether continuous or binary variable)
			Median L-ARMSS	β = 0.08, p = 0.49	
			Median L-MSSS (mild [n = 585] vs severe [n = 466])	OR = 1.04, p = 0.81	
			Median L-MSSS	β = 0.42, p = 0.10	
Kreft et al., 2023[48]	1,455 patients from South Wales MS register (mean disease duration 14 y)	rs10191329^{A} risk allele dosage	Rank inversed normalized ARMSS at last visit	β = −0.06, p = 0.28 NB: in 277 MS cases fulfilling IMSGC study[2] inclusion criteria (β = 0.70, p = 0.072)	No association with last ARMSS and opposite direction of effect to IMSGC study, but reverted when matching covariates and inclusion criteria
		rs10191329^{CC} vs rs10191329$^{AA/AC}$	Time to EDSS 4.0	HR = 1.09, p = 0.48	No association in survival analyses
			Time to EDSS 6.0	HR = 0.90, p = 0.47	
			Time to EDSS 8.0	HR = 0.91, p = 0.28	
			Time to SPMS	HR = 0.92, p = 0.33	
Gasperi et al., 2023[46]	Discovery cohort 748 patients with CIS and RRMS and replication cohort of 360 patients (median scan interval 3 y)	rs10191329^{A} risk allele dosage	Baseline EDSS	β = 0.078, p = 0.28	No association with baseline EDSS or yearly change in EDSS over 3 y, despite overlap (32% discovery, 87% replication) with IMSGC discovery cohort
			Yearly change in EDSS	β = 0.032, p = 0.19	
Sahi et al., 2024[31]	51 CIS cases followed prospectively for 30 y (mean disease duration 30.8 y)	rs10191329^{A} risk allele dosage	Cross-sectional EDSS at 30 y	EDSS: β = 0.44 (−0.80 to 1.67), p = 0.48	No association with cross-sectional EDSS or ARMSS at 30 y or earlier timepoints
			Cross-sectional ARMSS at 30 y	ARMSS: β = 0.65 (−0.73 to 2.03), p = 0.35	
			Time to EDSS 4.0	HR = 1.70 (0.50–5.72), p = 0.39	No associations in survival analyses or with risk of developing SPMS
			Time to EDSS 6.0	HR = 1.31 (0.38–4.56)	
			SPMS progression	HR = 0.56 (1.33–2.36), p = 0.43	

Abbreviations: CIS = clinically isolated syndrome; EDSS = expanded disability status scale; HR = hazard ratio; IMSGC = International Multiple Sclerosis Genetics Consortium; L-ARMSS = longitudinal age-related multiple sclerosis severity; L-MSSS = longitudinal multiple sclerosis severity score; MS = multiple sclerosis; OR = odds ratio; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
95% CIs provided where available in the original study.

inflammation and neurodegeneration may help explain the functional role of genetic variants in the causation of disability, change in genetic associations over time, and differences in genetic signals between cohorts.

While in the short to mid-term, genetic associations with disability may be driven by inflammatory pathology,[17,20,21] it is plausible that in the longer term, severity signals shift toward neurodegenerative pathology. For example, variants in the *NECTIN2* gene within the APOE 19q13.13 gene region are implicated in the development of Alzheimer disease in several GWAS and may also be implicated in MS severity, as observed in the 30-year London CIS cohort study where the rs4807366 variant in *NECTIN2* was associated with increased grey matter pathology, faster EDSS worsening, and an increased risk of developing SPMS.[19] While this variant was not associated with EDSS in the IMSGC GWAS, this may be due to more indolent disability progression in this cohort, who had lower mean EDSS despite being largely untreated. MS disability acquired due to different mechanisms may have different genetic influences and identifying genetic associations with later disability changes or progression independent of relapses and MRI activity[53] may offer insights into novel pathways driving progressive MS, where we currently have few treatment options.

Defining the Phenotype of Disease Progression and Severity

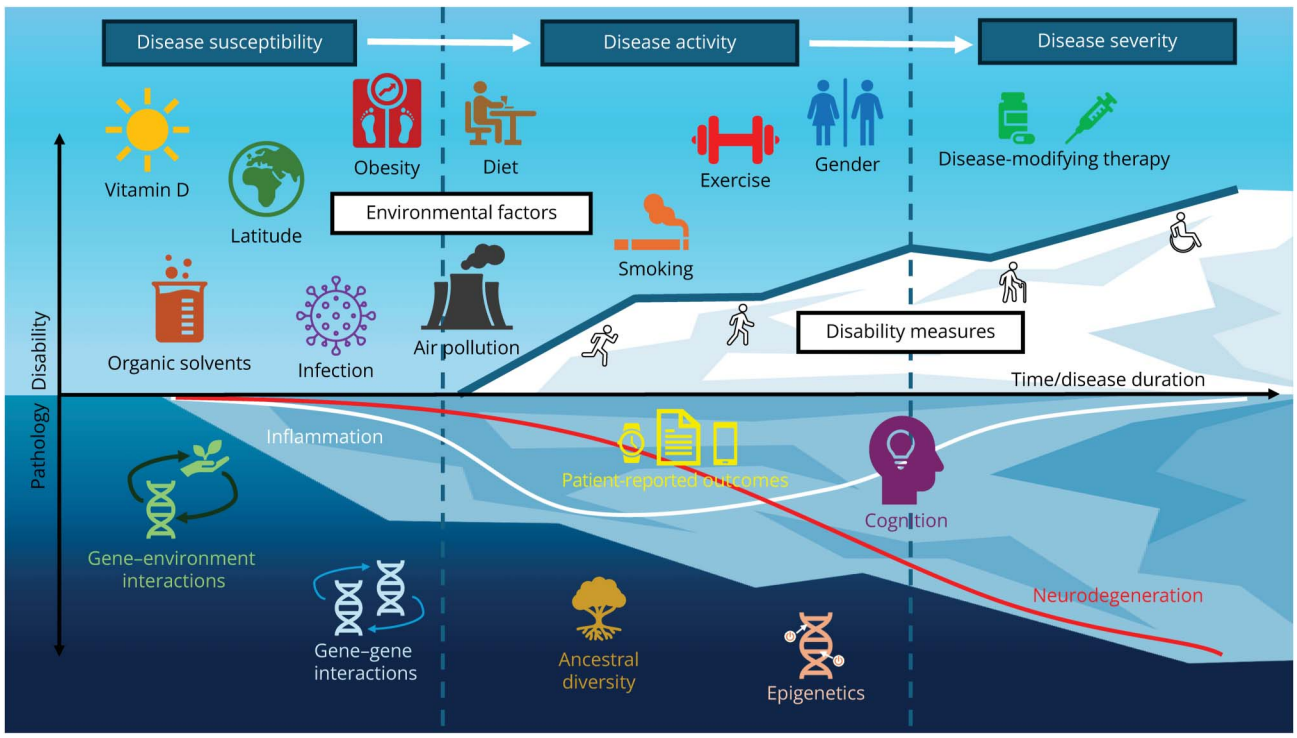
Current disability outcome measures (ARMSS and MSSS) improve sensitivity to detect change but are still based on the EDSS, which is heavily weighted toward ambulation and prone to inter-rater variability.[55] Furthermore, disease progression in MS goes beyond physical disability (Figure 2) and cognitive impairment is well recognized, particularly in progressive MS, yet often overlooked. Tests of upper-limb function and cognitive assessments are therefore increasingly recorded as secondary outcomes in clinical trials and often combined with EDSS into composite scores.[55] However, this may dilute domain-specific signals, and a more systematic approach to assessing outcomes, covering neurologic and cognitive outcomes separately, may reduce the risk of overlooking clinically significant effects. Furthermore, it is hoped that considering clinical metrics in concert with patient-reported outcome measures and patient generated data, for example, from wearable technologies, may help uncover previously unrecognized disease progression.[56]

Powering Prognostic Models

The explained heritability of MS severity is currently estimated at ~19%[2] and may increase as further severity variants are uncovered. However, novel variants are unlikely to have large effects, and prognostic power will depend on the accuracy of polygenic risk models. Heritability estimates assume additive genetic effects with increasing allele dosage, but genetic effects may be nonadditive, that is, a risk allele may have a dominant effect or have interactions with other genes.[52] Nonlinear machine learning algorithms may be able to capture this complexity beyond simple polygenic risk scores combining the linear effects of single variants. For example, the MSBase severity GWAS used a nonlinear machine learning algorithm to predict binary extremes of L-ARMSS outcome (severe vs mild) by combining 62,351 variants (associated at $p < 0.01$ with L-ARMSS GWAS) with clinical and demographic variables available at MS disease onset.[3] Their algorithm showed a high predictive accuracy and significantly outperformed a model including clinical and demographic variables alone despite the GWAS having no genome-wide significant variants. Although their clinical and demographic variables were limited (age at onset, sex, location of first symptoms), their findings suggest that the addition of genetic information could bolster clinical prognostic models of severity from clinical disease onset.

Beyond further increases in sample size, identification of low-frequency variants, not detected within conventional GWAS,

Figure 2 Looking Beneath the Surface of Genetic Involvement in MS



Although the genetic contribution to multiple sclerosis (MS) susceptibility is well established and implicates the peripheral immune system driving inflammation, uncovering the genetic underpinnings of MS severity has been murkier waters, with genetic signals and their functions harder to elucidate. While large-scale collaboration to increase statistical power, longer follow-up times, and disease duration in MS genetic studies will provide greater phenotypic clarity, physical disability is just the tip of the iceberg of disease progression and severity in MS, and we need to look "beneath the surface." Incorporating cognition and patient-reported outcomes may improve the phenotyping of disease severity, but we also need to consider the predominant underlying pathologic processes driving the different stages of MS progression to interpret genetic associations and causality. Meanwhile, work is needed to explore genetic signals in ethnically diverse populations and elucidate how putative severity variants exert function, interactions with other genes, environmental factors, and epigenetic mechanisms, all of which may vary over time and depend on exposure to certain environmental conditions.

through whole-genome sequencing or whole-exome sequencing may help increase heritability estimates and predictive power.[57] However, heritability as a measure is dependent on the space and time in which it is measured (genetically identical populations would exhibit different heritability estimates if exposed to different environments or if their environment changed over time). There are also practical difficulties in transferring predictive polygenic models which have been trained on one cohort to other genotyping technologies or to other populations (e.g., real-world settings).[52]

Expanding Ancestral Diversity

The ancestry or "population" that an individual is born into not only influences their genetic make-up but also the surrounding environmental factors they are exposed to and hence may be a confounder in genetic studies.[52] This issue of population structure is typically accounted for in GWAS through principal component analysis. Yet, pivotal GWAS in MS,[2-4,14] like most other large-scale genetic data sets, exclusively comprised individuals with European ancestry. Increasing the ancestral diversity of genetic data sets and replicating results across multiple ancestries in large-scale GWAS will widen the applicability of results, help reduce false-positive results driven by population structure, and strengthen the evidence for causality.[52]

As populations with different ancestry show different linkage disequilibrium structures, cross-ancestry genetic studies may also help in *fine-mapping* processes to identify causal variants.[52] However, this would only be successful if a genetic effect also occurs across different ancestries and not if it is unique to one population. Studies in different ancestral populations may uncover novel loci missed by GWAS, as well as variants with population-specific effects and provide insight into clinical differences in outcomes across ancestries.[13,58]

Establishing Causality and Understanding Pathogenesis

Causality is largely obscured in GWAS due to causal variants being held in linkage disequilibrium with several noncausal variants. While prognostic models hold significant utility even in the absence of causality or knowledge of the underlying mechanisms, this is not the case if we are to seek drug targets from genetic architecture. Here, it is necessary to pursue causality, disentangle gene interactions with environmental factors, and indeed with other genes. Even after identifying causal variants, we need methods to determine whether the genetic effects are *direct* or *indirect*, that is (from parents or sibling) and the biological mechanism, as most causal variants from GWAS do not code for proteins.

One potential solution to improve the identification of causal elements is to look toward larger genomic targets, such as genes or pathways. Gene-based methods aggregate the signal of several variants that affect the same gene and are associated with the same trait but are not held in linkage disequilibrium.[52] Pathway analyses extend this further, hypothesizing that biologically related genes, based on a prior knowledge of the biological pathways, are associated with a target phenotype. Both approaches effectively aggregate effects of numerous signals, with contextualized interpretation of associations within a biological pathway. This may increase discovery power and hence sample sizes required in comparison with GWAS by reducing the multiple testing burden, as these methods typically test thousands of genetic associations, compared with a million independent associations in GWAS.[59]

Elucidating Gene-Environment Interactions

Gene-environment interactions are not accounted for in GWAS, are notoriously difficult to study (as it almost impossible to adequately control for environment in human and animal experimental models), and yet may be important in MS. While there has been minimal exploration of gene-environment interactions in MS severity, there is evidence that deleterious environmental effects on MS risk, such as childhood obesity, smoking, solvent exposure, and infectious mononucleosis, are worse among carriers of *HLA-DRB1*1501* and may even be potentiated by polygenic autosomal genetic risk.[60]

Clarification of gene-environment interactions may also provide valuable insights into the mechanisms underpinning genetic associations. For example, a potential gene-environment interaction between the MS-risk variant rs7665090 near NF-κB1 and household chemical exposure has been associated with risk of pediatric-onset MS, implicating NF-κB signaling pathways in MS pathogenesis.[61] By assessing the performance of polygenic risk scores of severity across different groups, it may be possible to identify subsets of a population at the highest risk and who would benefit most from alteration of modifiable environmental factors.[52] For example, the relative risk differences between upper and low quartiles of a polygenic risk score for MS severity in patients who smoke could reveal the potential effect of smoking cessation on MS severity.

Similarly, we can explore the causality of modifiable environmental factors that are otherwise difficult to study through *Mendelian randomization* by assessing whether the genetic influences on a risk factor are associated with outcome. The IMSGC study used Mendelian randomization to show that heavier smoking was associated with worse MS severity, while suggesting educational attainment had a protective effect[2] and future genetic studies may be able to apply similar Mendelian randomization frameworks to identify gene-environment interactions.[62]

Gene-environment interactions may also be studied through *epigenetic* mechanisms, such as in the first epigenome-wide study of MS severity, which compared genome-wide methylation patterns (that are affected by environmental factors) between females at the extremes of relapse-onset MS

severity.[63] Consistent with the MS severity variants from GWAS, methylation signals were enriched in neuronal pathways, and machine learning models showed methylation levels classified disease severity more accurately than clinical features at diagnosis.

Conclusion

There has been significant progress in identifying the first MS severity variants, and the genetic architecture of MS severity now seems distinct from that of disease susceptibility. However, there remain significant knowledge gaps in understanding how these genetic variants exert their influence on disease progression. Although we are increasingly better able to characterize aspects of MS that are often overlooked clinically (such as cognition) and with routine MRI scans (e.g., gray matter pathology and chronic white matter inflammation), this is difficult to scale to the very large cohorts needed for GWAS, and so, other strategies are needed to derive genetic insight from deeply phenotyped but comparatively small cohorts. In clinical practice, we still lack reliable prognostic tools, and so, insights from GWAS and other group level studies will need to be distilled and likely combined with other features such as MRI findings, into models that provide actionable information at an individual level.

Author Contributions

N. Sahi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. O. Ciccarelli: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. H. Houlden: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. D.T. Chard: drafting/revision of the manuscript for content, including medical writing for content; study concept or design.

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