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# Multi-omics and Other Missing Pieces in the Genetic Mystery Puzzle of Multiple Sclerosis*

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## Commentary

Multiple Sclerosis (MS) is a neurological condition in which areas in the brain and spinal cord become damaged, causing the layer of protection around nerves, the myelin sheath, to be destroyed. MS is considered an autoimmune disorder, which means that the immune system is attacking the body due to a malfunction that triggers the body to attack itself. Other autoimmune disorders include lupus, type 1 diabetes, and rheumatoid arthritis.

The contribution of genetic inheritance in autoimmune disorders is difficult to explain because there are rarely families with direct evidence of parent-to-child inheritance of the disorder (Didonna and Oksenberg 2017; Patsopoulos 2018; Mo et al. 2019; Goris et al. 2022; Kim and Patsopoulos 2022; Liu et al. 2022; Shams et al. 2022). That type of inheritance, that is following Mendelian genetics, has been found in other adult-onset disorders, for example, cardiac arrhythmias, muscular dystrophies, or early onset Alzheimer disease. More often researchers find affected individuals have inherited potential risk alleles in a variety of genes. However, most geneticists believe that all human disease is genetic, or at least influenced by genetic or epigenetic factors (Mo et al. 2019). For example, how badly injured a person is after a car crash is influenced by genetic inheritance. If an individual has more fragile bones than others, they may have more fractures, even though they may not have a fragile bone disease.

Teasing out the genetic contribution to common diseases (ie, cancer, type II diabetes) and autoimmune disorders (ie, MS, lupus) has been difficult because we don't always know the impact of a combination of genetic factors, with or without adding in environmental or other factors (McCarthy et al. 2008). Some ways to work through these difficult problems are through very large studies, meta-analysis of many studies taken together, and adding in genome-wide association (GWA) studies. More recently, some researchers have used multi-omic approaches, that is, using genomic sequencing plus biochemical testing plus gene expression studies or other data amassed from the same patient set to look for the factors leading to disease onset (Mo et al. 2019; Liu et al. 2022; Shams et al. 2022).

Genetics and genomics have come a long way in the past 30 years. The human genome project published the rough sequence of the human genome 20 years ago. The complete human genome sequence was finally published last summer. There are still refinements underway (T2T or telomere-to-telomere genome and the pangenome project). We don't know the impact of alterations in a majority of the DNA that lies between genes. There are many regulatory elements that are still being elucidated. We are all still learning.

In a GWA study (McCarthy et al. 2008), a group of people, often selected because they have a similar ethnic ancestry, disease process, or just because they sign up and undergo testing for a specific set of DNA locations or single-nucleotide variants (SNVs). Some common sources of this type data include the UK Biobank, the All-of-US study, Geisinger Medical Center, Kaiser medical system, and the military or veterans' health services. The SNVs are often selected because the researchers already have the right reagents to test them or because there were prior studies that showed these were useful. The test is usually run on a microarray, although DNA sequencing may be used instead.

An analysis of the data will then show if the SNVs and the disease process are both found in the same individuals. GWAS results don't necessarily show a specific correlation of a gene, variant, and disease process, just an association in the tested population. Moreover, how the data are analyzed matters, and erroneous conclusions have been documented through secondary analyses. One recently published paper on the purported association of dementia with hormone replacement therapy used by middle-aged women contradicted prior studies and stated that even the short use of hormone replacements may be associated with later onset dementia (Pourhadi et al. 2023). Other researchers immediately stated that they did not agree with the analysis that hormone replacement therapy is causally associated with the later onset of dementia, including an editorial in the same journal (Kantarci and Manson 2023).

MS is usually not inherited as a Mendelian disorder. Instead, there are risk factors that may be inherited as well as environmental and other factors that influence whether a person develops MS. Most gene variants that may increase the risk of MS have been identified by GWA studies. Very few families with an inherited form of multiple sclerosis have been identified. Some of those families underwent sequencing studies. There are many other factors that are associated with MS, including the potential association with later onset infection with Epstein-Barr virus (EBV) (Bjornevik et al. 2022; Horwitz et al. 2022; Lanz et al. 2022; Rostgaard, Nielsen, et al. 2022; Rostgaard and Hjalgrim 2023).

A researcher can gauge the frequency of identifying specific alleles (SNVs), the number of people who show symptoms of a disease when they harbor a specific SNV, a concept known as penetrance, and the diagnosis of a disease. These types of studies may show that low-frequency variants with only intermediate penetrance may influence disease susceptibility (Figure 1 from McCarthy et al. (2008)). This diagram indicates that sometimes finding the correct genomic associations

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Figure 1: Frequency variants diagram reprinted from McCarthy et al. (2008) with attribution.

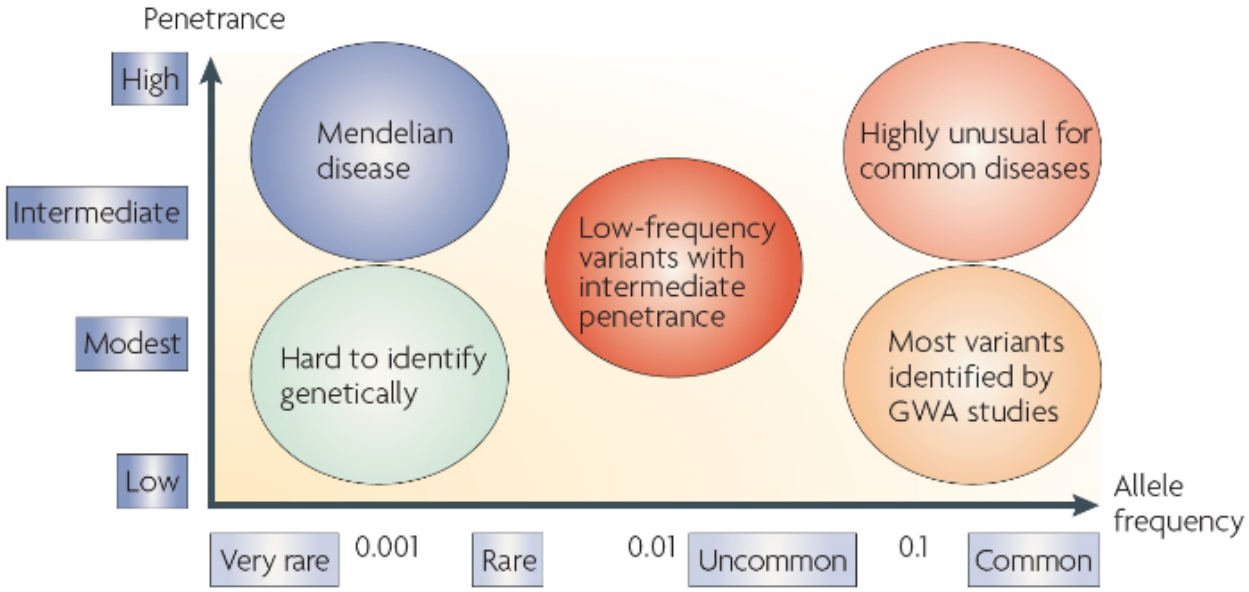



Figure 2: Multi-omics study workflow reprinted from Liu et al. (2022) with attribution.

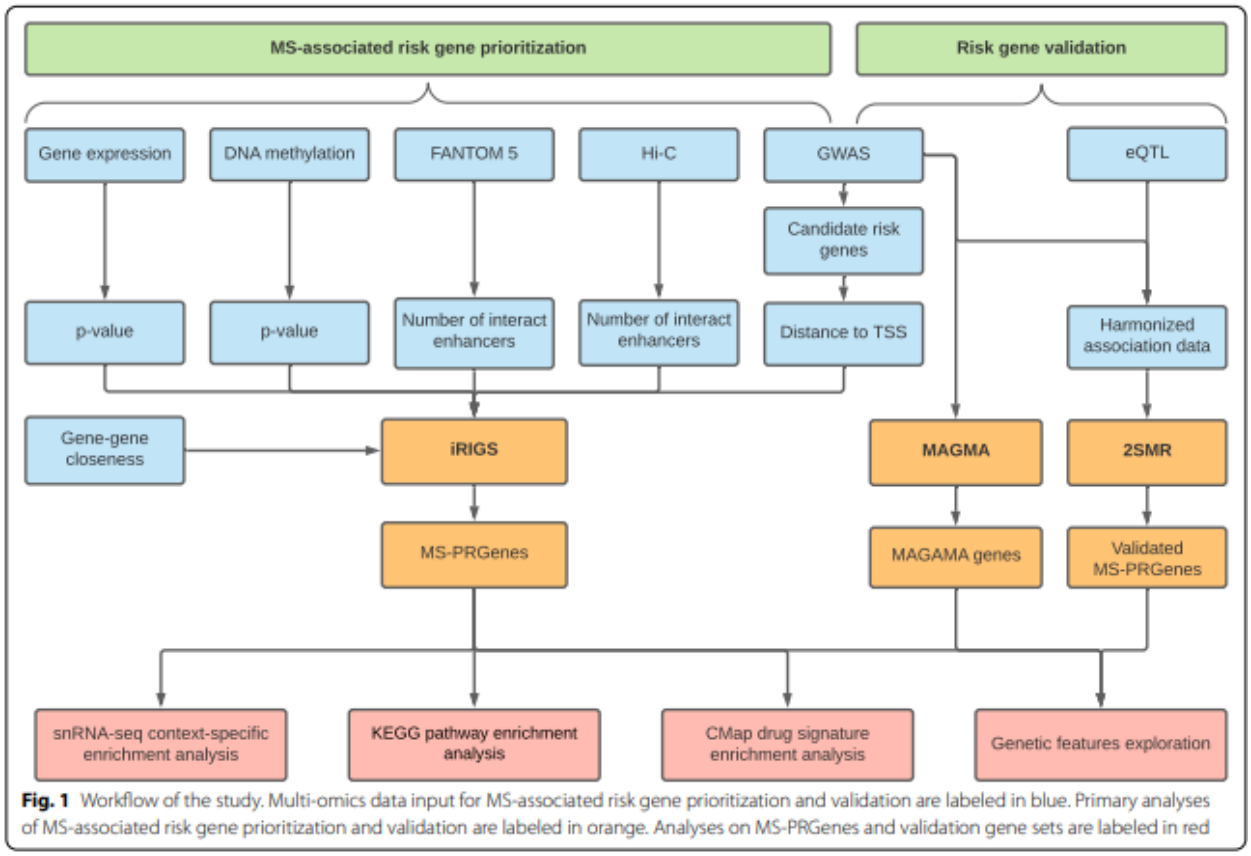



**Fig. 1** Workflow of the study. Multi-omics data input for MS-associated risk gene prioritization and validation are labeled in blue. Primary analyses of MS-associated risk gene prioritization and validation are labeled in orange. Analyses on MS-PRGenes and validation gene sets are labeled in red

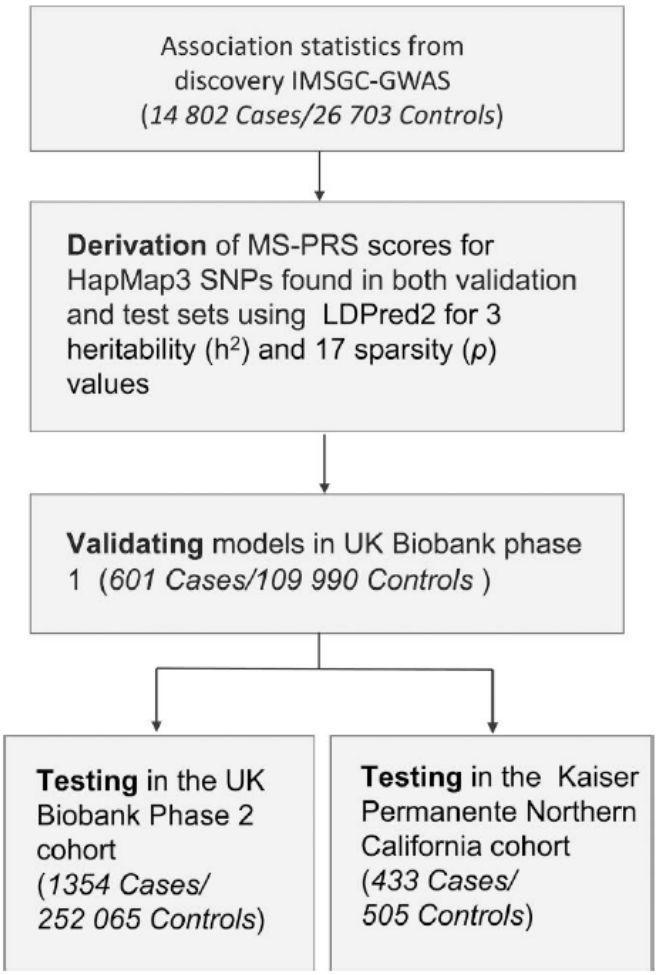
may not be easily found using GWA studies alone. Most variants that are identified by GWA studies are common variants with low penetrance, and not likely causal.

Recent research has concentrated on creating a risk assessment formula. Researchers have taken large datasets to tease out which factors are most likely to be combined in patients who are diagnosed with MS. For example, taking age plus genetic sex plus a score that is derived from the presence of several specific genetic variants may allow clinicians to better figure out which individuals have a greater risk of developing MS. Whether other members of the family have MS is a part

of the risk equation with some of the polygenic risk calculators. Usually there is one set of data used to figure out the formula, and a second separate dataset used to test whether the formula works. One research group published their workflow for creating a multifactor risk formula that includes sequencing studies and multi-omics in MS patients. The numbers of different types of analyses to create this risk assessment is large and these tests they used are both complex to understand and not available as clinical tests (Figure 2 from Liu et al. (2022)). Another

Figure 3: Workflow reprinted from Shams et al. (2022) with attribution.




workflow diagram from a different research group (Figure 3 from Shams et al. (2022)) discussed the numbers of research subjects with MS and control subjects from the discovery and verification arms of their study. It is easy to see that the research to identify risk factors and formulas to assess risk in patients who do not yet have MS takes a large number of data sets with thousands of research subjects and controls. From these two papers, we can infer that these studies are both costly and require individuals who participate to undergo many different laboratory tests and imaging studies.

From a review of many of the recently published articles on the genetics of MS, certain factors were found to increase risk to increase the risk of developing MS. Pathway-specific factors and genes that added risk (Liu et al. 2022) include:

- Adaptive immune response (IL-5 and IL-2 signaling)
- T cell receptor signaling
- MHC class II antigen presentation
- Interferon gamma signaling
- Complement cascade genes
- Viral and parasitic infection response pathways
- Pathways identified in other autoimmune diseases like lupus, Hashimoto thyroiditis, type 1 diabetes
- Cell adhesion and extracellular matrix organization, protein glycosylation genes
- VEGF and NOTCH pathways
- Chromosome 6 where some immune-response genes are located

In addition, several papers were published in 2022 that looked at large data sets, for example, military recruits who were tested for exposure to Epstein-Barr virus (EBV) or data from countries where the medical system regularly tests the whole population for viral exposure. Some of the analyses (Bjornevik et al. 2022; Horwitz et al. 2022; Lanz et al. 2022; Rostgaard, Nielsen, et al. 2022; Rostgaard and Hjalgrim 2023) have suggested that individuals infected with EBV for the first time as young adults may have an increased risk of developing MS. There were arguments about the quality of the analyses published at the same time. Most of these studies did not test the participants for genomic data, thus there was not list of genes or variants that accompanied these papers. There was no data showing that EBV alone causes MS in every infected individual. Perhaps there are specific genetic variants that allowed the people with later EBV infections to then develop MS? We don't have an answer to this question at this time.

Another avenue of research has been to look at the genetics of MS severity. The question asked is why do some individuals progress rapidly while others have a slower or intermittent course? In a 2023 paper, two large consortia worked together to perform a GWA study solely looking at the severity score of young adults and genetic variants found in those who progressed at different rates. They found an association between patients with more rapid progression and harboring two copies of a specific risk allele. Those individuals with two copies of this SNV required walking aids 3.7 years before other patients with no copies of this allele (Harroud et al. 2023; Beecham and Stridh 2023). The group who progressed rapidly also had more abnormalities in the brainstem and cortex of the brain. In addition, this consortia found a separate possible association between another SNV and heritability of better brain function. Among those participants in the research, there were genetic variants showing slower progression in those with higher educational attainment as well as a lower likelihood that the patient had smoked.

## Summary

Mendelian disorders usually follow specific patterns of inheritance: autosomal recessive, autosomal dominant, X-linked. There are also mitochondrial disorders caused by mitochondrial DNA variants. MS does not follow these modes of inheritance in most affected individuals. There may be factors other than direct genetic inheritance of a pathogenic variant or variants or in addition to a number of inherited

variants. There may be other risk factors, like late-onset EBV infections or other triggers that cause the immune system to attack the myelin sheath. Many types of studies have been done to uncover the genetics of MS. Risk alleles are often uncovered through large population GWAS studies. Families with several affected members may undergo sequencing studies. Scientists are then able to analyze the data to derive polygenic/multifactorial risk scores. New research uses multiple sources of scientific data to find risk alleles and other risk factors, and to calculate the relative risk that any individual might have using a number of these factors. The new multi-omics methods, where a number of research tools are used to test a large number of patients with MS and control subjects may be the best way to uncover the most accurate formula to derive a risk score.

## Citation

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