Before the genomics technology revolution allowed us to do genome-wide science, genetics research relied on our limited knowledge about a subject to generate hypothesis and candidate genes to study. Despite the level of naiveté, several associations with susceptibility to a complex disease such as multiple sclerosis (MS) were discovered. Of these, *HLA-DRB1* and *IL7R* stood out as being confirmed and refined early by the genome-wide association studies (GWAS) that followed.\(^2\) Despite the expense and gargantuan efforts, these GWAS have successfully led to the discovery of more than 100 additional genes, albeit with smaller effect sizes, that contribute to MS susceptibility.\(^3\) This list keeps growing, but it comes with no surprise that most of these genes identified the immune system as one large candidate for MS susceptibility.

In the early days of “candidate-gene” research in MS, one of the interesting and arguably more clinically relevant questions was whether some biologically plausible candidates were indeed more relevant to phenotypic variability of MS than susceptibility.\(^4\) Could the same genes contribute to both susceptibility to and severity of MS? Is it possible that what we call susceptibility to MS is indeed one huge heterogeneous group of phenotypic variability masquerading as a single disease? If the answer is yes to both of these questions, we could also potentially explain the small effect size of various genes that have been identified. Several endophenotypic clusters of patients could be driving the associations that appear weak because of dilution by the massive population sizes of GWAS. The tricky part now is to separate these endophenotypic clusters and decide on the outcome measure to be used. After all, despite the heterogeneity in pathology and clinical disease course in MS, susceptibility is still a low-hanging fruit for genetic association studies. A patient can be defined as having MS much easier than defining the endophenotype they belong to. The latter issue can also be plagued by the variability of assessment of such phenotypes in multicenter study designs needed to recruit the right sample size.

In this issue of *Neurology® Genetics*, George et al.,\(^5\) in a repurposing experiment (as opposed to a brand-new GWAS study), used susceptibility loci from previous MS GWAS experiments as candidate genes for potential severity determinants in MS. Their specific question was: Do the 52 risk alleles of MS also confer an increased severity of the disease analyzed by the Multiple Sclerosis Severity Score (MSSS)? The answer was a loud and clear NO.

First interpretation of this result would be that susceptibility and phenotypic variability genes potentially diverge as suggested previously.\(^1\) However, the problem may simply be the measure we are using as well. MSSS based on reranking of the Expanded Disability Status Scale (EDSS), essentially pushing the EDSS to normality in the studied population, may not be the most appropriate outcome when it comes to genotype-phenotype analyses. Another explanation for the negative finding could be that severity can potentially be affected by environmental factors such as life-long vitamin D availability, smoking, and obesity much more than susceptibility determined earlier in life. It is also possible that severity may still be a factor of multiple susceptibility variants acting in tandem in a given pathway to increase the effect of that pathway at an individual or subpopulation level. Finally, as is the case with all large studies to increase power, are we paradoxically missing an important signal just because of our assumption that each subpopulation of MS should behave similarly? Pooling patients for large studies might dilute the effect of such subpopulations. The studied population was selected based on having MS as a common denominator and not enriched for a specific phenotype under question. With all these possibilities, the current study raises many potential avenues to explore. This is just the dawn of such extensive studies targeting specific phenotypes. However, for success in such efforts, definition of biologically relevant phenotypes that can reliably be defined across centers is the key.

An example of such a proof-of-principle study recently demonstrated that *SCN10A* polymorphisms...
that affect Na\textsubscript{v}1.8 expression in the cerebellum in MS but not in the normal brain can contribute to functional impairment in cerebellar-thalamic connectivity in MS.\textsuperscript{6,7} The clinical outcome studied was focused on the motor-cerebellar system under question, and findings were revealing for a future potential drug development strategy. These contemporary approaches to candidate gene studies pave the way forward. We certainly have the powerful genomic tools. Our next step is to pause, go back to bedside to develop the fine-tuned endophenotypes well beyond MSSS, and build the cohorts for the specific endophenotypes of MS.

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A new dawn for genetic association studies in multiple sclerosis
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