COMMENTARY

Genetic Control of Nerve Conduction Velocity May Influence Multiple Sclerosis Phenotype

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CME Accreditation Statement: This activity (“ASIP 2014 AJP CME Program in Pathogenesis”) has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the American Society for Clinical Pathology (ASCP) and the American Society for Investigative Pathology (ASIP). ASCP is accredited by the ACCME to provide continuing medical education for physicians.

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CME Disclosures: The authors of this article and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, which leads to large focal demyelinated lesions and diffuse neurodegeneration in the entire brain and spinal cord. The cause of MS is unknown, but current concepts favor an inflammatory process driven by autoimmunity, which leads to demyelination and neurodegeneration through either antigen-specific immune mechanisms or activation of immune effector mechanisms by the chronic inflammatory process.1 Central aspects of the disease, such as inflammation, demyelination, and neurodegeneration, are, in part, reproduced by an autoimmune disease in different animal species, experimental autoimmune encephalomyelitis (EAE), which can be induced in genetically susceptible animals by active sensitization with brain antigens.2 The induction of the MS and EAE appears to be driven by genetic and environmental factors.

Many studies performed during the past three decades have tried to identify genes that are involved in determining the risk of developing MS, and they have shown that multiple genes are involved, each of them with only mild to moderate impact. Not unexpectedly, recent large genome-wide association studies have identified numerous genes involved in antigen recognition of T cells and in the control of immune reactions.3,4 Although it can be expected that genes regulating the susceptibility of the target nervous tissue may have an influence on disease incidence and phenotype, so far only few potential candidates have been identified.1 The reason for this situation may be that current gene association studies mainly focused on disease incidence but not on disease phenotype.

A study published in this issue of The American Journal of Pathology5 describes the association of a polymorphism in a new gene with MS and EAE, which is involved in the regulation of conduction velocity in the central nervous system. The study is based on the identification of a gene polymorphism, which is associated with disease susceptibility in EAE and with a decrease of nerve conduction velocity in the central nervous system in mice, detected electrophysiologically by analysis of motor-evoked potentials. Detailed fine mapping of the locus in mice allowed the authors to identify inositol-polyphoshate-4-phosphatase II (INPP4B) to be associated with this phenotype, and its involvement was directly validated in transgenic animals carrying this specific gene polymorphism under the control of a ubiquitous neuronal promoter. Finally, the authors show that this polymorphism is also conserved in humans and is significantly associated with MS incidence in a Spanish cohort of patients with MS. A replication analysis in a German patient and control cohort found a similar trend, which, however, did not reach statistical significance, possibly due to different allele frequencies between the population cohorts.

This study represents an interesting example on how minor changes in conduction velocity, which do not result in a clinical phenotype in control populations, may aggravate disease in conditions such as EAE or MS. Demyelination and neurodegeneration in the MS brain can be compensated...
in patients because of the large functional reserve capacity of the human brain. However, nerve conduction velocity is profoundly affected in conditions of demyelination and, therefore, even a minor deficit in conduction velocity may lead to an increased clinical phenotype, when the patients are on the verge of exhausting their functional reserve capacity. Thus, one could expect that in MS patients the association with the described gene polymorphism becomes more prominent, when instead of disease incidence, disease severity is used as a clinical outcome measure. This aspect has not been analyzed in this study. At this end, this study reports an interesting observation, but the neurobiological mechanisms, which provide a clear picture, of why *INPP4B* impairs conduction velocity remain unclear. The authors show no major loss of myelin in animals carrying the allele associated with reduced nerve conduction velocity, thus making a direct effect on myelination unlikely. According to previous studies, *INPP4B* may be involved in Ca\(^{2+}\) signaling in synapses, such as transmitter release. The questions, whether these mechanisms are responsible for reduced conduction velocities and what their precise role is in MS and EAE lesions, will have to be addressed in future research.

**References**