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Gene That Controls Nerve Conduction Velocity Linked to Multiple Sclerosis

Evidence Found in Both Human Multiple Sclerosis Patients and Experimental Mouse Models, According to Research Published in *The American Journal of Pathology*

Philadelphia, PA, August 13, 2014 – A new study published in *The American Journal of Pathology* identifies a novel gene that controls nerve conduction velocity. Investigators report that even minor reductions in conduction velocity may aggravate disease in multiple sclerosis (MS) patients and in mice bred for the MS-like condition experimental autoimmune encephalomyelitis (EAE).

A strong tool for investigating the pathophysiology of a complex disease is the identification of underlying genetic controls. Multiple genes have been implicated as contributing to the risk of developing MS. Unlike studies that have focused on genetic regulators of inflammation, autoimmunity, demyelination, and neurodegeneration in MS, this study focused on nerve conduction velocity. Investigators found that polymorphisms of the inositol polyphosphate-4-phosphatase, type II (*Inpp4b*) gene affect the speed of nerve conduction in both mice with EAE and humans with MS.

“Impairment of nerve conduction is a common feature in neurodegenerative and neuroinflammatory diseases such as MS. Measurement of evoked potentials (whether visual, motor, or sensory) is widely used for diagnosis and recently also as a prognostic marker for MS,” says lead investigator Saleh M. Ibrahim, MD, PhD, of the Department of Dermatology, Venereology, and Allergology of the University of Lubeck (Germany).

Using several genomic approaches, the investigators narrowed their search to the genetic region controlling the enzyme inositol-polyphosphate-4-phosphatase II (*INPP4B*), the product of which helps to regulate the phosphatidyl inositol signaling pathway. Enzymes in this family are involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival, and intracellular communication.

In one series of experiments, the researchers analyzed the genetic locus EAE31, which previously had been shown to control the latency of motor evoked potentials and clinical onset of EAE in mice. Using advanced techniques including congenic mapping, *in silico* haplotype analyses (computer simulations),

and comparative genomics (from rats, mice and humans), they were able to “finemap” the focus to *Inpp4b* as the quantitative trait gene for EAE31.

When the investigators analyzed this region in eight different strains of mice, they found they could divide the strains into two groups based on differences in amino acid sequences. The strains with the longer-latency SJL/J allele had the two amino acids (arginine and proline), whereas those with the shorter-latency C57BL/10S allele had others (serine and histidine). “These data suggest that *Inpp4b* structural polymorphism is associated with the speed of neuronal conduction,” comments Dr. Ibrahim.

In another experiment, the scientists compared motor conduction velocity in genetically modified mice with a mutant *Inpp4b* gene to that of control mice. The nerve conduction in this group was slower than in the control group.

Finally, the investigators studied *INPP4B* polymorphisms in MS patients. They looked at two cohorts: one from Spain (349 cases and 362 controls) and a second from Germany (562 cases and 3,314 controls). The association between the *INPP4B* polymorphisms and susceptibility to MS was statistically significant when the cohorts were pooled. However, although the Spanish cohort showed a strong association between *INPP4B* and MS, the association was weaker in the German cohort. “The exact reason for the diverging effect across these populations remains unresolved,” states Dr. Ibrahim.

In an accompanying commentary, Hans Lassmann, MD, of the Center for Brain Research of the Medical University of Vienna (Austria) notes, “This study represents an interesting example of 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.” In other words, impaired nerve conduction may have a greater impact on those with MS compared to healthy individuals. Noting that the study reported no major loss of myelin in animals carrying the mutant allele, Dr. Lassmann comments that it is still unclear which neurobiological mechanisms underlie the *INPP4B*-associated impaired conduction. One suggestion is that *INPP4B* may be involved in calcium ion signaling within synapses, affecting neurotransmitter release.

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NOTES FOR EDITORS

“Nerve Conduction Velocity Is Regulated by the Inositol-Polyphosphate-4-Phosphatase II Gene,” by Susanne Lemcke, Susen Müller, Steffen Möller, Arne Schillert, Andreas Ziegler, Sabine Cepok-Kauffeld, Manuel Comabella, Xavier Montalban, Thomas Rülicke, Kutty Selva Nandakumar, Bernhard Hemmer, Rikard Holmdahl, Jens Pahnke, and Saleh M. Ibrahim. (DOI: http://dx.doi.org/10.1016/j.ajpath.2014.05.021).

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“Commentary: Genetic Control of Nerve Conduction Velocity May Influence Multiple Sclerosis Phenotype,” by Hans Lassmann (DOI: http://dx.doi.org/10.1016/j.ajpath.2014.05.013).

Both appear online ahead of *The American Journal of Pathology*, Volume 185/Issue 3 (September 2014) published by Elsevier.

Full text of the article and commentary is available to credentialed journalists upon request; contact Eileen Leahy at 732-238-3628 or ajpmedia@elsevier.com. Journalists wishing to interview Dr. Saleh M. Ibrahim may contact him directly at +49 451 500 5250 or Saleh.Ibrahim@uksh.de.

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