Genetic differences may help explain response to multiple sclerosis treatment

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By comparing the DNA of patients with multiple sclerosis whose symptoms are reduced by interferon beta therapy to the DNA of those who continue to experience relapses, researchers may have identified important genetic differences between the two, according to an article posted online today that will appear in the March 2008 print issue of Archives of Neurology, one of the JAMA/Archives journals. These differences could eventually be used to help predict which treatments will help which patients.

Multiple sclerosis (MS) is a neurological disorder in which nerve fiber coatings degenerate, causing muscle weakness, spasms and partial or complete paralysis. A protein known as recombinant interferon beta is widely used to treat multiple sclerosis symptoms and possibly slow progression of the disease, according to background information in the article. “Despite interferon beta therapy, up to 50 percent of patients with MS continue to experience relapses and worsening disability,” the authors write. “In addition, adverse effects, such as flulike symptoms and depression, are common, leading many patients to discontinue therapy.”

Esther Byun, M.D., of the University of California, San Francisco, and colleagues of a multi-center international collaboration followed a group of 206 Southern European patients with relapsing-remitting MS—the most common type, in which patients experience periods of symptoms followed by periods of symptom-free remission—for two years after they began interferon beta therapy. Every three months, neurologists

analyzed patients' disability levels; throughout the study, 99 responded positively to interferon beta and 107 did not.

The researchers pooled the DNA of individuals in each group and used microarrays to identify, across the genome, genetic markers associated with the response to interferon beta. They identified the top 35 single nucleotide polymorphisms (SNPs), changes in a single base of DNA, that were candidates for further analysis. They then located these SNPs in each individual participant to see if the mutations apparent in responders differed from those in non-responders. After this analysis was complete, an additional 81 individuals with MS (44 responders and 35 non-responders) were included and the DNA of responders was again compared to that of non-responders.

Of the 35 candidate SNPs identified in the first screen, 18 were found to remain significantly associated with treatment response in the combined screen. Seven of the SNPs were located within genes, while the others were located in the space between genes. Some of the SNPs were located in genes previously linked to processes involved with MS, such as the growth and repair of nerve cells.

"The beneficial outcomes of interferon beta therapy for patients in the relapsing-remitting phase of MS have been clearly shown," the authors write. "On the other hand, the effect of this treatment is partial, and a substantial amount of patients are not responders. Hence, in the absence of prognostic clinical, neuroradiological and/or immunological markers of response, the question remains who and when to treat when adverse effects, inconvenience and the cost of the drug are significant."

The identification of genetic mutations that affect response to interferon provides important new information about how the drug functions in the body, bringing medicine one step closer to rational drug design and personalized medicine, the authors note. However, additional research

will be needed to fully predict treatment outcomes based on DNA analysis.

Source: JAMA and Archives Journals