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Exploring the Epigenetics of Alzheimer Disease

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Genome-wide association studies have been tremendously successful at unraveling the genetic architecture of neurological disorders (see <http://www.genome.gov/gwastudies/> for an updated list). Alzheimer disease is a particularly good example of the power of this technology, with multiple loci already identified.¹ Although the publication of a susceptibility locus is an important milestone in any disease, it represents only the opening act because the identity of the responsible gene within a locus is not always obvious. Without this knowledge, it becomes difficult (if not impossible) to establish a functional connection between genetic variation and the underlying pathobiology. Not surprisingly, this circumstance is a major challenge now faced by the entire genomics field. To bridge this gap, a multipronged approach has been adopted to delineate the effect of genetic variation on the expression of neighboring genes (known as expression quantitative trait loci mapping²) and to quantify the effects of epigenetic phenomena in regulating gene transcription. The term epigenetics covers a gamut of mechanisms such as DNA methylation, chromatin remodeling, gene expression regulation by microRNA, histone modification, and others.

The article by Yu and colleagues³ in this issue of *JAMA Neurology* focuses on the contribution of DNA methylation in Alzheimer disease loci to the susceptibility for this condition. In its simplest terms, methylation controls gene expression by blocking the binding of transcription factors to gene regulatory elements. The higher the methylation in and around a gene, the lower is its expression. In reality, the spatial and temporal biological consequences of methylation are more nuanced, but this paradigm remains useful when interpreting methylation data. Methylation studies are challenging to perform because this epigenetic parameter varies across and even within tissues. For example, the methylation pattern observed in blood cells of an individual significantly differs from that in his or her brain.⁴ A major strength of the study by Yu et al is that they analyzed the methylation status in the tissue involved in the disease process, namely, the brains of several hundred patients diagnosed as having Alzheimer disease. These samples were collected as part of 2 large prospective cohorts, highlighting the value of such tissue collections, something that needs to be done in other neurological diseases as well.

Conflict of Interest Disclosures

Dr Traynor reported having a patent pending on the clinical testing and therapeutic intervention for the hexanucleotide repeat expansion of C9ORF72. No other disclosures were reported.

So what did they find? First and foremost, the methylation of 5 loci (SORL1, ABCA7, HLA-DRB5, SLC24A4, and BIN1) was significantly associated with a pathological diagnosis of Alzheimer disease. Within each of these 5 genes, the authors also identified methylation patterns associated with the key pathological changes of Alzheimer disease, namely, β -amyloid load and tau tangle density. Finally, they examined expression data generated for the same samples to determine the effect of methylation on gene expression. Although this last analysis indicated only weak correlation, it showcases the ability of modern genomics to leverage different data sets. Future analysis of larger cohorts may have greater power to identify such methylation quantitative trait loci.²

In essence, the article by Yu and colleagues provides compelling evidence implicating DNA methylation in the pathogenesis of this common form of neurodegeneration. It replicates previous studies^{5,6} showing that the methylation of ABCA7, BIN1, and SORL1 is important in Alzheimer disease pathogenesis and nominates 2 additional loci as important, namely, HLA-DRB5 and SLC24A4. Plausible biological stories are already emerging for some of these genes. For example, the protein encoded by the SORL1 gene controls β -amyloid production.⁷ Reduced SORL1 protein levels (such as might be expected with increasing levels of DNA methylation in the locus) would lead to a corresponding increase in β -amyloid production and an increased risk of dementia. Presumably, data provided in the study by Yu et al will contribute to a deeper understanding of the biology underpinning other loci.

Like all good science, the article by Yu and colleagues has limitations and raises compelling questions. First, is the methylation pattern observed in these postmortem samples present at the start of the neurodegenerative process several decades before autopsy, or did these changes accumulate over the course of the illness as the patient aged?⁸ Second, DNA methylation in these 5 loci influences the neuropathological substrates of Alzheimer disease, but does that translate in the clinical setting to more severe cognitive impairment or a more rapidly progressive course? Third, studying methylation in autopsy material means that one is examining the status of surviving cells that did not degenerate. Is the methylation status in these surviving cells truly representative of the cells that have already died? Fourth, the study by Yu and colleagues focused on the methylation of CpG islands, but it is increasingly recognized that methylation occurs outside of these islands and may be important in determining gene expression.⁹ The answers to such questions are complicated, and some may have to wait until technology evolves further to allow the methylation status across the genome to be measured in the brain in living patients.

DNA methylation, and epigenetics more broadly, represents complex phenomena that likely have central roles in our susceptibility to neurodegeneration. The study by Yu et al represents an important milestone in our efforts to understand the part of methylation in the pathogenesis of Alzheimer disease.

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