In This Issue: The Genetic, Transcriptomic, and Proteomic Study of Alzheimer's Disease

Last year, we inaugurated a series of occasional research and scholarly review articles with the intent of capturing some of the progress now being made in the scientific understanding, diagnosis, treatment, and prevention of Alzheimer's disease (AD). In this issue of *The Journal of Clinical Psychiatry*, Andreas Papassotiropoulos, Michael Fountoulakis, Travis Dunckley, Dietrich Stephan, and I consider the progress now being made in the genetic, transcriptomic, and proteomic study of AD.

PROGRESS IN THE GENETIC STUDY OF ALZHEIMER'S DISEASE

Twin studies suggest that about 75% of the risk for late-onset AD may be attributable to heritable risk factors. During the past 2 decades, researchers have identified more than 100 relatively rare mutations of 3 genes—the presenilin 1 (*PSEN1*) gene on chromosome 14, the presenilin 2 (*PSEN2*) gene on chromosome 1, and the amyloid precursor protein (*APP*) gene on chromosome 21—which account for many cases of AD with an unusually early age at dementia onset and a pattern of autosomal-dominant inheritance. More than a dozen years ago, researchers identified a common susceptibility gene, the apolipoprotein E (*APOE*) type 4 allele, which may account for about 30% of AD cases with dementia onset after the age of 60 years. In the last few years, there has been remarkable progress in the development of the research tools needed to identify many of the other susceptibility genes that contribute to the risk for late-onset cases. For instance, researchers have developed genotyping platforms capable of reading about 500,000 letters from the genetic book of life (i.e., single nucleotide polymorphisms [SNPs] that are distributed throughout the human genome), making it possible to conduct sufficiently powerful gene association studies of AD cases and controls for the very first time; they have just begun to develop the multi-locus statistical methods needed to investigate the cluster of major and minor genes that contribute to the risk of AD and other disorders and to address the potentially confounding effects of heterogeneity in research subjects' genetic backgrounds, providing far greater power to characterize many of the susceptibility genes that have been left undiscovered using traditional single-locus methods; and they have made progress in the development of endophenotypes, biological measurements more closely related to the susceptibility to AD than to the clinical syndrome itself. Although several important technical and phenotypic challenges remain, hope for better characterizing the clusters of susceptibility genes for AD, and many of the psychiatric disorders that have proved so elusive, may be on the way.

Progress in the genetic understanding of AD will lead to new opportunities, including the chance to better understand the molecular mechanisms involved in the development of AD, to provide targets at which to aim new investigational treatments, to help predict a patient's response to certain AD treatments on the basis of his or her genetic profile, to help identify cognitively normal or mildly impaired persons who might benefit from early interventions, and to help in the cost-effective study of primary prevention therapies by selecting those individuals at higher risk for AD. As the opportunities unfold, so will the challenges: When and how does one disclose genetic information to affected patients or healthy persons in the most beneficial and least

disadvantageous way? What are the clinical, ethical, and public policy decisions needed to help ensure a person's privacy (without bankrupting the insurance companies that depend in part on the concept of shared risk)? What are the clinical and ethical implications for families? (For instance, some persons at risk for early onset of AD have already considered the implications for having children, and a few have considered the possibility of pre-implantation genetic diagnosis of embryos produced through in vitro fertilization.) To address these and other questions, clinicians, genetic counselors, ethicists, lawyers, and public policy makers will have to keep up with the accelerating pace of discoveries about the genetic contributions to AD and other psychiatric and nonpsychiatric medical disorders, as well as the discoveries that will be made about the genetic contributions to more or less desirable but normal human traits.

PROGRESS IN THE TRANSCRIPTOMIC STUDY OF ALZHEIMER'S DISEASE

While the study of inherited genes continues to provide important information about inherited risk factors for AD and other disorders, the study of differentially expressed genes (e.g., the gene "transcripts" composed of messenger RNAs) provides new opportunities to identify the molecular mechanisms involved in the pathogenesis of AD, which in turn may be influenced by genetic or nongenetic factors or their interaction. High-density microarray platforms are now being used to rapidly screen the entire genome for genes that are differentially expressed in easily accessible tissues (e.g., peripheral lymphocytes from blood samples), in tissues or cells from the postmortem human brain, and in brain samples from putative animal models of AD. For instance, we have recently identified a set of genes that appear to be differentially expressed in tangle-bearing genes in comparison with non–tangle-bearing genes from the same brain region of the same patients. This information has the potential to provide targets at which to aim new treatments and, in the case of more accessible tissues, help identify persons at risk for AD and perhaps who are more or less responsive to certain treatments.

Unfortunately, when researchers investigate the entire human genome, they commonly find a large number of genes that are differentially expressed. Some of the implicated genes might be causally related to the development of AD pathology and provide promising targets at which to aim new treatments. But some of the implicated genes may be differentially expressed as a consequence of the disorder (providing a misleading target for the discovery of new treatments), some may reflect a compensatory mechanism (another misleading target for new treatments), and some of the genes may be implicated by chance (i.e., a statistical type I error) due to the large number of comparisons made. For this reason, complementary tools are needed to further characterize the functions of the genes implicated in transcriptomic studies as well as the extent to which these genes, when silenced (e.g., using a relatively new tool known as a small-interfering RNA or using knock-out animals), contribute to AD pathology. Additional research tools, analytic methods, and experimental paradigms are still needed to help fulfill the promise of transcriptomics in the scientific understanding, early detection and tracking, diagnosis, treatment, and prevention of AD.

PROGRESS IN THE PROTEOMIC STUDY OF ALZHEIMER'S DISEASE

While information about differentially expressed genes promises to provide helpful information about the cascade of molecular events involved in the pathogenesis of AD, information about the products of these genes—the proteins, themselves, as well as their structure, folding, interactions with other proteins, and posttranslational events—has the potential to provide the most direct information of all. Proteomic methods can be used to quickly screen a relatively large number of proteins, also providing great promise in the scientific understanding, early detection and tracking, diagnosis, treatment, and prevention of AD. While proteomics has contributed to the understanding of potentially important pathogenic mechanisms, improvements in the power to detect low-abundance, hydrophobic, acidic or basic, and high– or low–molecular mass proteins are needed to help fulfill the promise of this approach to the scientific study or clinical management of AD.

CONCLUSION

The article in this issue of "Focus on Alzheimer's Disease and Related Disorders" is intended to briefly review the rapidly developing methods now being used in genetics, transcriptomics, and proteomics research, to review what has already been learned from using these methods in the study of AD, and to provide a sense of how these methods may help make a major difference in the understanding of AD and more elusive neuropsychiatric disorders in the coming years. It is also intended to provide a sense of the opportunities and challenges that scientists, clinicians, and the people we serve are likely to encounter in this new translational scientific era. If you have suggestions or comments regarding "Focus on Alzheimer's Disease and Related Disorders," please feel free to contact me at Eric.Reiman@bannerhealth.com

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