Book Review

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Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease. By Rudolph E. Tanzi and Ann B. Parson. Cambridge: Perseus Publishing. Pp. 281. $26.00.

This 12-chapter-book, written by neurogeneticist Rudolph E. Tanzi and science journalist Ann B. Parson, illustrates the revolution, during the past two decades of the past century, in research on Alzheimer disease (AD). This revolution was strongly influenced by creative and enthusiastic scientists such as Tanzi, one of the early protagonists of molecular neurogenetics. During his search for a longer-lasting perspective for his future, a job posting came to the attention of the young rock musician Tanzi. That's how he found, in 1980, his first position, as a technician in the lab of James Gusella, a visionary neuroscientist. Already, at this early stage, Gusella was convinced that it would be possible to track down, through molecular linkage analysis, the gene for Huntington disease (HD). The reader learns about "repetitive-motion syndrome" (p. 16), caused by the hard and monotonous work of transforming and growing lymphocytes from hundreds of study subjects to genotype RFLPs by classic Southern blotting. This strategy had an unexpectedly early success, and results were published, in 1983, in a seminal paper, coauthored by Tanzi, on the chromosomal localization of HD. Motivated by this experience, Tanzi felt challenged to find a genomic locus for AD. Devoted to neurogenetics and equipped with his skills and his trust in molecular genetics's "cookbook" science (p. 63), he joined the field of neuroscience, where, as a graduate student, he achieved notable success. The authors describe historic milestones in AD research that have contributed to the slow process of recognizing that dementia is a disease (most often, AD) but is not an obligatory sign of aging. Major contributions of some of the leading scientists in the field of AD research—particularly those crossing Tanzi's pathways in the United States—are described in more detail, along with anecdotes telling us about their friendships, rivalries, hopes, fears, and jealousies, thereby giving an interesting insight into some facets of this highly competitive field as well as into Tanzi's personal view of those aspects of their interaction. The authors describe an insider's perspective on the findings and circumstances that led to the discovery of four genes (*APP, APOE, PSEN1,* and *PSEN2*) of major importance in today's experimental research on AD. In the final pages of *Decoding Darkness,* Tanzi takes the opportunity to defend his group's association studies of α2 macroglobulin (*A2M*), a candidate gene for AD. The authors are very optimistic that further progress will be made, in the near future, in the identification of both other risk alleles of candidate genes for AD and new drugs for efficient treatment of AD.

Essential terms and basic principles of molecular genetics, alongside figures, are introduced to the lay reader. Therefore, the book may be an informative and entertaining lesson for scientists, physicians, students, and the lay public interested in this field.

Decoding Darkness tells about the great successes of molecular-genetics research in AD, most often a multifactorial disease. Many other multifactorial diseases are still awaiting such key discoveries. Meanwhile, autosomal dominant familial AD (FAD) is one of the several hundred rare Mendelian disorders that are the subjects of continuing genetic counseling and, possibly, of molecular diagnostics. Most likely, <1% of all cases of AD that occur worldwide are caused by FAD-related mutations in *APP,* in *PSEN1,* in *PSEN2,* or in yet-unknown genes. In whites, *APOE*'s allelic variant ε4 seems to be responsible for 10%–20% of all cases of AD (a percentage that may increase with life expectancy). Similar to other areas in neuropsychiatric genetics, the search for additional risk alleles in candidate genes of AD is characterized by an endless series of discoveries followed, sooner or later, by nonconfirmatory findings (usually reported in lower-impact journals). In spite of distinct breakthroughs in genetic research on AD, the proportion of cases of AD attributable to genetic factors remains unknown. Until now, the new molecular insights facilitated by genetic discoveries have left us with unresolved paradoxes (Checler 2001) requiring further intense research, both for an understanding of the molecular cascade causing AD and for the development of novel therapies. In conclusion, this book—and its authors' optimism—may give the lay public (1) incorrect perceptions about the impact that genes have on AD and (2) unwarranted expectations about the therapeutic potential of next-generation drugs.

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Reference

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