

*Forum Minireview***Novel Etiological and Therapeutic Strategies for Neurodiseases:
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Although many gene mutations have been identified to be responsible for brain disorders and thus have been considered as potential targets of therapeutic treatment, the majority of neurological diseases are sporadic. For example, several genes are found to be causal for Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, but more than 90% of these diseases do not have apparent familial relationships. Even in spinocerebellar degeneration, which shows relatively high heredity, the ratio of the genetic inheritance is estimated to be only 30%–40%.

There are some reasons why it is not easy to find the etiologic causes in specific genes. First, the relationship is weak, even though it is significant. In this case, the relevant genes are called risk factors, which do not strictly determine the etiology but do readily increase the probability of the incidence rates. A good example is the apolipoprotein E type 4 allele (APOE4) (1). With increasing number of the APOE4 alleles, the risk for Alzheimer's disease increases from 20% to 90%, and the mean age at onset decreases from 84 to 68 years.

Second, postnatal experiences often have epigenetic and anatomical effects that may last throughout the entire life span, increasing the risk for brain malfunction or mental disorders. Animal models have provided bases for evaluating how brain development and physiological function are affected in children or adults exposed to inappropriate environments or habituations, such as abuse,

neglect, and trauma, and have revealed that the disease causes cannot be searched for in specific genes or molecules, but instead, the illness should be understood as "bio-systems" malfunctions.

The epigenetic effects usually attribute to DNA methylation, histone acetylation, histone methylation, RNA editing, and post-translational protein modification. In this review series, Kubota et al. (2) and Hideyama et al. (3) summarize the epigenetic aspects, DNA/histone modification and RNA editing, respectively. For example, in amyotrophic lateral sclerosis, the abnormal enzymatic activity of RNA editing by adenosine deaminase results in an increase in unedited glutamate receptors, thereby elevating the risk for excitotoxicity (3). As for the anatomical factors, Koyama and Matsuki (4) describe the long-lasting effect of childhood epilepsy on the risk for adult temporal lobe epilepsy. Specifically, infancy febrile seizures disturb normal brain network formation, leading to an increased risk of epileptic seizures.

Recent endeavors are being made to establish clinical treatments for such intractable, sporadic diseases. Yokota et al. (5) attempt to take a new genetic approach with RNA interference. Another approach that has received increasing attention is to enhance the quality of life. For example, in transgenic mice expressing genes related to familial Alzheimer's disease, exposure to an enriched environment results in reductions in cerebral β -amyloid levels and amyloid deposits, compared to animals raised under lab-housing conditions (6). This suggests that even genetically elicited diseases can be rescued by etiologic strategies.

Burgeoning literature now begins to suggest possible

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clinical treatments for the consequences on physical health and emotional and cognitive development. This review series focuses on new challenges for etiological and therapeutic strategies against sporadic neurodegenerative diseases.

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References

- 1 Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921–923.
- 2 Kubota T, Miyake K, Hirasawa T, Nagai K, Koide T. Novel etiological and therapeutic strategies for neurodegenerative diseases: Epigenetic understanding of gene–environment interactions. *J Pharmacol Sci*. 2010;113:3–8.
- 3 Hideyama T, Yamashita T, Nishimoto Y, Suzuki T, Kwak S. Novel etiological and therapeutic strategies for neurodegenerative diseases: RNA editing enzyme abnormality in sporadic amyotrophic lateral sclerosis. *J Pharmacol Sci*. 2010;113:9–13.
- 4 Koyama R, Matsuki N. Novel etiological and therapeutic strategies for neurodegenerative diseases: Mechanisms and consequences of febrile seizures: lessons from animal models. *J Pharmacol Sci*. 2010;113:14–22.
- 5 Yokota T. Gene therapy with RNA interference. *J Pharmacol Sci*. 2009;109 Suppl 1;43P.
- 6 Lazarov O, Robinson J, Tang YP, Hairston IS, Korade-Mirnics Z, Lee VM, et al. Environmental enrichment reduces A β levels and amyloid deposition in transgenic mice. *Cell*. 2005;120:701–713.