

Analysis of molecular biology of epilepsy: Development of personalized medicine for epilepsy based upon genetic polymorphisms

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【 Outline of survey 】

Epilepsy affects more than 0.6% of the world's population and has a large genetic component. All identified causative genes of human familial epilepsy syndromes, with few exceptions, encode ion channels or their auxiliary subunits expressed in the brain. However, genes responsible for common phenotypes of epilepsy have been uncovered yet. Therefore, the purpose of this study is to define the genes coding for common epilepsy phenotypes such as juvenile myoclonic epilepsy, generalized epilepsy febrile seizure plus, generalized epilepsy on awakening, severe myoclonic epilepsy in infancy, and febrile seizure, to clarify the pathogenesis of epilepsy, and ultimately to establish personalized medicine of epilepsy. Establishment of the direct molecular diagnosis of epilepsy, an improvement of the genetic counseling of epilepsy, and providing necessary information for the developing new remedies for epilepsy, are also included in the purpose of the present study project. To identify responsible and/or susceptible genes in epilepsy, coding ion channels or their auxiliary subunits expressed in the brain, will be intensively screened for DNA mutations. To facilitate the functional analysis of mutated genes, a highly reliable approach to transmembrane topology prediction, high-through put tools and transgenic or knock-in mutant animals are developed. To identify possible genetic factors that determine clinical response and to predict clinical outcome even before starting the treatment, cytochrome P450 (CYP) enzyme genetic status-clinical responses and significant implication of genetic polymorphisms in the drug target sites are studied.

【 Expected results 】

The identification of responsible and/or susceptible genes will enable direct molecular diagnosis and thereby improve genetic counseling of epilepsy. The analysis of molecular pathogenesis can contribute to the introduction of new remedies for epilepsy, and the production of transgenic animals bearing mutations of genes found in human epilepsy and high-through put tools undoubtedly contribute to the progress of brain sciences. Screening for genetic polymorphisms of CYP enzymes, and those of receptors and ion channels in the CNS provide evidence-based prediction of clinical response and help to select the drug most likely to produce beneficial effects with minimal risks according to their genetic profile. This pharmacogenetic strategy constitutes the basis for personalized medicine of epilepsy. Database of genetic polymorphisms of ion channels and receptors in the CNS, transporters, and CYPs in Japanese patients with epilepsy can be extended to the development of personalized medicine of diseases other than epilepsy. This study, thus, contribute to characterization of pathologic mechanisms and to identification of potential therapeutic strategies of epilepsy.

【 References by the principal researcher 】

Ueno S, Kaneko S et al. The gene encoding a newly discovered protein chorein is mutated in chorea-acanthocytosis. *Nature Genetics*, 28: 121-122, 2001.

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【 Term of project 】 FY 2004 - 2008	【 Budget allocation 】 92,200,000 yen
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【 Homepage address 】	none
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