Molecular Pathological Evaluation of Familial Spontaneous Epileptic Cats

Abstract of Doctoral Thesis

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Epilepsy is one of the common neurological disorder which is characterized by recurrent epileptic seizures, and genetic factors are thought to be involved in the disease occurrence in most epileptic patients. Familial spontaneous epileptic cats (FSEC) is the unique colony which is considered as feline genetic epilepsy, and they show two types of seizures, including spontaneous limbic seizures and vestibular stimulation-induced seizures. However, genetic architecture has not yet been elucidated. In this study, comprehensive genetic analysis has been performed that included neuropathological evaluation, candidate gene approach, genome-wide association study (GWAS), genome-wide linkage analysis, and whole genome sequencing (WGS). In the pathological evaluation, the neuronal decrease in the hippocampal CA3 region and amygdaloid central nuclei was found. In addition, gliosis in hippocampal CA4 region without neuronal loss was also found. Mutational analysis for LGI gene family was conducted, which were considered as a candidate gene family of FSEC based on the human and animal model literatures, the causative variant was not detected in this gene family. GWAS was performed to detect the associated loci with epilepsy. Assuming that all the phenotypes were caused by the common variant(s), or each type of seizures (phenotype) was caused by (a) different variant(s), tests were conducted in different patterns. Different loci in each phenotype were detected by GWAS, however, none of them were genome-wide significant. In genome-wide linkage analysis, tests were performed in different patterns as well as GWAS, and multiple loci with suggestive linkage were detected in each phenotype. Furthermore, WGS was performed on four FSECs. After the filtering in different patterns based on the phenotype, unique variants that were not present in feline WGS database were detected in the suggested region by GWAS and linkage analysis. Variants located within genes that were considered to be associated with epilepsy, most of them were not located within the coding region. In this study, the comprehensive genetic analysis was conducted, and it was essential to understand the genetic architecture of epilepsy occurrence in FSEC. This study suggested the complexity of the genetic architecture in FSEC. Variants found in this study are considered not to have large effect, however, these variants may have the contribution to epileptogenesis in FSEC in some way.