Evolutionary genetics of socioemotional behavior in humans and other mammals

博士論文（要約）

Evolutionary genetics of socioemotional behavior in humans and other mammals

(ヒト及び他の哺乳類における社会的情動行動に関する進化遺伝学的研究)

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東北大学大学院生命科学研究科

生態システム生命科学専攻

佐藤 大気

Emotion is a fundamental process that mediates animal behavior and thus, its inter-specific and/or inter-individual diversity has been a major concern in evolutionary biology. Fear and anxiety are the most prevalent and distinct kinds of emotions in animals and are thought to have evolved by natural selection for increased fitness in response to specific objects, predators, and situations in the environment. The neural mechanism of emotion is well studied; however, the genetic underpinnings behind its evolution within and among mammalian species have not been fully investigated. In humans, dysfunctions in emotional regulation are associated with the onset of psychiatric disorders, putting this study into clinical importance as well. This thesis attempts to address the evolutionary question regarding animal emotions. Identifying genetic changes underlying the socioemotional evolution of humans and other mammals will provide a better understanding of the evolutionary aspects of animal emotions and the consequent psychopathological phenotypes.

To this end, I first focused on a domestic animal, the European rabbit, and examined the evolutionary changes in gene expression throughout the brain compared to their wild conspecifics (Chapter I). Given the striking behavioral changes (*i.e.*, tameness) throughout the process of domestication, domestic rabbits are considered to be a good model to deal with the question above. Investigating transcriptomic changes between wild and domestic rabbits in multiple areas in the brain resulted in detecting the differential expression of genes related to dopamine signaling or ciliary organization in amygdala and hippocampus, respectively. These results provide the genetic substrates underlying neurological and/or behavioral changes in domestic rabbits.

I next tried molecular evolutionary and population genetic approaches to identify genes under natural selection in the human lineage, which could be associated with the evolutionary emergence of psychiatric disorders (Chapter II). Out of a few candidate genes detected, vesicular monoamine transporter 1 (VMAT1; encoded by *SLC18A1*), a gene relevant to neurochemical signaling, showed striking signatures of selection on its non-synonymous substitutions. One of the substitutions was a human-specific polymorphism (Thr136Ile; Fig. 1), out of which 136Thr has been implicated in a number of psychiatric disorders and dimensions of personality traits. Population genetic analyses showed that this functional variant has been maintained by balancing selection in non-African populations, possibly suggesting that natural selection favors diversity in our psychological traits. Coalescent simulations estimated that 136Ile had originated around the time of the Out-of-Africa migration of modern humans, which implies a striking pattern of natural selection acting on this variant.

I then turned to an experimental approach to examine the functional alterations possibly caused by the human-specific substitutions in VMAT1 in cultured cells (Chapter III). In an assay with fluorescent false neurochemicals, the ancestral substitutions were shown to reduce the monoamine uptake of VMAT1, suggesting that higher levels of anxiety had initially been favored in human evolution. Lastly, I investigated

the extensive phenotypic effects of the humanized substitutions in the mouse Vmat1 with the CRISPR/Cas9-mediated genome editing technique (Chapter IV). Transcriptome, neurophysiological, and behavioral experiments revealed the comprehensive effects of the humanized mutations on the amygdala neuronal circuits, likely responsible for the observed phenotypic variation in anxiety-related behavior (Fig. 1).

In my work on inclusive studies of humans, mice, and rabbits, I have shown that genetic variation underlying neurochemical signaling in the amygdala is ubiquitously involved in the evolution of mammalian socioemotional behaviors. The results presented here support both the universality and diversity behind the evolution of our emotions and suggest the importance of understanding the heterogeneous nature of genes, cells, circuits, and the brain.

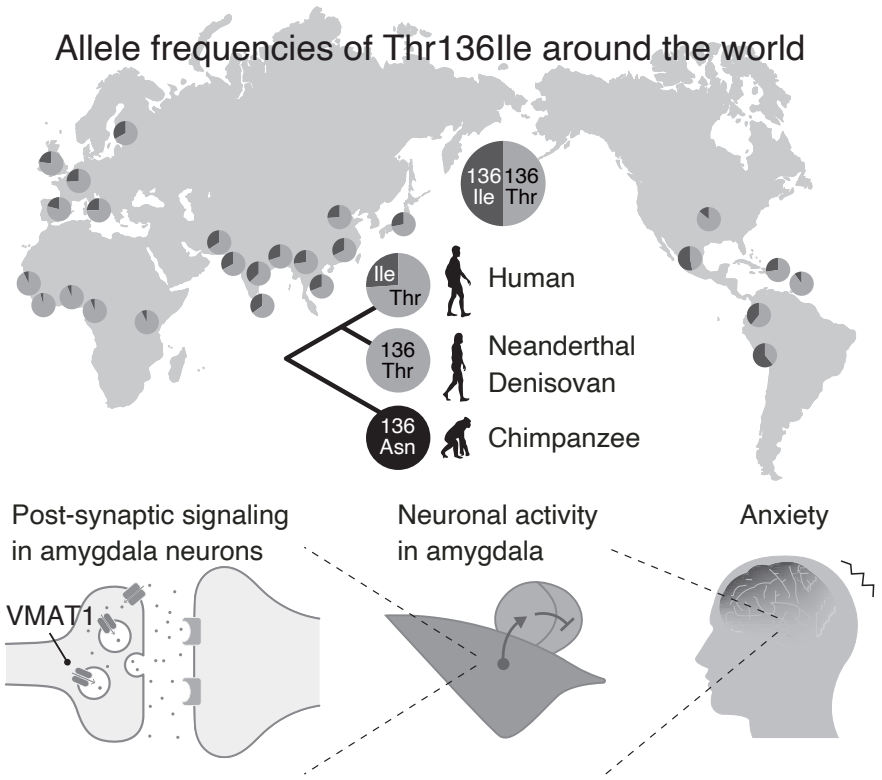

Figure 1. Allele frequencies of Thr136Ile variant of VMAT1 in modern human populations (upper image) and the schematic image of the functional effects and mechanism mediated by the VMAT1 variant (lower image).