（課程-2）

審査の結果の要旨

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The main objective of this PhD thesis is to identify genetic susceptibility variants that contribute to the risk of essential hypersomnia (EHS) in Japanese population. EHS is a sleep disorder characterized by excessive daytime sleepiness (EDS), can be divided into two broad classes based on the presence or absence of the Human Leukocyte Antigen (*HLA)-DQB1*06:02* allele. This PhD candidate has focused on *HLA-DQB1*06:02* negative EHS in which previous reports showed that this group of patients is pathophysiologically different from that of narcolepsy with cataplexy (another similar sleep disorder defined of excessive daytime sleepiness). A wide-range of experiments and analysis were performed in the search of genetic susceptibility variants for *HLA-DQB1*06:02* negative EHS and the results are as follows:

1. 3 SNPs that each represented a unique locus, rs16826005 (*P* = 1.02E-07; *NCKAP5*), rs11854769 (*P* = 6.69E-07; *SPRED1*), and rs10988217 (*P* = 3.43E-06; *CRAT*) were associated with an increased risk of EHS in this Japanese population.

2. rs10988217 in *CRAT* gene is associated with both *HLA-DQB1*06:02* negative EHS and narcolepsy with cataplexy in both Japanese and Caucasian populations. In addition, eQTL analysis showed that risk allele of rs10988217 increased the expression of *CRAT*. Regulatory SNP in *CRAT* gene, together with previously identified *CPT1B* as susceptibility gene for narcolepsy through the long-chain fatty acid β-oxidation pathway contribute to the risk of having *HLA-DQB1*06:02* negative EHS.

3. *MBP* (*P* = 2.74E-06) and *QKI* (*P* = 2.22E-05) can act as potential markers to differentiate EHS from narcolepsy with cataplexy and the follow-up study of MBP level in the cerebrospinal fluid (CSF) showed EHS had a significant elevated level of CSF MBP(*P* = 2.50E-02) compared with those of narcolepsy with cataplexy. These results suggest that demyelination might occur in EHS patients.

4. Pathway analysis of the EHS identified the glutamate metabolism to be significant (*P* = 1.70E-03) with the risk of having *HLA-DQB1*06:02* negative EHS. High-performance liquid chromatography (HPLC) analysis on the *HLA-DQB1*06:02* negative EHS CSF samples revealed that gamma-aminobutyric acid (GABA) is elevated compared to narcolepsy with cataplexy while glutamate and glutamine showed no associations. This result is parallel with the severity of EDS in narcolepsy with cataplexy

The results above improve the understanding of genetic variations' contribution to the pathogenesis for EHS. EHS is a relatively newly defined disease; a lot of studies remain to be done to fully understand the underlying mechanism which leads to the disease. These studies provided a comprehensive analysis from the identification of novel genetics factors to some preliminary functional study of the genetic variants identified, the results have been published in PeerJ journal and we think that it is sufficient for the PhD candidate to obtain a PhD degree.