Systematic Behavioral Test Battery for *Sleepy* and *Dreamless*, Newly Identified Mouse Pedigrees with Sleep Abnormalities

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Why and how do we sleep? – this is a very simple but difficult question to answer. We human beings spend nearly one-third of our lives asleep. However, the mechanism and function of sleep remains unclear. Understanding the neurobiological basis for “sleepiness” has not only a biological significance, but also a great benefit for human society. In Japan, it has been reported that the economical losses reach 3.5 trillion yen per year due to people’s troubles with sleep. Moreover, sleep disorders have reciprocal risk relations with metabolic syndromes, as well as cognitive and mood disorders. It is required to crack this black box and develop a way to control it. As a biggest unrevealed issue in sleep biology, the mechanism for homeostatic sleep/wakefulness regulation, as well as the neural substrate for “sleepiness”, remains a mystery.

To make a breakthrough in this question, our laboratory has initiated a large-scale forward genetic screen of sleep/wake abnormalities in mice, based on somnographic (EEG/EMG) measurements, the gold standard in mammalian sleep/wake assessment. We have so far screened >7,000 heterozygous ENU-mutagenized mice and established 10 pedigrees exhibiting heritable and specific sleep/wake abnormalities. By combining linkage analysis and whole-exome sequencing, we have so far identified three mutations: *Sleepy* and *Sleepy2*, causing marked hypersomnia (increased non-REM sleep), and *Dreamless*, causing short and highly fragmented REM sleep. Since these dominant mutations cause very strong phenotypes, we expect that the mutated genes play central role for regulating sleep/wake amounts. Furthermore, these mutant mice can be a sleep disease model to approach the relationship between sleep and other cognitive and mental functions such as learning and memory, depression, anxiety, sociability and more.

Here, we examined the following series of behavioral analyses for both *Sleepy* and *Dreamless* mutant mice: 1) Morris water maze, 2) forced swim test, 3) tail suspension test, 4) open field test, 5) novel object recognition, 6) elevated plus maze, 7) social interaction test, 8) sucrose preference, 9) nest building, and 10) fear conditioning. We detected significant behavioral phenotypes in these mice, including an impaired hippocampus-dependent memory formation in *Dreamless*, and a depression-like phenotype of *Sleepy* mutant mice. These results of behavioral test battery provide us the landmark information to approach the link between sleep and other behaviors.