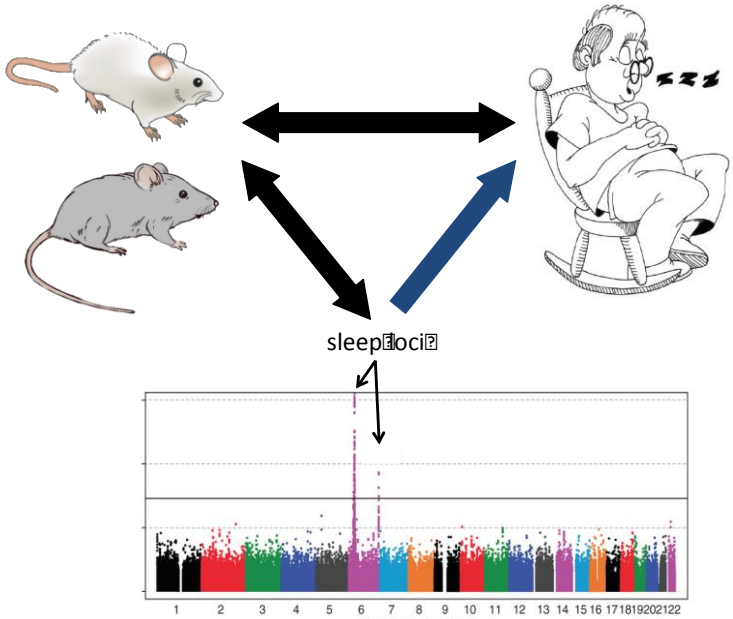
Identifying new genetic targets to help treat sleep disorders

Project directors: Ketema Paul, Ph.D. and Jason DeBruyne, Ph.D.

In today's demanding 24-hour society the prevalence of sleep disorders continues to increase; however, the development of effective treatments for those disorders has not kept pace. One of the primary reasons is that many of the genetic and molecular pathways that underlie basic sleep processes are still undefined. Forward genetics approaches have yielded novel therapeutic targets and more effective treatments for a variety of diseases; however, similar milestones in the study of sleep disorders have been elusive. It has become apparent in the last several years that the genetics of sleep are complex, involving multiple genes and gene interactions with potentially small effect sizes. Larger-scale genomic approaches are likely to provide the necessary power uncover the genes that underlie sleep processes. These studies use a forward genetics approach that takes advantage of natural variation occurring in inbred mice. This endeavor will combine a well-established paradigm of comparative phenotyping of a genetically tractable animal model with powerful genetic mapping tools to identify novel sleep-regulatory genes. Consequently, these experiments will not only identify new sleep genes, they will also help verify and clarify previously mapped genes whose roles are not yet clearly defined. Ancillary benefits of this proposal include the potential identification of practical biomarkers of sleepiness, which is often cited as one of the most pressing needs in contemporary sleep research.



INNOVATION

This study will combine a well-established paradigm of comparative comprehensive phenotyping of genetically homogenous samples with powerful genetic mapping tools to identify novel sleep-regulatory genes. Since the mouse is the primary mammalian genetic model of disease and 99% of mouse genes have human homologues, 96% in the same chromosomal location, this project has high potential translational value. Moreover, a comprehensive analysis of the genetic regulation of complex sleep traits has yet to be undertaken. This proposal will take advantage of the alliance of three critical components of gene mining: 1) the newest and most innovative in silico genetic tools, 2) recently developed genomic sequences and maps of genetically homogenous mouse strains, and 3) comprehensive phenotyping of quantitative sleep traits under sleep-replete, and sleep-deprived conditions. The analysis of phenotypes during challenges (sleep deprivation) that manipulate core sleep regulatory systems is particularly important for the success of the proposed experiments. In addition, access to tools such as panels of recombinant inbred hybrids, and murine progenitors of collaborative crosses that have been phenotyped for sleep-related behaviors will enhance our ability to focus on the most promising potential genes. Consequently, these experiments will not only identify new sleep genes, they will also help verify and clarify previously mapped genes whose roles are not yet clearly defined.