Results: 94 nodes and 264 edges were identified in the network, representing regulatory factors, adipokines, molecular pathways, and disease processes. Two adipokines, leptin and adiponectin, were found to have higher degrees than other adipokines, indicating their central roles in connecting sleep disturbance to metabolic dysregulations. Among the regulatory factors, obesity and obstructive sleep apnea were found to be major drivers for the sleep associated metabolic dysregulation based on their higher degrees. The important pathways adipokines act on in the network included insulin signaling, inflammation, food intake, and energy expenditure. The main disease processes adipokines act on included cardiovascular, reproductive, and autoimmune diseases. Leptin, AMPK, and fatty acid oxidation were found to have global influence in the network based on their high betweenness.
Conclusion: Adipokines are important players in the metabolic dysregulations associated with sleep disturbance. Adipokines such as leptin and adiponectin act on diverse metabolic pathways in response to sleep disturbance, obesity, insulin resistance, and inflammation.They play important roles in cardiovascular, reproductive, and autoimmune diseases. Adipokines and their targets, such as leptin, AMPK, and fatty acid oxidation are likely important interventional/pharmaceutical targets for these disease processes.
Support (If Any): none

0029

DEVELOPING A PIPELINE FOR TRANSLATING GENOME-WIDE ASSOCIATION SIGNALS TO BEHAVIORAL CORRELATES OF SLEEP DYSFUNCTION

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0**Introduction:** Insomnia is a pervasive sleep disorder affecting up to one-third of the adult U.S. population. An extensive amount of genetic association data from genome wide association studies (GWAS) has uncovered hundreds of loci associated with insomnia and other sleep traits, yet few of these targets have undergone full characterization and their contribution to sleep traits remain poorly understood. Additionally, GWAS does not necessarily determine the true effector gene(s) at a given locus, leading to frequent mischaracterization and misinterpretation of genotype-phenotype interactions.
Methods: Our group has developed a variant-to-gene mapping approach that integrates existing insomnia GWAS loci with a combination of ATAC-seq and promoter-focused Capture C-derived data in human induced pluripotent stem cell-derived neural progenitor cells. We identified candidate genes with accessible promoter regions that were contacted at high resolution by insomnia-associated SNPs residing in open chromatin. Target genes with known orthologs and available Drosophila RNAi lines were then subjected to deep phenotyping of sleep traits. Candidate genes producing greater than 20 percent change in sleep duration in Drosophila were then screened in a vertebrate zebrafish model using CRISPR/Cas9 mutagenesis in F0 larvae.
Results: This pipeline revealed fifteen genes producing robust sleep phenotypes with more than a 20 percent change in sleep duration in Drosophila. Of the candidate genes screened thus far in zebrafish, we found that disruption of pigq expression significantly ($p<0.05$) increased sleep duration in both zebrafish and Drosophila through regulation of sleep bout length and frequency, revealing a conserved, yet novel regulator of sleep duration. Additionally, CRISPR mutations in cbx1b and meis1b in zebrafish resulted in reduced sleep duration similar to results in Drosophila.
Conclusion: This pipeline uses cutting-edge genomic and behavioral approaches to perform high-throughput screening of existing GWAS-identified insomnia loci. This genotype-to-phenotype approach emphasizes the importance of behavioral validation following large cohort studies and narrowed the candidate gene list from more than 200 to fewer than 20 providing a more tractable set of gene targets for further molecular characterization. Cross-species validation also improves our understanding of the conservation of sleep characteristics throughout evolution.
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0030

DEVELOPMENT AND VALIDATION OF A METABOLOMIC RISK SCORE FOR OBSTRUCTIVE SLEEP APNEA ACROSS RACE/ETHNICITIES

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Introduction: Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent episodes of upper airway obstruction during sleep resulting in oxygen desaturation and sleep fragmentation, and associated with increased risk of adverse health outcomes. Metabolites are being increasingly used for biomarker discovery and evaluation of disease processes and progression. We aimed to develop a metabolomic risk score (MRS) for OSA and identify individual metabolites associated with OSA to provide insights into the pathogenesis of OSA.
Methods: We studied 219 metabolites and their associations the apnea hypopnea index (AHI) and with OSA, defined as AHI , in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (n=3507) using two methods: (1) association analysis of individual metabolites, and (2) least absolute shrinkage and selection operator (LASSO) regression to identify a subset of metabolites that are jointly associated with OSA, and develop an MRS. We then validated the results in Multi-Ethnic Study of Atherosclerosis (MESA) (n=475), an independent dataset.
Results: HCHS/SOL participants were 41.72 years old on average, 50.7% female, and 10.2% had OSA. MESA individuals were 68.45 years old on average, 56.2% females, and 46.7% had OSA.