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

Amber Zimmerman[1], Justin Palermo[2], Alessandra Chesi[3], Shilpa Sonti[3], Chiara Lasconi[3], Elizabeth Brown[2], James Pippin[3], Andrew Wells[3], Fusun Doldur-Balli[1], Diego Mazzotti[4], Allan Pack[1], Philip Gehrman[1], Alex Keene[2], Struan Grant[3]
University of Pennsylvania Perelman School of Medicine [1] Texas A&M University [2] Center for Spatial and Functional Genomics, Children's Hospital of Philadelphia [3] University of Kansa Medical Center [4]

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.
Support (If Any): NIH grants R01 HL143790, P01 HL094307, T32 HL07953

0030

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

Ying Zhang[1], Debby Ngo[2], Bing Yu[3], Neomi Shah[4], Han Chen[3], Alberto Ramos[5], Phylis Zee[6], Robert Kaplan[4], Jerome Rotter[7], Clary Clish[8], Robert Gerszten[9], Bruce Kristal[10], Sina Gharib[11], Susan Redline[12], Tamar Sofer[13]
Brigham and Women's Hospital [1] Beth Israel Deaconess Medical Center [2] School of Public Health, The University of Texas Health Science Center at Houston [3] Albert Einstein College of Medicine[4] University of Miami Miller School of Medicine [5] Northwestern University [6] The Institute for Translational Genomics and Population Sciences, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center [7] Broad Institute of MIT and Harvard[8] Massachusetts General Hospital, Harvard Medical School [9] Harvard Medical School [10] University of Washington [11] Brigham and Women's Hospital and Harvard Medical School [12] Harvard Medical School and Harvard T.H. Chan School of Public Health [13]

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.

When assessing the associations between OSA/AHI and individual metabolites, we identified seven metabolites significantly and positively associated with OSA in HCHS/SOL (FDR p<0.05), of which four associations - glutamate, oleoyl-linoleoyl-glycerol (18:1/18:2) (DAG(36:3)), linoleoyl-linoleoyl-glycerol (18:2/18:2) (DAG(36:4)) and phenylalanine, replicated in MESA (one sided-p value<0.05). The OSA-MRS, composed of 14 metabolites, was associated with 52% increase of risk for moderate to severe OSA (OR=1.52 [95% CI: 1.23-1.87] per 1 SD of OSA-MRS, p<.001) in the discovery dataset of HCHS/SOL and 44% increased risk (OR=1.44 [95% CI: 1.03-2.03] per 1 SD of OSA-MRS, p=0.034) in the validation dataset of MESA, both adjusted for demographic, lifestyle, and comorbidities. Similar albeit less significant associations were observed for AHI modeled continuously.

Conclusion: We developed an MRS that replicated in an independent multi-ethnic dataset, demonstrating the robustness of metabolomic-based OSA risk score to population heterogeneity. Replicated metabolite associations may provide insights into OSA-related molecular and metabolic mechanisms.

Support (If Any): Support for metabolomics data was graciously provided by the JLH Foundation (Houston, Texas). The Hispanic Community Health Study/Study of Latinos was carried out as a collaborative study supported by contracts from the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (N01-HC65233), University of Miami (N01-HC65234), Albert Einstein College of Medicine (N01-HC65235), Northwestern University (N01-HC65236), and San Diego State University (N01-HC65237). The following Institutes/Centers/Offices contribute to the HCHS/SOL through a transfer of funds to the NHLBI: National Center on Minority Health and Health Disparities, the National Institute of Deafness and Other Communications Disorders, the National Institute of Dental and Craniofacial Research, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the Office of Dietary Supplements. The authors thank the staff and participants of HCHS/SOL for their important contributions. MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, UL1-TR-001420. MESA Family is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support is provided by grants and contracts R01HL071051, R01HL071205, R01HL071250, R01HL071251, R01HL071258, R01HL071259, and by the National Center for Research Resources, Grant UL1RR033176. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. Molecular data for the Trans-Omics in Precision Medicine (TOPMed) program was supported by the National Heart, Lung and Blood Institute (NHLBI).). Metabolomics for "NHLBI TOPMed: Multi-Ethnic Study of Atherosclerosis (MESA)" (phs001416) was performed at Broad Institute and Beth Israel Metabolomics Platform (HHSN268201600038I). Core support including centralized genomic read mapping and genotype calling, along with variant quality metrics and filtering were provided by the TOPMed Informatics Research Center (3R01HL-117626-02S1; contract HHSN268201800002I). Core support including phenotype harmonization, data management, sample-identity QC, and general program coordination were provided by the TOPMed Data Coordinating Center (R01HL-120393; U01HL-120393; contract HHSN268201800001I). We gratefully acknowledge the studies and participants who provided biological samples and data for TOPMed. This study was supported by NHLBI grant R35HL135818.

0031

SLEEP REGULARITY IS ASSOCIATED WITH DNA METHYLATION IN COGNITIVE, CARDIOVASCULAR AND MOOD-RELATED GENES: A GWAS-INFORMED STUDY IN ADOLESCENTS

Michael Larsen[1], Natasha Morales-Ghinaglia[1], Fan He[1], Yuka Imamura[1], Arthur Berg[1], Alexandros Vgontzas[1], Duanping Liao[1], Edward Bixler[1], Julio Fernandez-Mendoza[1]

Penn State College of Medicine [1]

Introduction: Adolescence is associated with a delay in the circadian timing of sleep. However, social factors prevent adolescents from adapting to a later sleep-wake pattern, leading to different forms of circadian misalignment that may increase the risk of cardiovascular and mental health disorders. Several GWAS have identified genes associated with sleep and circadian phenotypes, however, little is known regarding the epigenetic basis and significance of sleep timing and its regularity in adolescence.

Methods: We analyzed data from 230 adolescents from the Penn State Child Cohort follow-up study who provided a blood sample for DNA extraction and had complete at-home 7-night (at least 3) actigraphy (ACT) data. ACT-measured sleep midpoint was calculated as the intra-individual mean of the 7-night midpoint (zeroed to midnight) of the sleep period. ACT-measured sleep regularity was calculated as the intra-individual standard deviation of the 7-night sleep midpoint. Epigenome-wide single nucleotide resolution of DNA methylation in cytosine-phosphate-guanine (CpG) sites and surrounding regions were obtained from peripheral leukocytes. This study focuses on methylation sites in GWAS-informed genes previously associated with sleep and circadian phenotypes. Linear regression assessed the association between sleep midpoint and sleep regularity with site-specific methylation levels, adjusting for sex, age, race/ethnicity, body mass index, and psychotropic medication use. Using the Benjamini & Hochberg method to adjust for a false discovery rate. Adjusted p-values are reported as q-values.

Results: Sleep midpoint was not associated with a significant change in methylation at any of the measured intragenic sites. Sleep regularity was significantly associated with differential methylation at 238 intragenic sites in 147 genes with an adjusted p<0.05, of which, three sites were within GWAS-informed sleep/circadian-related genes. Higher sleep irregularity was associated with hypermethylation in MAD1L1 (q=2.4x10-2) and with hypomethylation in CALN1 (q=3.8 x 10-4) and ZNF618 (q=3.8 x 10-2).

Conclusion: Sleep irregularity is associated with altered DNA methylation in genes previously identified in GWAS of sleep/circadian phenotypes. Our data provides evidence for a potential epigenetic link between sleep irregularity and genes