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The Association Between Sleep Phenotypes and Epilepsy Genes

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Abstract

Objectives

Sleep and epilepsy have a complex and bidirectional relationship. We aimed to uncover genetic mechanisms underlying this connection.

Methods

We leveraged genome-wide association studies that link sleep phenotypes and genetic loci and compared epilepsy genes with a random set of genes. Pathway analysis was applied to genes associated with both epilepsy and sleep phenotypes. To determine the specificity of our findings, we compared genes from other neurologic diseases and CNS cell types.

Results

A total of 8.1% of epilepsy genes (26/320) were associated with sleep phenotypes, 2.7-fold the rate of a random gene set (36/1,200 = 3%). Sleep-associated epilepsy genes were enriched in biological processes involving brain development and neuronal function. Other CNS disease genes also demonstrated strong genetic links to sleep phenotypes while peripheral nervous system diseases genes did not. Genes expressed in neurons, astrocytes, and oligodendrocytes were highly associated with sleep phenotypes while those in microglia and endothelial cells were not.

Discussion

While epilepsy and sleep phenotypes share genetic links, this finding extends to other CNS diseases and genes expressed in brain cells. The brain's effect on sleep likely has a genetic underpinning, as variation in genes expressed in cells responsible for brain function affects sleep phenotypes.

Introduction

Sleep and epilepsy are bidirectionally related, yet the mechanisms of this relationship remain uncertain. Disordered sleep and sleep concerns are often comorbid with epilepsy,[1-3] and sleep deprivation can increase epileptiform discharges and seizure burden.[4,5] Adults with epilepsy report sleep disorders twice as often and children with epilepsy 12 times as often as controls.[6,7]

The complex relationship between sleep and epilepsy is likely to have multiple biological mechanisms as there are many epilepsy-associated genes and there are many genes associated with sleep phenotypes. In a study of 356 individuals with early-life, predominantly rare, genetic epilepsies, 45% had frequent nighttime awakenings, 38% had difficulty falling asleep, and 34% had restless sleep.[3] We, therefore, hypothesized that epilepsy and sleep phenotypes share genetic links and aimed to identify their shared biological processes.

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Table 1 List of All Sleep Phenotypes From the Sleep Disorders Knowledge Portal (SDKP)

Phenotype
Apnea-hypopnea index
Apnea-hypopnea index in NREM sleep
Apnea-hypopnea index in REM sleep
Average oxyhemoglobin saturation during sleep
Chronotype (binary sMEQ score)[a]
Chronotype (continuous sMEQ score)[a]
Chronotype (morningness)[a]
Chronotype (single question)[a]
Diurnal inactivity duration, rank-normalized
Ease of waking up
Excessive daytime sleepiness
Frequent insomnia symptoms
Least-active 5-hour timing, rank-normalized
Long sleep duration
Mean sleep duration, rank-normalized
Minimum oxyhemoglobin saturation during sleep
Most-active 10-hour timing, rank-normalized
Naps
Number of sleep episodes, rank-normalized
Percentage of sleep with oxyhemoglobin saturation under 90%
Relative amplitude
Short sleep duration
Sleep duration
Sleep duration in children adjusting by BMI
Sleep midpoint timing, rank-normalized
Snoring
Snoring adjusting by BMI
SD of sleep duration, rank-normalized

Abbreviation: sMEQ = Shortened Morningness-Eveningness Questionnaire.
[a] The chronotype variable used in the analysis was a combination of the 4 chronotype phenotypes listed above.

Methods

Gene Sets for Conditions and Cell Types

Using commercially available gene panels, we generated 10 gene sets for diseases affecting the CNS and peripheral nervous system (PNS), including epilepsy (320 genes), ataxia (1,311 genes), brain malformations (163 genes), cerebral palsy (425 genes), leukodystrophy (729 genes), neurodevelopmental disorders (241 genes), muscular dystrophy (60 genes), myopathy (74 genes), neuromuscular disorders (224 genes), and neuropathy (111 genes). A control gene set was generated by randomly selecting 1,200 genes from a list of all protein-encoding genes. Gene sets associated with specific CNS cell types (neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells) were generated from the top 1,000 highly expressed protein-encoding genes for each cell type.[8] The biomaRt R package extracted the genomic positions from the start of the first exon to the end of the last exon of each gene.[9]

Sleep GWAS Data Extraction

The Sleep Disorders Knowledge Portal (SDKP)[10] provides summary statistics for genome-wide association study (GWAS) data for each single-nucleotide variant (SNV) across a range of sleep phenotypes (Table 1). For each gene, we identified all SNVs in the SDKP between the genomic start and end positions. Of the typically hundreds to thousands of SNVs for a single gene, we tabulated all p values that reached genome-wide significance ($\leq 5 \times 10^{-8}$) and their associated sleep phenotypes. The smallest p value (MIN-P) for each gene was used to compare gene sets.

Pathway Analysis

A list of epilepsy genes associated with sleep phenotypes ($p \leq 5 \times 10^{-8}$) was generated and is designated herein as "SIG-P." The Database for Annotation, Visualization and Integrated Discovery (DAVID) bioinformatics tool analyzed enriched terms in SIG-P.[11-13] Gene ontology (GO) terms that were over-represented in the SIG-P gene set were considered enriched. Among the GO terms, biological process, cellular component, and molecular function were examined.

Statistical Analysis

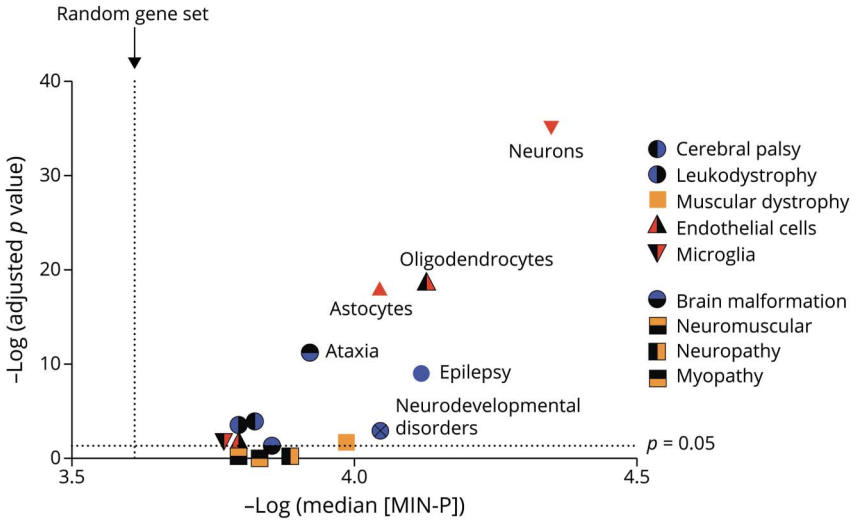
The distribution of MIN-P values for the gene sets was compared using the Wilcoxon rank-sum test, with adjustment for multiple comparisons (Bonferroni method). Overlapping genes between any 2 sets were eliminated from analysis. DAVID tool p values were adjusted for multiple comparisons (Benjamini correction). p Values <0.05 were deemed significant.

Results

Epilepsy Genes Are More Strongly Associated With Sleep Phenotypes Than Random Genes

In a comparison of the distribution of the MIN-P values for epilepsy and random gene sets, the median MIN-P value for the epilepsy gene set (7.6×10^{-5}) was lower than that for the random gene set (2.4×10^{-4}), showing that epilepsy genes are more strongly associated with sleep phenotypes (Wilcoxon rank-sum test, $p < 1 \times 10^{-9}$, Figure). In addition, the epilepsy set had a 2.7-fold higher proportion of genes containing SNVs that were significantly associated with a sleep phenotype (defined as $p \leq 5 \times 10^{-8}$) compared with the random gene set (epilepsy 26/320 = 8.1%, random 36/1,200 = 3%, Fisher exact test $p = 0.0002$).

Figure Comparison of the Smallest *p* Values (MIN-P) for Each Gene Set vs Those for Random Genes



For all single-nucleotide variants (SNVs) associated with each gene in a gene set, the sleep GWAS data set was queried to extract *p* values, which indicate how significantly a SNV is associated with a sleep phenotype. The smallest *p* value for each gene was designated as MIN-P. From the MIN-P values for all the genes in a gene set, the median was determined, subject to a negative $\log_{10}$ transformation, and plotted along the x-axis, with higher values showing stronger association of the gene set with sleep phenotypes. For comparison, this value for a random set of 1,200 genes was 3.6 (vertical dotted line). For the y-axis, the distribution of MIN-P values for each gene set was compared with those of a random gene set, using a Wilcoxon rank-sum test, and the negative $\log_{10}$ transformation of the Bonferroni-adjusted *p*-value for this comparison was plotted, with higher values carrying higher statistical significance. The horizontal dotted line designates a threshold of significance of $p = 0.05$. Genes expressed in neurons had the largest degree of difference in MIN-P values when compared with random genes. GWAS = genome-wide association study.

Next, we determined whether specific sleep phenotypes were recurrently associated with epilepsy genes (Table 2). The sleep phenotypes with the highest number of significantly associated epilepsy genes were ease of waking up (9), sleep chronotype (9), sleep duration (6), and sleep naps (6). Several epilepsy genes showed association with multiple sleep phenotypes. The genes associated with the highest number of different sleep phenotypes were *KANSL1*, *GNAO1*, and *TCF4* (6, 5, and 4 sleep phenotypes, respectively).

Pathway Analysis for Sleep-Associated Genes

From the 26 epilepsy genes significantly associated with sleep phenotypes, there were 6 enriched biological processes, including "regulation of NMDA receptor activity," "brain development," "regulation of presynaptic membrane potential," "regulation of ion transmembrane transport," "positive regulation of synaptic transmission (glutamatergic)," and "positive regulation of excitatory postsynaptic potential." There was no significant enrichment of cellular components or molecular function.

CNS Disease Genes and Genes Expressed in the Brain Are More Strongly Associated With Sleep Phenotypes Than PNS Disease Genes

CNS-based neurologic disorders, including ataxia, cerebral palsy, leukodystrophy, and neurodevelopmental disorders, but not brain malformations, had gene sets that were more significantly associated with sleep phenotypes than the random gene set ($p_{adj} < 0.05$, Figure). Of the PNS disorders, only muscular dystrophy had a significant association with sleep phenotypes compared with random genes ($p_{adj} = 0.02$, Figure). While genes from any of the cell types were more significantly associated with sleep phenotypes compared with the random gene set, those expressed in neurons, astrocytes, and oligodendrocytes were the most significantly associated (Figure).

Discussion

Our findings suggest a genetic link between sleep phenotypes and epilepsy, which extends to other CNS diseases—particularly ataxia, but also cerebral palsy, leukodystrophy, and neurodevelopmental disorders. Muscular dystrophy has both CNS and PNS manifestations and was also genetically linked to sleep phenotypes. The strong association between sleep and CNS disorders may be explained by the strong association between sleep and genes expressed in neural cells of the CNS (neurons, astrocytes, and oligodendrocytes).

A prior study reported that synaptic pathways are shared between sleep and neurodevelopmental syndromes.[14] While that study analyzed the overlap between a list of sleep-related genes (extrapolated from GWAS data) and lists of developmental delay–related and epileptic encephalopathy–related genes, our study used the *p* values in the GWAS data set to better determine degrees of association between gene sets. Of interest, only 4 genes (*GNAO1, TCF4, RBFOX1*, and *SCN1A*) were common between the 2 studies' lists of overlapping sleep/epilepsy genes. This is likely due to the differences in GWAS data sets used, as the SDKP pools data from 76 genetic data sets, and the prior study used data from 3 publications. It is important to note that our analysis extends to other neurologic diseases and genes expressed in CNS cell types, and these additional findings give context to the degree of genetic overlap between epilepsy and sleep phenotypes.

Table 2 SIG-P Genes

Gene	# Of sleep phenotypes associated	Smallest *p* value	Associated sleep phenotypes
KANSL1	6	9.40E-47	**Naps**, ease of waking up, sleep duration, excessive daytime sleepiness, long sleep duration, snoring adjusting by BMI
CLN5	2	4.70E-22	**Chronotype,** ease of waking up
IER3IP1	1	2.10E-21	**Naps**
GNAO1	5	1.30E-18	**Chronotype**, ease of waking up, sleep duration, naps, short sleep duration
TCF4	4	8.30E-15	**Sleep duration**, ease of waking up, frequent insomnia symptoms, short sleep duration
MEF2C	2	1.80E-13	**Chronotype,** ease of waking up
DDC	1	1.20E-12	**Chronotype**
KCNH5	2	1.70E-12	**Mean sleep duration, rank-normalized;** diurnal inactivity duration, rank-normalized
QARS	1	1.80E-12	**Chronotype**
KCNQ5	1	6.40E-12	**Number of sleep episodes, rank-normalized**
NRXN1	2	1.10E-11	**Ease of waking up**, chronotype
RELN	3	1.70E-11	**Number of sleep episodes, rank-normalized**; chronotype; percentage of sleep with oxyhemoglobin saturation under 90%
RBFOX1	1	3.10E-11	**Sleep duration**
CACNA2D2	2	7.50E-11	**Chronotype,** ease of waking up
GRIN2A	1	4.50E-10	**Naps**
PAFAH1B1	1	4.60E-10	**Ease of waking up**
RAI1	1	7.10E-10	**Excessive daytime sleepiness**
SCN1A	1	8.60E-10	**Sleep duration**
COG5	1	1.50E-09	**Naps**
PRICKLE2	1	8.60E-09	**Snoring adjusting by BMI**
CHD2	1	1.00E-08	**Naps**
PNPO	1	1.40E-08	**Ease of waking up**
EHMT1	1	1.90E-08	**Sleep duration**
SUMF1	1	3.20E-08	**Number of sleep episodes, rank-normalized**
GABRA2	1	3.80E-08	**Excessive daytime sleepiness**
PEX12	1	4.10E-08	**Chronotype**

Epilepsy genes with at least one *p* value that reached genome-wide statistical significance ($p < 5 \times 10^{-8}$). The smallest *p* value (MIN-P) is included along with all the significantly associated sleep phenotypes. The sleep phenotype associated with the smallest *p* value for each gene is in bold.

The top epilepsy genes associated with sleep phenotypes have varied and broad functions. For example, *KANSL1*, associated with Koolen-DeVries syndrome, encodes a chromatin modifier that affects numerous cellular processes. *CLN5*, associated with neuronal ceroid lipofuscinosis, is involved in protein degradation in lysosomes. *TCF4*, associated with Pitt-Hopkins syndrome, encodes a transcription factor that is broadly expressed. The diverse functions of sleep/epilepsy genes may reflect the complex physiology of sleep.

The pathway analysis implies that sleep is affected by alterations in CNS function, particularly in biological processes of brain development, membrane physiology, and synaptic neurotransmission, rather than in peripheral nerve or neuromuscular function. As the GWAS data reflect common genetic changes with small effects on sleep while the epilepsy genes show typically rare genetic changes with large effect sizes, we hypothesize that individuals with disease-associated variants in epilepsy genes that are also linked to sleep phenotypes (SIG-P) are at a particularly high risk of having disordered sleep, which can in turn exacerbate seizures. Indeed, Koolen-de Vries syndrome is associated with continuous spike wave in sleep[15] as well as sleep problems (difficulty settling, night waking, and early

rising). Further clinical studies will define the spectrum of sleep disorders among people with genetic epilepsies, and this will enable better screening, diagnosis, and treatment.

Author Contributions

J.R. Gaillard: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. G. Gupta: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. H.C. Mefford: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. L.M. O'Brien: drafting/revision of the manuscript for content, including medical writing for content. R.A. Shellhaas: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. L.T. Dang: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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Disclosure

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