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RESEARCH ARTICLE

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Genetic basis of sleep phenotypes and rare neurodevelopmental syndromes reveal shared molecular pathways

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Abstract

Sleep-related phenotypes have been frequently reported in early on-set epileptic encephalopathies and in developmental delay syndromes, in particular in syndromes related to autism spectrum disorder. Yet the convergent pathogenetic mechanisms between these comorbidities are largely unknown. We first performed a gene enrichment study that identified shared risk genes among rare epileptic encephalopathies/neurodevelopmental disorders, rare developmental delay genetic syndromes and sleep disturbances. We then determined cellular and molecular pathways enriched among genes shared between sleep phenotypes and those two early onset mental illnesses, aiming to identify genetic disparities and commonalities among these phenotypic groups. The sleep gene set was observed as significantly overlapped with the two gene lists associated to rare genetic syndromes (i.e., epileptic encephalopathies/neurodevelopmental disorders and developmental delay gene sets), suggesting shared genetic contribution. Similarities across significantly enriched pathways between the two intersect lists comprehended mostly synapse-related pathways, such as retrograde endocannabinoid signaling, serotonergic, and GABAergic synapse. Network analysis indicates epileptic encephalopathies/neurodevelopmental disorders versus sleep-specific clusters and developmental delay versus sleep-specific clusters related to synaptic and transcriptional regulation, respectively. Longstanding functional patterns previously described in epileptic encephalopathies and neurodevelopmental disorders genetic architecture were recaptured after dissecting the overlap between the genes associated to those developmental phenotypes and sleep disturbances, suggesting that during neurodevelopment different molecular and functional mechanisms are related to alterations on circadian rhythm. The overlapping gene set and biological pathways highlighted by this study may serve as a primer for new functional investigations of shared molecular mechanisms between sleep disturbances and rare developmental syndromes.

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KEYWORDS
autism, epileptic encephalopathy, genetic syndromes, insomnia, sleep-associated genes

1 | INTRODUCTION

During early stages of postnatal neurodevelopment, sleep predominates over wakefulness. In this period, both stages of sleep, the non-rapid eye movement (NREM) and rapid eye movement (REM), reach their greatest amounts in mammalian lifetime (Frank et al., 2017). Since those stages of life are associated with critical organization and regulation of synaptic plasticity, it has been suggested that the neural activity characteristic of sleep may be critical for normal maturation of the central nervous system. In accordance with this hypothesis, sleep disturbances can impact on brain maturation. More adverse progression of childhood sleep disturbances is associated with smaller gray matter volumes and thinner dorsolateral prefrontal cortex (Kocevska et al., 2017). Additionally, it has been demonstrated that sleep improves memory consolidation in children (Backhaus et al., 2008; Wilhelm et al., 2008). Yet the convergent pathogenetic mechanisms that link neurodevelopment and sleep are largely unknown.

Epilepsy affects around 70 million individuals worldwide and is an important risk of disability, economic, and psychosocial problem (Guilhoto et al., 2021). When seizure and interictal epileptiform activity influence cognitive functions, this phenotype is referred as epileptic encephalopathies (EEs) (Raga et al., 2021), which comprise a heterogeneous group of epilepsy syndromes characterized by frequent seizures that are thought to contribute to developmental regression (Scheffer et al., 2017). In those patients, electrical status epilepticus during sleep is characterized by spike and wave discharges in up to 85%–100% of NREM sleep (Yan Liu & Wong, 2000). Indeed, rare genetic syndromes associated to early-onset EE (e.g., Landau–Kleffner and Lennox–Gastaut syndromes) are frequently associated with electroencephalographic alterations during NREM sleep (Morrison-Levy et al., 2021), suggesting that the link between abnormal sleep during early life and abnormal neurodevelopment might include genetic factors. The preponderance of NREM-related seizures in patients with frontal lobe epilepsy seems to be related to the seizure-promoting effect of unstable vigilance (Gibbs et al., 2016). In addition, memory consolidation is impaired in idiopathic focal epilepsies of childhood, showing association between higher spike–wave index during NREM sleep and poorer nonverbal declarative memory consolidation (Galer et al., 2015), which supports the hypothesis that interictal epileptic activity could disrupt sleep memory consolidation. Early-onset EEs are often comorbid with neurodevelopmental disorders (NDDs), such as developmental delay (DD), intellectual disability (ID), and autism spectrum disorders (ASDs) (Scheffer et al., 2017). The rate of epilepsy is correlated with the severity of ID (Thomas et al., 2017), and several genes have been implicated in both NDDs and epilepsy disorders (Deciphering Developmental Disorders Study, 2017), demonstrating that epilepsy and NDDs have overlapping genetic contributions.

Significance

Sleep-related phenotypes are frequently reported in early on-set epileptic encephalopathies and in developmental delay conditions, yet the convergent pathogenetic mechanisms between these comorbidities are largely unknown. Benefited from the enormous advances in recent populational genetics studies, this study provides a novel outlook on the relationship between sleep disorders and rare monogenetic syndromes. From updated gene lists based on the largest genetic studies for those traits, we demonstrate significant overlap between sleep- and neurodevelopment-associated genes. Using functional interaction networks from the set of intersect genes, we discuss critical nodes of coalescence between biological processes related to sleep and neurodevelopment.

Alterations in circadian sleep rhythmicity are also associated with NDD independently of EE phenotypes (Carmassi et al., 2019), and this association is replicated when only NDD-related rare genetic syndromes are considered (Agar et al., 2021; Tesfaye et al., 2022). Children with ASD have a sleep disturbance prevalence rate of 50%–80%, compared to 9%–50% in neurotypical children (Maxwell-Horn & Malow, 2017; Souders et al., 2017), and sleep problems are predictive of severity of ASD core symptoms (Mazurek et al., 2019; Veatch et al., 2017). Trajectory analyses showed that the severity and frequency of sleep problems decreases in typically developing children (Kocevska et al., 2017), whereas sleep problems worsen over time in children with NDD (Verhoeff et al., 2018).

The causes of sleep problems in EE/NDD are multifactorial, involving factors intrinsic to abnormal neurodevelopment (neurotransmitter abnormalities) as well as medical (gastrointestinal disorders, epilepsy) and behavioral (poor sleep habits) etiologies (Reynolds & Malow, 2011). One possibility is that the underlying cellular and molecular abnormalities causal to EE/NDD also produce abnormal sleep (i.e., abnormal sleep is one of many outcomes of an underlying problem). Another non-mutually exclusive possibility is that there is an interaction between the genetic variants linked to EE/NDD and the role of sleep early in life, which influences both the presence of sleep problems and the severity of EE/NDD. Sleep disturbances have been reported in mouse models for rare genetic variants causative of syndromic NDD in humans (Wintler et al., 2020), endorsing the line latter hypothesis. Consistently, in ASD patients, copy number variants encompassing circadian and insomnia risk genes increase liability for neurodevelopmental phenotypes (Tesfaye et al., 2022). Mutations in core clock genes are

observed in NDD patients (Hoang et al., 2021). We thus sought to investigate the interplay between sleep and rare genetic syndromes.

We performed a gene enrichment study that identified risk genes that contribute to (1) rare EE/NDD genetic syndromes, (2) rare DD genetic syndromes (with or without epilepsies), and (3) sleep phenotypes. We then determined cellular and molecular pathways enriched among genes shared between sleep phenotypes and those two early onset mental illnesses, aiming to identify genetic disparities and commonalities among these phenotypic groups.

2 | MATERIALS AND METHODS

2.1 | Manual curation of gene lists

We manually curated three sets of genes: the first one associated to sleep phenotypes, the second one associated to rare EE syndromes associated to NDD, and the third one associated to rare genetic DD. Since most of the sleep phenotypes follow a complex inheritance pattern, the first gene list was heavily driven by hits from genome-wide association studies (GWAS), while the other two gene lists, focused on rare genetic syndromes, were based on genes affected by de novo coding variants leveraged by exome studies.

2.2 | Sleep gene set

To create the sleep gene list, a previously published gene list (Abel et al., 2020) was merged to genes implicated in two recent large scale GWAS for insomnia (Jansen et al., 2019; Watanabe et al., 2022). Single nucleotide polymorphism (SNP)-to-gene linking analysis previously performed by the GWAS reference studies base the gene list composition. SNP hits from Jansen et al. (2019) and Watanabe et al. (2022) were associated to genes using Multi-marker Analysis of GenoMic Annotation (MAGMA) strategy. Based on a comprehensive literature review, Abel et al. (2020) curated a sleep gene set, including genes associated with insomnia, narcolepsy, sleep apnea, chronotype, sleep latency, sleep efficiency, sleep duration, and daytime sleepiness. The union of the genes leveraged by those three studies yielded a set of 1065 genes total (Table S1).

2.3 | Epileptic encephalopathy gene set

The EE/NDD gene set was driven by the two large-scale sequencing studies which are primary engines for new gene discovery related to this spectrum of phenotypes (Heyne et al., 2018, 2019). From Heyne et al. (2019), genes considered as targets in their analysis settings (i.e., genes commonly included in diagnostic sequencing panels) were included. From Heyne et al. (2018), two gene lists were considered: the list of genes with at least two de novo variants in EE/NDD patients and the list of genes previously known as associated to this phenotype. A total of 781 genes composed the EE/NDD gene set (Table S2).

2.4 | Developmental delay gene set

The gene set for DD did not account for epilepsy phenotypes as a selection criterion and was created from the union of the two largest exome study to date of cases ascertained for a diagnosis of autism spectrum disorder and DD, respectively (Fu et al., 2022; Kaplanis et al., 2020). Given the wide spectrum and heterogeneity of this phenotype, only genome-wide significant genes which were affected by de novo variants were considered. A total of 307 genes composed this gene set (Table S3).

2.5 | Gene overlap analysis

Using Fisher's exact test, statistical threshold of p-value $< .05$, and considering a total 21,196 genes in the human genome, we tested the statistical significance of the overlap between gene lists. Two comparisons were performed: (1) sleep gene set versus EE/NDD gene set and (2) sleep gene set versus DD gene set. Each comparison generated a new gene list containing the intersection of the contrasted gene sets. Statistical tests were performed in R using the GeneOverlap package.

2.6 | Pathway enrichment analysis

Benjamini–Hochberg test, adjusting for multiple comparisons, was used to identify enriched pathways, with a significance threshold of Adjusted p-value $< .05$. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) terms that were over-represented among the intersect gene lists were considered as enriched. Among GO terms, Biological Processes, Molecular Function and Cellular Components terms were considered. Statistical tests were performed using the Enrichr online tool (https://maayanlab.cloud/Enrichr/).

2.7 | Protein–protein interaction network analysis

Intersect gene lists were used as input on a protein–protein interaction (PPI) analysis via String database (https://string- db.org/), a minimal interaction score of .7. Protein clustering was defined using the Markov Clustering Algorithm (MCL) algorithm with an inflation value of 3.0. Network visualization was retrieved from Cytoscape 3.9.1.

3 | RESULTS

3.1 | Overlap between gene sets associated to sleep and rare genetic syndromes

The sleep gene set was observed as significantly overlapped with the two gene lists associated to rare genetic syndromes (i.e., EE/NDD and DD gene sets). There were 62 overlapping genes between

the gene lists associated to sleep phenotypes (1065 genes total) and the gene list associated to EE/NDD (781 genes total), indicating significantly more overlap than expected by chance (p-value = 2.5E−4, OR = 1.7) (Figure 1a, Table S4). When gene lists associated with sleep phenotypes (1065 genes total) and DD (307 genes total) were contrasted, there were 41 overlapping genes, indicating significantly more overlap than expected by chance (p-value = 1.1E−8, OR = 3.0) (Figure 1b, Table S4).

3.2 | Biological pathways enriched among the interest gene lists

The 62 intersect genes between sleep and EE/NDD sets yielded 15 significantly enriched terms, of which 13 were driven by genes with functions directly associated with synapse regulation and neuronal maintenance, while the other two terms were related to intracellular signaling processes (Table 1). In the 41 intersect gene list retrieved from the comparison sleep versus DD, 16 out of the 48 significantly enriched terms were driven by genes directly involved in transcription regulation, and other 23 terms were driven by genes related to synapse regulation (Table 2). Enriched terms detected in the latter intersect list also included intracellular signaling (1 term), endocrine (2 terms), and cardiac-related pathways (3 terms) (Table 2).

Similarities across significantly enriched pathways between the two intersect lists comprehended mostly synapse-related pathways, with a smaller contribution from intracellular signaling pathways (Tables 1 and 2). Those commonalities include retrograde endocannabinoid signaling, serotonergic and GABAergic synapse. Although some genes contained in those common pathways are shared between the two intersect lists, the final collection of genes under endocannabinoid, serotonergic and GABAergic KEEG pathways is unique for the sleep versus EE/NDD set and the sleep versus DD set (Tables 1 and 2).

Besides the presence of transcription-regulation terms in the sleep versus DD intersect set only, pathway enrichment discrepancies among the two intersect lists also included long-term regulation of the neuronal action potential in opposite directions. While the sleep versus EE/NDD intersect is significantly enriched for genes associated with long-term depression, the sleep versus DD intersect is significantly enriched for long-term potentiation (Tables 1 and 2).

3.3 | Interaction networks underlying intersect gene lists

PPI analysis using the sleep versus EE/NDD intersect set (62 proteins total) as input generated a network with 11 nodes (Figure 2a), while the analysis retrieved from sleep versus DD intersect set (41 proteins total) contained two networks, one with 10 nodes and the other with four nodes (Figure 2b). When comparing those two networks, there are eight nodes in common (Figure 2), being those shared nodes related to pathways enriched in both intersect gene lists (i.e., retrograde endocannabinoid signaling, serotonergic, and GABAergic synapse). One cluster in the sleep versus DD network, which is not seen in the sleep versus EE/NDD network, is related to transcriptional regulation (Figure 2b, cluster 4). The cluster specific to the sleep versus EE/NDD network is composed of proteins related to neuronal activity (Figure 2a, cluster 3). Divergencies and commonalities between both network analysis are summarized.

4 | DISCUSSION

Sleep problems are associated with a significant amount of distress for patients with rare genetic epileptic and/or neurodevelopmental syndromes and their caregivers. Additionally, it has been shown that sleep disturbances impact negatively on cognitive daytime performance and quality of life (Ballester et al., 2019), and may interfere in patients and caregivers' daily activities (Martins et al., 2015). Despite the recognition of the important association between sleep and neurodevelopment, the cause and consequence relationship between these phenotypes has not been directly established. Thus, it is scientifically and socially relevant to understand the biological processes underlying the association between sleep, epilepsy, and neurodevelopment.

Our over-representation analysis identified enriched pathways that suggest endocannabinoid, serotonergic and GABAergic circuits as

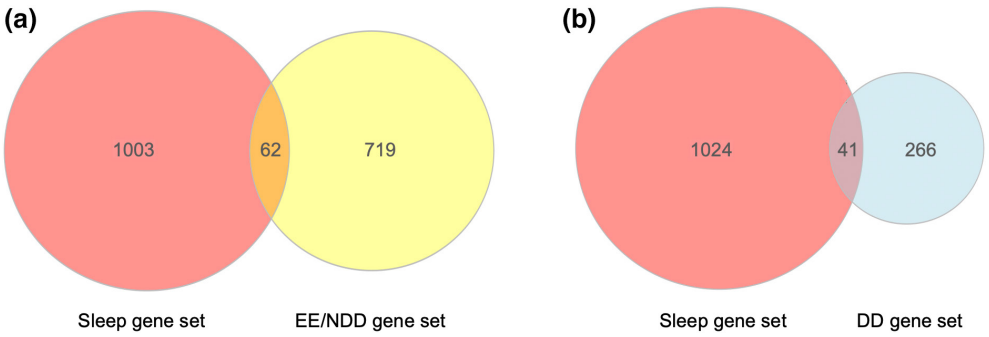

FIGURE 1 Gene overlap between sleep set and sets related to rare genetic syndromes. (a) There were 62 overlapping genes yielded by the sleep phenotypes (gene list with 1065 genes total) versus epileptic encephalopathies/neurodevelopmental disorders (EE/NDD, gene list with 781 genes total) comparison. (b) There were 41 overlapping genes yielded by the sleep phenotypes (gene list with 1065 genes total) and developmental delay (DD, gene list with 307 genes total) comparison.

TABLE 1 Significantly enriched pathways on epileptic encephalopathies/neurodevelopmental disorders (EE/NDD) versus sleep gene intersect.

Term	Overlap	*p*-Value	Adjusted *p*-value	Odds ratio	Genes
Neuron projection (GO:0043005)	11/556	9.8E−07	1.1E−04	7.7E+00	*GRIA1; GABRB2; GABRA1; SCN8A; SLC4A10; NF1; KIF1A; ANK1; DNM1; SLC6A4; SCN1A*
Nicotine addiction (KEEG)	4/40	7.0E−06	5.8E−04	3.8E+01	*GRIA1; GABRB2; GABRA1; GRIA3*
Retrograde endocannabinoid signaling (KEEG)	6/148	6.5E−06	5.8E−04	1.5E+01	*GRIA1; GNAO1; GABRB2; GABRA1; NDUFS3; GRIA3*
Serotonergic synapse (KEEG)	5/113	2.6E−05	1.5E−03	1.6E+01	*GNAO1; GABRB2; MAP2K1; CYP2D6; SLC6A4*
Long-term depression (KEEG)	4/60	3.6E−05	1.5E−03	2.4E+01	*GRIA1; GNAO1; MAP2K1; GRIA3*
Dopaminergic synapse (KEEG)	5/132	5.6E−05	1.8E−03	1.4E+01	*GRIA1; GNAO1; AKT3; GRIA3; SCN1A*
GABAergic synapse (KEEG)	4/89	1.7E−04	4.3E−03	1.6E+01	*GNAO1; GABRB2; GABRA1; GABBR1*
Morphine addiction (KEEG)	4/91	1.8E−04	4.3E−03	1.6E+01	*GNAO1; GABRB2; GABRA1; GABBR1*
GABA receptor activity (GO:0016917)	3/22	4.2E−05	6.7E−03	5.3E+01	*GABRA1; GABRB2; GABBR1*
Dendrite (GO:0030425)	6/270	1.9E−04	1.0E−02	8.0E+00	*GRIA1; GABRA1; CDKL5; SLC4A10; NF1; KIF1A*
Peroxisome proliferator activated receptor binding (GO:0042975)	2/7	2.0E−04	1.6E−02	1.3E+02	*ASXL1; ASXL3*
Axon (GO:0030424)	5/204	4.2E−04	1.6E−02	8.7E+00	*SCN8A; NF1; KIF1A; DNM1; SCN1A*
Beta-catenin-TCF complex (GO:1990907)	2/13	7.2E−04	2.0E−02	6.0E+01	*TCF7L2; TCF4*
GABA-gated chloride ion channel activity (GO:0022851)	2/13	7.2E−04	3.9E−02	6.0E+01	*GABRA1; GABRB2*
Peripheral nervous system development (GO:0007422)	3/25	6.2E−05	4.3E−02	4.6E+01	*NFASC; SCN8A; NF1*

Note: **Term:** term assigned to a given biological process, pathway or compartment in Gene Ontology (GO) or Kyoto Encyclopedia of Genes and Genomes (KEGG) databases. **Overlap:** number of genes in EE/NDD versus sleep intersect gene list which are contained in a given term relative to the total number of genes contained in this term. ***p*-Value, Adjusted *p*-value and Odds Ratio:** descriptive statistics retrieved from pathway enrichment analysis using Benjamini–Hochberg test, adjusting for multiple comparisons**. Genes:** names of the intersect genes contained in a given term.

potential shared mechanisms between sleep and both neurodevelopmental phenotypes evaluated (i.e., EE/NDD and DD). This functional convergence cannot be attributed to the commonalities between EE/NDD and DD genetic factors, since the final collection of shared genes under terms associated with those neuronal circuits is unique. It is important to highlight that genes shared between epileptic/neurodevelopmental phenotypes and sleep are subjected to different mutation patterns according to the associated condition. For instance, all six genes contained in the enriched KEEG endocannabinoid-related term are affected by common variation when associated with sleep disorders—four of them implicated in insomnia GWAS—and rare coding variants when associated with EE/NDD syndromes. This observation indicates that diverse mutational mechanisms drive the association of this pathway with the evaluated phenotypes.

The fact that long-term depression and potentiation terms were enriched among EE/NDD and DD analysis, respectively, might indicate an unbalance of excitatory/inhibitory circuits underlying the pathogenesis of those phenotypes and sleep. This has been confirmed by in vitro neuronal functional studies that addressed the biological role of genes shared between the evaluated traits. In a CRISPR modeling using induced pluripotent stem cell (iPSC)-derived neuronal lines, *SCN1A* loss-of-function led to increased action potential thresholds in GABAergic neurons and led to weak spontaneous inhibitory postsynaptic currents (Liu et al., 2016). iPSC-derived neural cell lines established from *CDKL5* deficiency disorder (CDD) patients have shown hyperexcitability and desynchronized network (Negraes et al., 2021). Both of those genes have longstanding association with rare epileptic and neurodevelopmental syndromes related to severe sleep abnormalities (Dhamija et al., 2014; Hagebeuk et al., 2013; Leoncini et al., 2022; Tascini et al., 2022) and have mouse models affected by sleep disturbances (Lo Martire et al., 2017; Papale et al., 2013). In addition to electrophysiological disturbances, in our over-representation analysis, neuronal projection also corresponds to a recurrently implicated pathway. *NF1* and *TCF7L2* are examples of genes previously associated with neurogenesis and neurite outgrowth in animal or cellular functional modeling (Anastasaki & Gutmann, 2014; Lee et al., 2017). Although those two genes are affected by rare coding variants in epileptic and neurodevelopmental syndromes, they were associated with sleep disturbances through GWAS hits (Jansen et al., 2019; Watanabe et al., 2022), indicating the complex genetic architecture underlying the intersection of the evaluated phenotypes.

When shared genetic factors between EE/NDD and sleep are contrasted to overlapping factors between DD and sleep, the major detected discrepancy is related to genes under functional class of chromatin/transcriptional regulation. Longstanding statements leveraged by ASD gene discovery efforts point to two main functional classes among genes commonly affected by rare genetic variation: synapse and chromatin regulation (de Rubeis et al., 2014). Transcriptional expression trajectories of ASD genes associated with chromatin regulation in particular are generally detected at

TABLE 2 Significantly enriched pathways on Developmental Delay (DD) versus sleep gene intersect.

Term	Overlap	*p*-Value	Adjusted *p*-value	Odds ratio	Genes
Regulation of transcription by RNA polymerase II (GO:0006357)	19/2206	1.3E−08	6.0E−06	7.0E+00	*TCF7L2; KMT2A; MYT1L; BCL11A; SATB2; ZBTB20; TCF20; EBF3; RORB; ZFHX4; FOXP2; FOXP1; ASXL1; KLF7; PSMC5; ASXL3; EP300; TCF4; SOX5*
Regulation of transcription, DNA-templated (GO:0006355)	19/2244	1.8E−08	6.0E−06	6.9E+00	*TCF7L2; MAP2K1; KMT2A; MYT1L; BCL11A; SATB2; ZBTB20; TCF20; EBF3; RORB; ZFHX4; FOXP2; FOXP1; KLF7; PSMC5; EP300; QRICH1; TCF4; SOX5*
Positive regulation of transcription, DNA-templated (GO:0045893)	14/1183	4.6E−08	1.1E−05	8.3E+00	*TCF7L2; MAP2K1; KMT2A; SATB2; TCF20; EBF3; RORB; ASXL1; KLF7; PSMC5; ASXL3; EP300; QRICH1; TCF4*
Cis-regulatory region sequence-specific DNA binding (GO:0000987)	13/1149	2.7E−07	1.6E−05	7.7E+00	*TCF7L2; MYT1L; BCL11A; SATB2; ZBTB20; EBF3; RORB; ZFHX4; FOXP2; FOXP1; KLF7; TCF4; SOX5*
RNA polymerase II cis-regulatory region sequence-specific DNA binding (GO:0000978)	13/1149	2.7E−07	1.6E−05	7.7E+00	*TCF7L2; MYT1L; BCL11A; SATB2; ZBTB20; EBF3; RORB; ZFHX4; FOXP2; FOXP1; KLF7; TCF4; SOX5*
Nucleus (GO:0005634)	24/4484	6.3E−07	3.4E−05	4.9E+00	*SRRM2; TCF7L2; MAP2K1; CDKL5; KMT2A; CSNK2A1; MYT1L; BCL11A; ZBTB20; TCF20; EBF3; RORB; ZFHX4; FOXP2; FOXP1; KLF7; PSMC5; U2AF2; NF1; EP300; QRICH1; TCF4; FGF12; SOX5*
Intracellular membrane-bounded organelle (GO:0043231)	25/5192	2.4E−06	6.3E−05	4.5E+00	*KMT2A; MYT1L; ZBTB20; TCF20; RORB; U2AF2; EP300; SOX5; SRRM2; TCF7L2; MAP2K1; CDKL5; CSNK2A1; BCL11A; ATP2B2; EBF3; ZFHX4; FOXP2; FOXP1; KLF7; PSMC5; NF1; QRICH1; TCF4; FGF12*
Axon (GO:0030424)	6/204	3.5E−06	6.3E−05	1.7E+01	*DSCAM; SCN8A; NF1; KIF1A; DNM1; SCN1A*
RNA polymerase II transcription regulatory region sequence-specific DNA binding (GO:0000977)	13/1359	1.8E−06	7.1E−05	6.4E+00	*TCF7L2; MYT1L; BCL11A; SATB2; ZBTB20; EBF3; RORB; ZFHX4; FOXP2; FOXP1; KLF7; TCF4; SOX5*
Neuron projection (GO:0043005)	8/556	1.4E−05	1.9E−04	8.6E+00	*GABRB2; GABRA1; DSCAM; SCN8A; NF1; KIF1A; DNM1; SCN1A*
Cardiac muscle cell contraction (GO:0086003)	3/19	7.6E−06	1.1E−03	9.8E+01	*CACNA1C; FGF12; SCN1A*
Positive regulation of nucleic acid-templated transcription (GO:1903508)	8/511	7.8E−06	1.1E−03	9.4E+00	*MAP2K1; PSMC5; KMT2A; EP300; EBF3; QRICH1; TCF4; RORB*
Positive regulation of transcription by RNA polymerase II (GO:0045944)	10/908	1.1E−05	1.2E−03	6.8E+00	*ASXL1; TCF7L2; KLF7; KMT2A; SATB2; ASXL3; EP300; TCF20; TCF4; RORB*
Membrane depolarization during action potential (GO:0086010)	3/26	2.0E−05	2.0E−03	6.8E+01	*SCN8A; CACNA1C; SCN1A*
Dendrite (GO:0030425)	5/270	2.2E−04	2.3E−03	1.0E+01	*GABRA1; CDKL5; DSCAM; NF1; KIF1A*
Nuclear receptor binding (GO:0016922)	4/120	1.1E−04	2.5E−03	1.8E+01	*ASXL1; TCF7L2; EP300; FOXP1*
Peroxisome proliferator activated receptor binding (GO:0042975)	2/7	8.6E−05	2.5E−03	2.0E+02	*ASXL1; ASXL3*
Cardiac muscle cell action potential (GO:0086001)	3/30	3.1E−05	2.6E−03	5.8E+01	*CACNA1C; FGF12; SCN1A*
Cardiac muscle cell action potential involved in contraction (GO:0086002)	3/31	3.5E−05	2.6E−03	5.6E+01	*CACNA1C; FGF12; SCN1A*
Beta-catenin-TCF complex (GO:1990907)	2/13	3.2E−04	2.8E−03	9.3E+01	*TCF7L2; TCF4*
DNA-binding transcription repressor activity. RNA polymerase II-specific (GO:0001227)	5/256	1.7E−04	3.3E−03	1.1E+01	*MYT1L; BCL11A; ZBTB20; FOXP2; FOXP1*
GABAergic synapse (KEEG)	4/89	3.3E−05	4.0E−03	2.5E+01	*GNAO1; GABRB2; GABRA1; CACNA1C*
Melanogenesis (KEEG)	4/101	5.4E−05	4.0E−03	2.2E+01	*GNAO1; TCF7L2; MAP2K1; EP300*
Serotonergic synapse (KEEG)	4/113	8.3E−05	4.1E−03	2.0E+01	*GNAO1; GABRB2; MAP2K1; CACNA1C*

TABLE 2 (Continued)

Term	Overlap	*p*-Value	Adjusted *p*-value	Odds ratio	Genes
Voltage-gated sodium channel complex (GO:0001518)	2/17	5.5E−04	4.2E−03	6.8E+01	*SCN8A; SCN1A*
GABA-A receptor complex (GO:1902711)	2/19	6.9E−04	4.6E−03	6.0E+01	*GABRA1; GABRB2*
GABA-gated chloride ion channel activity (GO:0022851)	2/13	3.2E−04	5.3E−03	9.3E+01	*GABRA1; GABRB2*
Positive regulation of adenylate cyclase activity (GO:0045762)	2/7	8.6E−05	5.8E−03	2.0E+02	*NF1; CACNA1C*
Sodium channel complex (GO:0034706)	2/25	1.2E−03	7.2E−03	4.4E+01	*SCN8A; SCN1A*
Sequence-specific DNA binding (GO:0043565)	7/707	5.3E−04	7.7E−03	5.7E+00	*TCF7L2; KMT2A; ZBTB20; TCF4; RORB; FOXP2; FOXP1*
Ligand-gated anion channel activity (GO:0099095)	2/18	6.1E−04	8.0E−03	6.4E+01	*GABRA1; GABRB2*
GABA-A receptor activity (GO:0004890)	2/19	6.9E−04	8.0E−03	6.0E+01	*GABRA1; GABRB2*
Cushing syndrome (KEEG)	4/155	2.8E−04	8.3E−03	1.4E+01	*TCF7L2; MAP2K1; KMT2A; CACNA1C*
Retrograde endocannabinoid signaling (KEEG)	4/148	2.4E−04	8.3E−03	1.5E+01	*GNAO1; GABRB2; GABRA1; CACNA1C*
Long-term potentiation (KEEG)	3/67	3.5E−04	8.6E−03	2.5E+01	*MAP2K1; EP300; CACNA1C*
Dendrite membrane (GO:0032590)	2/29	1.6E−03	8.7E−03	3.8E+01	*GABRA1; ATP2B2*
Adherens junction (KEEG)	3/71	4.1E−04	8.8E−03	2.3E+01	*TCF7L2; CSNK2A1; EP300*
GABA receptor activity (GO:0016917)	2/22	9.2E−04	9.0E−03	5.1E+01	*GABRA1; GABRB2*
Voltage-gated sodium channel activity (GO:0005248)	2/22	9.2E−04	9.0E−03	5.1E+01	*SCN8A; SCN1A*
Androgen receptor binding (GO:0050681)	2/27	1.4E−03	1.3E−02	4.1E+01	*EP300; FOXP1*
Transmitter-gated ion channel activity (GO:0022824)	2/34	2.2E−03	1.8E−02	3.2E+01	*GABRB2; GABRA1*
Sodium channel activity (GO:0005272)	2/8	2.8E−03	2.1E−02	2.8E+01	*SCN8A; SCN1A*
Sequence-specific double-stranded DNA binding (GO:1990837)	6/712	3.1E−03	2.3E−02	4.7E+00	*TCF7L2; ZBTB20; TCF4; RORB; SOX5; FOXP1*
Transcription cis-regulatory region binding (GO:0000976)	5/549	5.1E−03	3.5E−02	5.0E+00	*TCF7L2; SATB2; ZBTB20; SOX5; FOXP1*
Anion channel activity (GO:0005253)	2/68	8.6E−03	4.8E−02	1.5E+01	*GABRB2; GABRA1*
Chloride channel activity (GO:0005254)	2/64	7.6E−03	4.8E−02	1.6E+01	*GABRB2; GABRA1*
DNA-binding transcription factor binding (GO:0140297)	3/208	8.8E−03	4.8E−02	7.6E+00	*TCF7L2; PSMC5; EP300*
Transcription regulatory region nucleic acid binding (GO:0001067)	3/212	9.3E−03	4.8E−02	7.5E+00	*TCF7L2; ZBTB20; SOX5*

Note: **Term:** term assigned to a given biological process, pathway or compartment in Gene Ontology (GO) or Kyoto Encyclopedia of Genes and Genomes (KEGG) databases. **Overlap:** number of genes in DD versus sleep intersect gene list which are contained in a given term relative to the total number of genes contained in this term. ***p*-Value, Adjusted *p*-value and Odds Ratio:** descriptive statistics retrieved from pathway enrichment analysis using Benjamini–Hochberg test, adjusting for multiple comparisons**. Genes:** names of the intersect genes contained in a given term.

their highest levels during early neurodevelopmental stages (Li et al., 2018). Protein truncating variants on those chromatin genes are a well-established ASD risk factor (Fu et al., 2022) and have also been implicated with sleep disturbances in NDD patients (Leoncini et al., 2022; Rapp et al., 2022; Smith & Harris, 2021; Tascini et al., 2022). On the other hand, previous populational studies have demonstrated that when de novo genetic variants affecting NDD patients with and without EE are compared, missense variation is more likely to affect individuals with EE, and this association is driven by ion channels related to synapse regulation (Heyne et al., 2018). Consistently, many epilepsy disorders act as channelopathies (Myers & Mefford, 2015). These same functional patterns were recaptured after dissecting the overlap between the genes associated to those neurodevelopmental phenotypes and sleep disturbances, suggesting that different molecular and functional mechanisms are related to alterations on circadian rhythm during neurodevelopment.

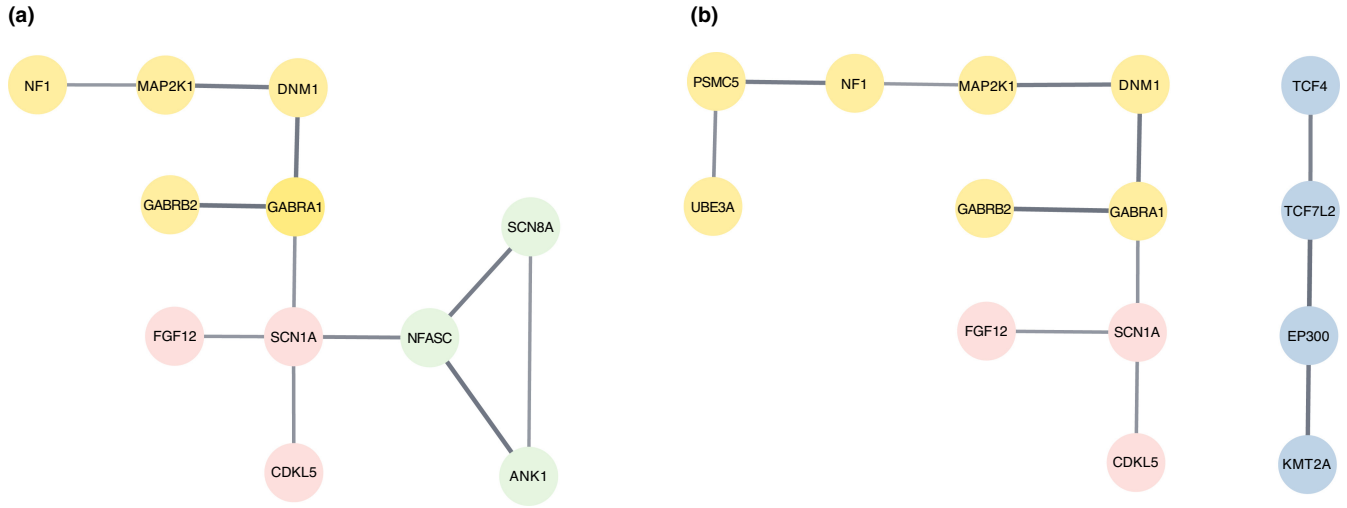

FIGURE 2 Protein–protein interaction (PPI) networks generated from intersect gene lists. (a) PPI network retrieved from sleep versus epileptic encephalopathies/neurodevelopmental disorders (EE/NDD) intersect gene set yielded three clusters: cluster 1 (colored in yellow), cluster 2 (colored in pink), and cluster 3 (colored in green). (b) PPI network retrieved from sleep versus developmental delay (DD) intersect gene set yielded three clusters: cluster 1 (colored in yellow), cluster 2 (colored in pink), and cluster 4 (colored in blue).

The gene overlap strategy proposed in this study contains limitations. First, the most standard SNP-to-gene linking strategies lack functional information, which can restrict the list of implicated genes. Second, the pathway enrichment and PPI procedures depend on the availability and accuracy of functional annotations of biological processes, proteins, and genes. Third, the undoubtful association of the highlighted pathways to the evaluated phenotypes depends on the availability and reliability of functional assay at large scale, which is currently not abundantly reported in the literature. We do believe that the use of over-representation analysis greatly aids in identifying patterns among the vast list of associated genes, and the current study shows that this strategy indicates specific biological functions in shared molecular mechanisms underlying sleep disturbances, epileptic and neurodevelopmental disorders. Despite the identification of these shared molecular mechanisms, our results still cannot be used to infer a putative cause and consequence relationship between sleep and neurodevelopment disturbances.

The evaluation and treatment of circadian sleep disorders may be useful to improve the trajectories of subjects with neurodevelopmental symptoms. Advances in understanding circadian influences on excitatory and inhibitory mechanisms could help to clarify the factors involved in seizure generation and inhibition of spread of epileptic activity, as well as circuits relevant to neuronal plasticity required for the development of cognition, memory and learning consolidation. Such discoveries could potentially lead to novel treatment approaches, including gene therapy or optogenetics as tools for controlling and monitoring neuronal activity. The overlapping gene set and biological pathways highlighted by this study may serve as a primer for new functional investigations of sleep and EE/NDD shared molecular mechanisms.

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CONFLICT OF INTEREST STATEMENT

GNP is a shareholder at SleepUp©.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jnr.25180.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

TABLE S1 Sleep gene set

TABLE S2 EE/NDD gene set

TABLE S3 DD gene set

TABLE S4 Intersect gene sets

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