### S2 | (Table)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Abnormal sleep/circadian phenotype co-morbid with disease. Data from human subjects</th>
<th>Molecular/genetic associations that might give rise to the sleep/circadian abnormalities observed. Data from human and mouse studies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric diseases</strong></td>
<td></td>
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<tr>
<td><strong>Affective disorders</strong></td>
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</tbody>
</table>
| Unipolar depression      | ∞ Reduced latency to REM sleep.  
∞ 1st REM episode longer.  
∞ Reduced eye movements in REM sleep.  
∞ Reduced amount of SWS.  
∞ Disrupted plasma cortisol and IL-6.  
∞ Altered diurnal changes in mood.  
∞ Mood elevating effect of sleep deprivation.  
∞ SSRI-induced deficit in REM sleep. | 5-HTTLPR  
MAO-A  
5HT1A  
Glucocorticoid receptor  
CRF1  
FKBP5 | 1-8 |
| Seasonal affective disorder (SAD) | ∞ Hypersomnia in winter.  
∞ Craving for carbohydrate-rich food.  
∞ Sensitive to bright light therapy. | 5-HT1B  
NPAS2  
PER2  
PER3  
BMAL1 (ARNTL)  
OPN4 | 2, 9-13 |
| Bipolar (BP) depression  | ∞ Hypersomnia and low day-time activity.  
∞ Advanced sleep/wake timing. | PER3  
GSK3  
BMAL 1  
CLOCK  
DBP  
TIMELESS  
CSNK1E | 14-21 |
| Mania                    | ∞ Ultra-rapid sleep/wake cycling.  
∞ Decreased need for sleep.  
∞ Lower anxiety. | CLOCK | 22-24 |
| **General Anxiety Disorder** |                                                                                    |                                                                                                                              |            |
| Panic disorder           | ∞ Daytime panic attacks.  
∞ Nocturnal panic attacks associated with sensation of choking, heart palpitations, and accelerated heart rate. Respiratory problems. | Adenosine 2A receptor  
NPS | 25-29 |
### Post-traumatic stress disorder
- Nightmares.
- Increased stage 1 sleep.
- Reduced slow-wave-sleep.
- Sleep apnoea.
- Periodic leg movements.
- Greater REM sleep density.

### Obsessive-compulsive disorder
- Delayed sleep/wake timing.
- Reduced stage 4 NREM sleep.
- Reduced REM sleep latency.
- Elevated 1st REM episode.
- Increased cortisol, ACTH and GH during sleep.

### Developmental Disorders
#### Attention-deficit hyperactive disorder
- Increased nocturnal activity.
- Nocturnal awakenings.
- Reduced sleep efficiency.
- Reduced REM sleep.
- Hyperactivity.

#### Autism
- Bedtime resistance, fragmented/disrupted sleep and circadian rhythms.
- Delayed sleep/wake timing.
- Reduced REM onset latency.
- Irritability.
- Enuresis.
- Epileptiform EEG abnormalities.

#### Fragile X Syndrome
- Hyperactivity and autistic behavior.
- High variability in sleep duration.
- High variability in sleep timing.
- Nocturnal awakenings.
- Increased melatonin amplitude.

### Eating disorders
#### Anorexia Nervosa
- Fragmented sleep.
- Reduced SWS.
- Decreased theta power.
- OGF-1 levels and leptin decreased.

### Substance Abuse
### Alcoholism
- Insomnia
- Delayed sleep onset
- Decreased SWS
- Decreased REM latency
- Decreased sleep duration
- Sleep disturbances promote relapse

### Psychotic disorders
- **Schizophrenia**
  - SWS deficit
  - Decreased REM latency
  - Defective REM rebound
  - Abnormal circadian sleep/wake cycles (Irregular, delayed, free-running)

### Neurodegenerative Disorders
- **Alzheimer's Disease (AD)**
  - Nocturnal awakenings
  - Altered K complex and sleep spindles
  - Decrease in 4 wave activity in REM and awake states
  - SWS deficits
  - Prevalence of day-time sleep

- **Parkinson's Disease (PD)**
  - Insomnia and parasomnia
  - REM sleep behaviour disorder
  - REM/NREM sleep abnormalities
  - Day-time sleepiness
  - Hallucinations

- **Huntington Disease (HD)**
  - Sleep-wake timing disruption
  - Nocturnal awakening
  - Reduced sleep efficiency
  - Nocturnal anxiety during arousals

- **Multiple Sclerosis (MS)**
  - Daytime fatigue which is highly correlated with nocturnal sleep disruption
  - Delayed and irregular sleep/wake timing

<table>
<thead>
<tr>
<th>Disease</th>
<th>Abnormality</th>
<th>Genes/Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>Nocturnal awakenings</td>
<td>ApoE4</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>SWS deficit</td>
<td>CALHM1</td>
</tr>
<tr>
<td>Alzheimer's Disease (AD)</td>
<td>Nocturnal awakenings</td>
<td>HLA-DR2</td>
</tr>
<tr>
<td>Parkinson's Disease (PD)</td>
<td>Nocturnal awakening</td>
<td>Beta-amyloid precursor protein (Tg 2576)</td>
</tr>
<tr>
<td>Huntington Disease (HD)</td>
<td>Sleep-wake timing disruption</td>
<td>mPer2 and mBmal1 expression in SCN, motor cortex, striatum</td>
</tr>
<tr>
<td>Multiple Sclerosis (MS)</td>
<td>Daytime fatigue which is highly correlated with nocturnal sleep disruption</td>
<td>HLA-DR2 positive individuals show shorter sleep onset latency</td>
</tr>
</tbody>
</table>

### Supplementary Table 1: Circadian/sleep-related abnormalities observed in a range of syndromes with some emerging sleep/circadian genetic associations

**Abbreviations:**
- 5-HTR = 5-hydroxytryptamine (serotonin) receptor
- 5-HT1A = presynaptic serotonin 1A receptor
- 5-HT1B = presynaptic serotonin 1B receptor
- 5-HTTLP = Serotonin transporter
- ACTH = Adrenocorticotropic hormone (ACTH)

- **SERAC**: Serotonin receptor 2C antagonist; 5-HTTLP-1: Serotonin transporter ligand binding protein 1

**Genes/Proteins:**
- **5-HT1A**: Presynaptic serotonin 1A receptor
- **5-HT1B**: Presynaptic serotonin 1B receptor
- **5-HTTLP**: Serotonin transporter ligand binding protein
- **ACTH**: Adrenocorticotropic hormone

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in response to biological stress; ApoE4 = Apolipoprotein A; BMAL1 (ARNTL) = Aryl hydrocarbon receptor nuclear translocator-like, the protein encoded by this gene is a basic-helix-loop-helix PAS (bHLH-PAS) domain containing protein; BDNE = Brain-derived neurotrophic factor. BDNF is a protein of the neurotrophin family of growth factors, which help support the survival of existing neurons and encourage the growth and differentiation of new neurons and synapses; CALHM1 = calcium channel protein; CLOCK = Circadian Locomotor Output Cycles Kaput, is a gene/protein which regulates circadian rhythms (see Box 3); CRF1 = corticotropin-releasing factor 1; COMT = Catechol-O-methyl transferase, a catabolic enzyme involved in the degradation of bioactive molecules including dopamine; CSNK1E = Casein kinase 1, epsilon; DAT1 = Dopamine transporter; DBP = D site of albumin promoter (albumin D-box) binding protein, a member of the PAR bZIP transcription factor family; DRD2 = Dopamine receptor D2; DRD4 = Dopamine receptor D4; Fmr1/Fxr2 = Fragile X mental mouse mutant; FKBP5 = FK506 binding protein 5, a member of the immunophilin protein family; FXR2P/FRMRP = proteins of fragile X gene; GABA-A/B = receptor = ionotropic receptor and ligand-gated ion channels. Thier endogenous ligand is γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system; GH = growth hormone; GSK3 = Glycogen synthase kinase 3 is a serine/threonine protein kinase; HD = Huntington's disease, chorea, or disorder (HD), is an incurable neurodegenerative genetic disorder that affects muscle coordination and some cognitive functions; HLA-DR2 = a broad antigen serotype; IL-6 = Interleukin-6 (pro-inflammatory cytokine); MAO-A = Monoaminoxidase A; Npas2 = neuronal PAS domain protein 2, a transcriptom factor and peripheral clock gene; NPY = Neuropeptide Y (NPY) is a 36 amino acid peptide neurotransmitter found in the brain and autonomic nervous system; OPN4 = melanopsin; PER1 = Period homolog 1 = Period clock genes; SNAP-25, a synaposomal-associated protein of 25kDa; SSRI = Selective Serotonin Reuptake Inhibitor; SWS = Slow wave sleep; TIMELESS (TIM) is a gene/protein which is associated with circadian regulation. 

References

18. Mansour, H.A. et al. Association study of eight circadian genes with bipolar I disorder,
SUPPLEMENTARY INFORMATION


