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Circadian biology and sleep in monogenic neurological disorders and its potential application in drug discovery

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Sleep disturbances are common in people with monogenic neurological disorders and they dramatically affect the life of individuals with the disorders and their families. The associated sleep problems are probably caused by multiple factors that have not been elucidated. Study of the underlying molecular cause, behavioral phenotypes, and reciprocal interactions in several single-gene disorders (Angelman Syndrome, Fragile X Syndrome, Rett Syndrome, and Huntington's Disease) leads to the suggestion that sleep disruption and other symptoms may directly result from abnormal operation of circadian systems due to genetic alteration and/or conflicting environmental cues for clock entrainment. Therefore, because circadian patterns modify the symptoms of neurological disorders, treatments that modulate our daily rhythms may identify heretofore unappreciated therapies for the underlying disorders.

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Introduction: single gene neurological disorders

The vast majority of neurological disorders are complex or multifactorial disorders. Those diseases include schizophrenia, depression, autism, epilepsy, Alzheimer's Disease, Parkinson's Disease, etc., all of which are influenced by multiple genetic and environmental factors. In contrast, single-gene neurological disorders are caused by variations/mutations in the DNA sequence of a specific gene [1]. For example, the core symptoms of Angelman Syndrome (AS), Fragile X Syndrome (FXS), Rett Syndrome (RTT), and Huntington's Disease (HD) are caused by single-gene variants [2,3]. Moreover, environmental factors often play important roles in the initiation and development of single gene disorders [4,5]. Although single-gene neurological disorders are not very common, they are extremely valuable to investigate the genetic and pathological causes of disorders because of the simpler genetic underpinings as compared with complex genetic disorders [6••]. Investigation of monogenic diseases can create a foundation for new preventive treatments and therapeutic drug discovery, as well as providing conceptual and technical bases for studying more complex disorders.

Interplay of sleep and circadian rhythms

Many physiological processes display day–night rhythms, including sleep–wake behavior and metabolism. These daily oscillations are regulated and coordinated by the master circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus and by tissue-specific clocks [7]. In mammals, the expression of approximately 50% of genes are circadianly regulated at primarily posttranscriptional levels in at least one tissue [8,9]. Those rhythmic transcripts are translated into proteins and processed by posttranslational modifications, and then act functionally and rhythmically in myriad cellular processes [10,11]. Disruption of these rhythmic gene expression patterns, as in human circadian desynchrony (e.g. from shiftwork, jet-lag, and/or sleep disruption) can have profound effects on mental health [12•,13]. Improper circadian entrainment is associated with the onset of neurological disorders, and circadian disruption may interact with other susceptibility factors to precipitate disease states [14].

Circadian rhythms also help determine our sleep patterns. The body's master SCN clock controls the production of melatonin and corticosterone, two hormones that are involved in sleep regulation [15,16]. The SCN receives environmental light/dark information via retinal-hypothalamic tracts from specialized ganglion cells in the eyes to the brain. The circadian clock is thereby enabled to anticipate, sense, and respond to light-dark changes so as to create physiological plasticity to predictable alterations in the external environment [4]. For decades, circadian rhythms have been thought to dictate sleep timing. In addition to affecting the timing of sleep, emerging evidence shows that circadian rhythms in the brain and even in peripheral tissues such as muscle [14,17•] are also able to regulate and coordinate the sleep quality and sleep duration by affecting 'sleep homeostasis.' Circadian

rhythms and sleep therefore interact, balancing each other to fine-tune the daily cycles of behavior, metabolism and physiology in the body [18].

Ube3a imprinting and AS

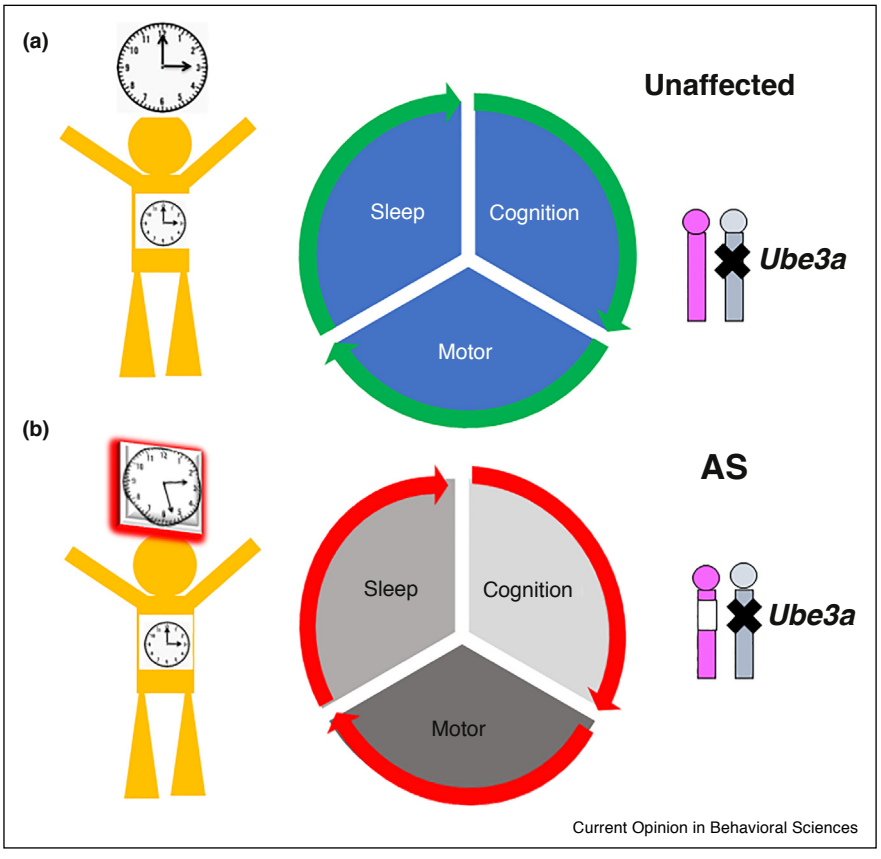
AS is a neurodevelopmental disorder of imprinting characterized by mental disability, developmental delays, sleep disorders, epileptic seizures, motor difficulties, and speech impairment [19••,20,21]. There is no specific therapy for AS and treatment for seizures usually becomes necessary. About 70% of AS patients have deletions of the maternal copy of chromosome 15 in the region of 15q11-q13 (Figure 1). The *Ube3a* gene within this region was identified as the genetic locus for AS [21]. *Ube3a* encodes a HECT-domain E3 ubiquitin ligase that adds ubiquitin to substrates, thereby targeting them for destruction in the proteasome. AS is an example of genomic imprinting that is caused by the deletion or inactivation of the maternal copy of *Ube3a*, while the paternal copy is imprinted and therefore silenced. It has been thought that the paternal imprinting involved in AS occurs only in the brain and is not imprinted in non-neural peripheral tissues or in glia [22,23]. However, detailed analyses in a variety of cell types using the *Ube3a*::YFP mouse as a tool demonstrated spatiotemporal confirmation of allele-specific *Ube3a* expression in neurons, astrocytes and oligodendrocytes [24–26]. Besides the allele-specific expression of *Ube3a* in different cell types, the three known isoforms of its transcript may play different and critical roles in the pathology of AS [27,28••]. Therefore, improving our understanding of the developmental parameters of paternal *Ube3a* imprinting, including its isoform-specific silencing and cellular basis could facilitate the therapeutic treatment of AS.

Sleep/circadian disruption in AS

Sleep syndrome in AS individuals

Sleep problems are very common in AS patients. Up to 75% of subjects with AS suffer from sleep disturbances [29,30], and these sleep disruptions are one of the syndrome's most stressful manifestations to families with an AS member [31]. Disrupted sleep phenotypes such as short sleep duration, frequent arousal during sleep, and increased sleep onset latency are observed very often in

Figure 1



Angelman Syndrome (AS) results from deletion (open box on chromosome 15 in lower right corner of the figure) of the *Ube3a* gene on maternal chromosome 15 and concomitant imprinting (X) of the *Ube3a* gene on paternal chromosome 15. In addition to motor and cognition deficits (middle panels), AS has significant effects on sleep and the circadian clock (note desynchrony of brain vs. peripheral clocks in left panels) [19••].