From Gene Mutation to Sleep Phenotype: DEC2 in Natural Short Sleepers

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ABSTRACT

This review focuses on the role of sleep in overall health, specifically its physiological activities, and the consequences of sleep disorders. We review the DEC2 gene mutation, which is associated with familial natural short sleep (FNSS) that allows people to remain healthy despite chronic sleep deprivation. This mutation not only extends life expectancy but also enhances stress resistance by influencing circadian rhythms and overall physiological responses. With the rising prevalence of sleep disruptions in modern culture, understanding genetic markers like the DEC2 provides critical insights into potential pro-longevity pathways, opening the way for approaches that maintain health during sleep deprivation and extend overall health span.

Keywords: DEC2, Gene therapy, Sleep physiology, Sleep disorders, Natural short sleep, Longevity

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Introduction

Sleep is a state of reduced mental and physical activity in which consciousness is altered and responsiveness to external stimuli is diminished. During this state, there is a marked decrease in muscle activity and limited interaction with the surrounding environment. Although sleep differs from wakefulness in terms of responsiveness, the brain remains active, exhibiting distinct patterns that differentiate it from a coma or other states of consciousness. Sleep constitutes roughly one-third of our lives, and its quality and quantity are as crucial to survival as food and water. Adequate sleep supports the formation and maintenance of neural pathways in the brain, which are essential for learning, memory consolidation, and cognitive function. On the other hand, sleep deprivation hinders concentration, reaction time, and the ability to process information.[1]

The biological function of sleep remains an area of extensive research, yet its importance across various bodily systems is well established. Sleep significantly impacts the brain, the cardiovascular system, the lungs, metabolism, the immune system, mood, and even disease resistance.[1] Chronic sleep deficiency or poor-quality sleep has been linked to several adverse health outcomes, including high blood pressure, cardiovascular disease, diabetes, depression, and obesity.[2] Emerging evidence suggests that sleep may also serve a "housekeeping" role in clearing toxins from the brain that accumulate during wakefulness.[1]

The exact purpose of sleep is still not fully understood, and several theories attempt to explain its role. The inactivity theory is rooted in evolutionary biology, proposing that being inactive at night reduces the risk of harm from predators and accidents in the dark, thus conferring a survival advantage. According to the energy conservation theory, sleep serves to lower the energy demand during periods when it would be less efficient to search for food. This idea is supported by findings that show a reduction in metabolism of up to 10% during sleep. The restorative theory suggests that sleep allows the body to repair itself and restore biological functions depleted throughout the day. Processes such as muscle repair, tissue growth, protein synthesis, and the release of growth-promoting hormones predominantly occur during sleep.

Meanwhile, the brain plasticity theory emphasizes the role of sleep in supporting neural reorganization and brain development. This is particularly evident during infancy and childhood, where sleep requirements can exceed 14 hours per day to accommodate rapid brain growth.[3–6]

These theories offer valuable perspectives, but none completely illuminate the complexity of sleep on its own. It is more likely that a combination of these ideas provides a comprehensive understanding of sleep's function. The many-sided nature of sleep reflects its broad influence on human health and well-being.

While individual sleep requirements vary, the Sleep Research Society recommendations suggest that adults should aim for at least 7 hours of sleep per night for optimal health.[7] The National Sleep Foundation further advises 7–9 hours for adults and slightly less for older adults at 7–8 hours.[8] Recommendations for children and adolescents are higher, acknowledging the increased need for sleep during developmental stages.[8,9] Despite these guidelines, data from the Centers for Disease Control and Prevention and the Maternal and Child Health Bureau show that a substantial portion of the population falls short of adequate sleep. Surveys reveal that approximately 34.1% of children, 74.6% of high school students, and 32.5% of adults fail to get sufficient sleep regularly.[10–12] This widespread sleep deficiency poses significant public health challenges, warranting increased efforts to improve sleep duration and quality across all age groups.

Sleep Physiology and Biochemistry

Sleep involves pronounced physiological changes, especially within the brain which uses significantly less energy during sleep compared to wakefulness, particularly in non-rapid eye movement (NREM) sleep. During this period, the brain replenishes its stores of adenosine triphosphate (ATP), a crucial molecule for energy storage and transport.[13] Given that the brain accounts for about 20% of the body's energy consumption while awake, this reduction in energy use during sleep has a notable impact on overall energy expenditure.[14]

As a person falls asleep, the body's sensory threshold increases, meaning that fewer external stimuli are perceived. However, the ability to respond to more intense stimuli, like loud noises, is generally retained.[14,15] Sleep is also linked to hormonal activity; during slow-wave sleep, bursts of growth hormone are secreted, while prolactin release is associated with all sleep stages, even daytime naps.[16]

Monitoring sleep involves several key physiological measurements. Electroencephalography (EEG) records brain wave activity, electrooculography tracks eye movements, and electromyography measures skeletal muscle activity. When these are collected simultaneously, the process is known as polysomnography, typically performed in sleep labs. Additional tools such as electrocardiography for cardiac activity and actigraphy for detecting body movements can also provide insights into sleep patterns.[17]

Sleep follows a predictable cyclical pattern divided into two primary phases: NREM sleep and rapid eye movement (REM) sleep. NREM is further subdivided into three stages, with each stage representing varying depths of sleep characterized by distinct brain wave patterns, muscle tone, and eye movement activity. NREM occupies about 75%–80% of the total sleep time, while REM accounts for the remaining 20%–25%. Throughout the night, the sleep cycle repeats, typically four to five times, with each cycle lasting around 90–120 minutes. As the night progresses, the proportion of REM sleep in each cycle increases, starting with minimal REM during the initial phase and rising to about 30% of the cycle later on.[18]

Stages of NREM Sleep

Stage 1: The shallowest stage, lasting 1–7 minutes, where individuals are still easily awakened. EEG recordings show rhythmic alpha waves at a frequency of 8–13 cycles per second.

Stage 2: This stage, initially lasting 10–25 minutes, becomes the predominant phase of sleep as the night continues, making up about 50% of the total sleep time. EEG activity during this stage features "sleep spindles" and "K-complexes." Memory consolidation is thought to primarily occur in this stage.

Stage 3: Also known as slow-wave sleep, this stage lasts 20–40 minutes in the initial cycles. The EEG displays high-voltage, slow-wave activity, indicating deeper sleep.[18] REM sleep is characterized by REMs and is the stage associated with vivid dreaming.[19] During REM, the body experiences a state of voluntary muscle paralysis, except for the extraocular muscles. This paralysis serves as a protective mechanism, preventing the enactment of dreams. The EEG during REM sleep shows a desynchronized pattern of sawtooth waveforms, theta waves, and slow alpha waves.[20,21] Patients with nightmare disorders often exhibit increased high alpha activity and frontocentral delta power during REM sleep.[22]

The mechanisms generating and sustaining sleep are primarily regulated by two brain systems: homeostatic processes and the circadian rhythm. The homeostatic system tracks the body's need for sleep, while the circadian rhythm acts as an internal clock for the sleep-wake cycle, largely controlled by the hypothalamus. Within the hypothalamus, the ventrolateral preoptic nucleus inhibits arousal centers, including regions like the tuberomammillary nucleus and locus coeruleus. Hypocretin (orexin) neurons in the lateral hypothalamus also play a role, aiding in the transition to sleep.[18]

NREM sleep is characterized by a functional disconnection between the brainstem, thalamus, and cortex, maintained by GABAergic neurons in the reticular activating system. Corticothalamic signaling results in hyperpolarization of thalamic neurons, leading to the generation of delta waves observed during deeper stages of NREM sleep. Conversely, REM sleep is initiated by cholinergic neurons in the mesencephalon and pons, with specific nuclei like the pedunculopontine and laterodorsal tegmental areas triggering desynchronized cortical activity. The parasympathetic nervous system mediates the tonic component of REM sleep, while the sympathetic nervous system governs the phasic component.[18]

The circadian rhythm governs the body's natural desire for sleep and wakefulness. The suprachiasmatic nucleus (Figure 1) of the hypothalamus, informed by light signals from the retina, orchestrates this rhythm, which follows an approximate 24.2-hour cycle. Melatonin, a hormone produced in the pineal gland, modulates the circadian rhythm, with levels peaking at night and declining during the day.[18] Body temperature fluctuations also play a role, with lower temperatures in the morning and higher levels in the evening.[20,23]

Considering the circadian rhythm's influence on sleep, napping becomes an important approach to managing rest while being attentive during the day. Naps are small intervals of sleep that people take during the day to receive enough rest. Although napping is commonly associated with kids, over one-third of American adults nap daily. The ideal nap duration is 10–20 minutes, as studies have shown that it takes at least 30 minutes to enter slow-wave sleep, the deepest stage of sleep.[24] Napping for too long and entering slow-wave cycles might make it difficult to wake up and leave you feeling exhausted. This interval of drowsiness is known as sleep inertia. A siesta is a short nap taken in the early afternoon, usually following a midday meal. This type of sleep is a popular practice in various countries, particularly those with warm climates. It has lately been linked to a 37% lower coronary death rate, presumably due to decreased circulatory stress caused by daytime sleep.[25] Short midday naps and light evening exercise have been shown to benefit elderly people's sleep, cognitive tasks, and mental wellness.[26]

Sleep deprivation can have far-reaching consequences, impacting not only daytime alertness but also various physiological functions. Symptoms such as fatigue, impaired cognitive performance, heightened pain sensitivity, and increased inflammation are often associated with insufficient sleep. Research has linked

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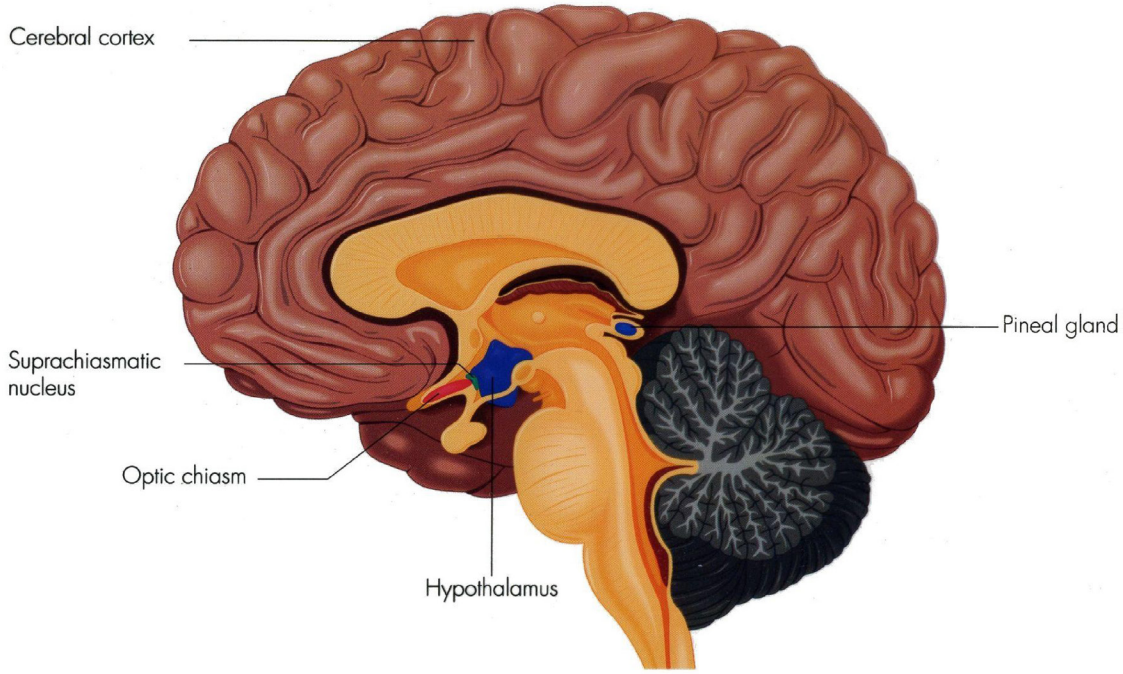

Fig 1 | The suprachiasmatic nucleus (SCN) is found in the hypothalamus. It is the main system where the circadian rhythm is regulated

these symptoms to elevated levels of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) in the brain and bloodstream. These cytokines regulate NREM sleep in both healthy and inflammatory states, and their presence can replicate the adverse effects of sleep deprivation. A deeper look into the molecular mechanisms reveals that ATP, released during neurotransmission, activates purinergic receptors such as P2X7, leading to the release of TNF-α and IL-1β from glial cells. This inflammatory cascade then influences neuronal properties by altering their responsiveness to key neurotransmitters such as adenosine, glutamate, and GABA, ultimately impacting the sleep-wake state.[27]

Clinical Significance of Sleep Disorders

Sleep disorders are increasingly recognized as both a cause and a consequence of various health conditions.

Low-quality sleep has been linked to cardiovascular disease, obesity, and mental health problems. Research suggests that poor sleep may be not only a symptom but also a contributing factor in the development of these conditions. The following is an overview of several sleep disorders and their implications on health.

Poor sleep is prevalent among individuals with cardiovascular disease, with evidence suggesting that inadequate sleep may contribute to its onset. Both short sleep duration (<7 hours) and long sleep duration (>9 hours) are linked to coronary heart disease, stroke, and other cardiovascular events. Individuals who experience <7 hours of sleep per night have a higher risk of developing coronary heart disease and dying from it. On the other hand, sleeping >9 hours has also been associated with adverse cardiovascular outcomes.[28,29]

Short sleep duration is associated with an increased risk of obesity in both children and adults, with studies showing a 45–55% higher risk among those who sleep less. Various aspects of sleep health, including daytime napping, sleep timing, sleep variability, and sleep efficiency, also correlate with obesity risk. However, sleep duration remains the most extensively studied factor in relation to weight gain.[28]

Historically, sleep problems have been viewed mainly as symptoms of mental illnesses. However, growing evidence indicates that they can also be contributing factors. Insomnia, for instance, significantly increases the risk of developing a major depressive disorder. A meta-analysis of over 170,000 individuals found that insomnia was associated with more than twice the risk of future depression. Insomnia has also been linked with anxiety, post-traumatic stress disorder, and even increased suicidal risk. Additionally, sleep disorders can exacerbate psychosis and intensify psychotic episodes.[28]

DEC2 Gene Research and Natural Short Sleepers

Familial natural short sleep (FNSS) is a rare, genetically inherited trait in which individuals sleep for significantly fewer hours than the average population without experiencing the negative effects typically associated with sleep deprivation, such as daytime sleepiness, cognitive impairment, or irritability. Unlike intentional sleep restriction, which can impair cognitive function and mood, individuals with FNSS naturally require less

sleep and maintain optimal health and functionality despite their shorter sleep duration. This condition is not considered a disorder and is regarded as a benign genetic trait, without known adverse health effects of natural short sleep [30,31]

Research has identified several genes that regulate the natural short sleep phenotype, including DEC2, ADRB1, NPSR1, and GRM1. These genes are believed to influence sleep quality, duration, and overall sleep homeostasis. Understanding their roles may help in developing therapeutic interventions for sleep disturbances, alleviating sleep debt, and addressing related health conditions.

Among these, DEC2 (Figure 2) stands out for its strong association with short sleep duration. DEC2 belongs to the basic helix-loop-helix (bHLH) transcription factor family, a superfamily of transcriptional regulators present in organisms ranging from yeast to humans. These bHLH proteins play key roles in various developmental processes, including sex determination, nervous system development, and muscle growth.[32,33]

Studies have shown that a mutation in DEC2 can impact sleep duration by interacting with CLOCK and BMAL1 proteins, which act as metabolic sensors in macrophages and regulate the production of pro-IL-1β.[34,35] The transcription factor BMAL1, a key clock protein, helps generate daily or circadian rhythms in physiological functions, including the inflammatory response. CLOCK and BMAL1 form a heterodimer that activates the expression of period genes through E-box elements in gene promoter regions.

DEC2 modulates sleep duration by repressing this activation, either through direct interaction with BMAL1 or by competing for binding to the E-box. This mechanism helps fine-tune sleep patterns, offering insights into the genetic regulation of sleep.[36]

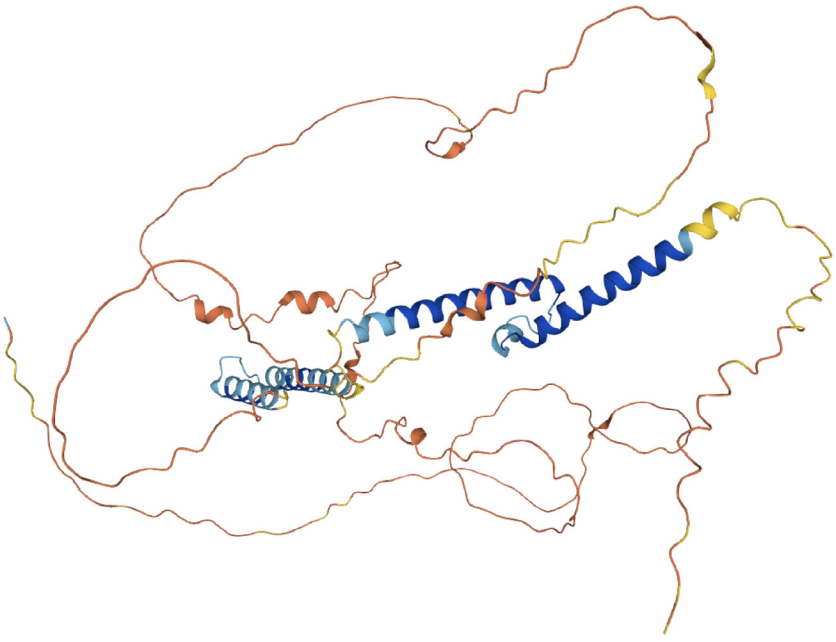

Fig 2 | AlphaFold-produced DEC2 gene structure

FNSS was first demonstrated through the discovery of a hDEC2 point mutation (P385R) in two individuals from a family who displayed habitual sleep durations averaging 6.25 hours, compared to 8.06 hours in non-carrier relatives.[37] The P385R mutation involves a missense mutation in which proline is replaced by arginine at position 385 in exon 5.[37] Studies using mouse and fly models with this mutation showed shorter NREM and REM sleep durations, increased wakefulness, and altered sleep recovery after sleep deprivation, indicating a modification in sleep homeostasis in carriers.[37]

Further additional DEC2 variants, including p.Tyr362His, p.Pro384Arg, p.Pro384Gln, and p.Ala380Ser, were evaluated using luciferase assays and plasmid constructions.[36] While p.Pro384Gln did not significantly affect molecular activities, the other variants altered the repressive activity of DEC2 on CLOCK/BMAL1, likely leading to reduced sleep duration and a decreased impact of sleep deprivation.[36] Interestingly, these variants also affected the NPAS2-BMAL1 complex, another sleep-modulating factor, raising questions about whether DEC2 variants exert their effects through interactions with CLOCK, NPAS2, or both.

The significance of DEC2 in FNSS was further explained with one twin carrying a DEC2 mutation who had a total sleep time of 299.3 minutes, while the non-carrier twin slept for 364.7 minutes.[37] Despite a shorter sleep duration, the carrier twin exhibited fewer lapses in alertness, higher delta power (a measure of sleep drive), and similar body mass index readings compared to the non-carrier, suggesting a robust adaptation to shorter sleep. It was proposed that these observations might result from quicker neurohormonal changes, such as an earlier rise in cortisol levels following sleep deprivation, although the underlying molecular mechanisms remain unclear.[37]

The DEC2 gene's role extends beyond sleep processes, including memory. A study of mice with both DEC1 and DEC2 genes knocked out (double null mutants) demonstrated altered sleep architecture, reduced alertness levels, and impaired working memory.[37] While DEC2-P385R mutant mice exhibited a short sleep phenotype without cognitive deficits, the double null mutants showed enhanced memory consolidation in the cortex and an increased expression of insulin-like growth factor 2, linked to long-term memory formation.[37] These findings suggest that DEC2 may influence cognitive processes via mechanisms distinct from its role in sleep regulation.

Orexin, also known as hypocretin, is a neuropeptide that promotes wakefulness and controls sleep (Figure 3). According to studies, DEC2 can affect orexin signaling by suppressing the expression of the prepro-orexin gene via interactions with transcription factors such as MyoD1 and E12.[38] In vitro, studies showed that mutant DEC2-P384R proteins had reduced repressive activity, potentially making DEC2 a target for treating insomnia by influencing orexinergic pathways.[39]

A recent study identified a familial natural short sleep mutation, Dec2P384R, as a potential factor for

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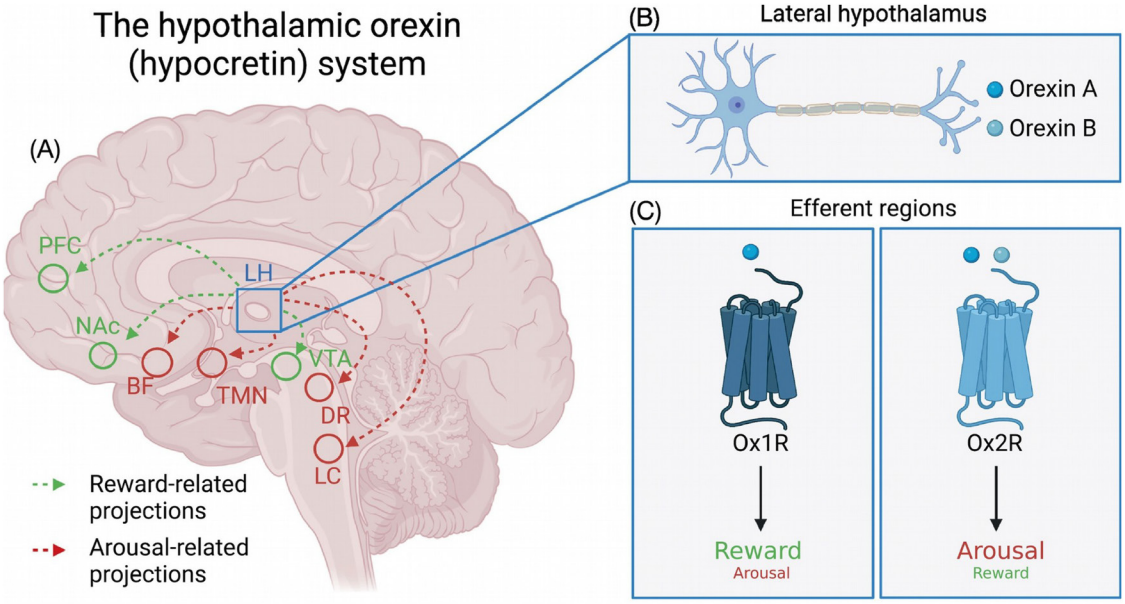

Fig 3 | Orexin-producing neurons are mostly located in the perifornical and lateral hypothalamus, which control the reward, arousal, and wakefulness systems

promoting longevity.[40] While previous suggestions have linked natural short sleepers to thriving despite chronic sleep deprivation, this concept has not been rigorously tested experimentally. Using a Drosophila model, the researchers demonstrated that the expression of the Dec2P384R mutation indeed extends the lifespan and supports healthy aging.[40] Furthermore, the study uncovered metabolic adaptations and genetic pathways influenced by neuronal DEC2 that contribute to the extended lifespan and enhanced stress resistance seen in DEC2P384R mutants. Specifically, several pathways involved in metabolic and xenobiotic stress responses were upregulated.[40]

Although the extended lifespan seen in Dec2P384R mutants likely results from a combination of genetic factors, the researchers highlighted the critical role of the increased expression of mtnB, a metallothionein protein, in achieving the full lifespan extension effects. Metallothioneins are small proteins involved in cellular stress responses and have established links to longevity.[41] Increased metallothionein expression is associated with resistance to mitochondrial-induced stress and prevention of apoptotic signaling,[41] aligning with the observed resistance of Dec2P384R mutants to mitochondrial inhibitors.

The research suggests that the mutation's effects extend beyond neurons to non-neuronal tissues, such as muscle, indicating cell non-autonomous systemic changes. Dec2, as a transcription factor, regulates circadian genes impacting health and longevity.[40] For instance, inhibiting the *Caenorhabditis elegans* period ortholog lin-42 accelerates aging, while in Drosophila, null mutations in the period ortholog reduce oxidative stress resistance.[40]

The improved health of Dec2P384R mutants may also underlie their short sleep phenotype. Although sleep deprivation is generally linked to reduced health and longevity, certain studies suggest that shorter sleep does not always correlate with a decreased lifespan.[42] There are even examples of species that evolved to thrive with minimal sleep. The findings raise intriguing questions about the relationship between sleep, longevity, and potential compensatory mechanisms that sustain health despite sleep reduction.

Conclusion

Sleep is a vital physiological process, essential for maintaining physical, cognitive, and emotional health. It orchestrates complex regulatory mechanisms, such as metabolism, immune function, and neuroplasticity. Sleep disruptions, whether due to lifestyle, environmental factors, or underlying sleep disorders, are increasingly linked to negative health outcomes, including metabolic dysfunction, cardiovascular disease, and neurodegenerative conditions. Sleep disorders such as insomnia, sleep apnea, and circadian rhythm disorders significantly contribute to reduced quality of life and increased morbidity, underscoring the importance of understanding the underlying mechanisms governing sleep regulation.

The discovery of the Dec2P384R mutation and its association with natural short sleepers present a unique opportunity to explore the genetic foundations of sleep duration and its broader implications for health and longevity. Individuals with this mutation exhibit an unusual ability to function optimally with significantly less sleep than the average population, without evident detriments to health. This characteristic challenges the conventional understanding of sleep requirements, suggesting that some genetic adaptations can support a healthy, short-sleep phenotype.

The broader implications of the research extend to understanding the genetic factors that may promote longevity and healthy aging. While more studies are

needed to clarify the mutation's effects on circadian regulation and to identify additional genes involved, Dec2 provides a promising model for uncovering novel pro-longevity mechanisms.

Given the increasing prevalence of sleep disturbances in modern society, understanding genetic factors like Dec2 that can promote health in the face of chronic sleep deprivation is of considerable public health interest.

Overall, these findings highlight the complex relationship between sleep, genetics, and health, and emphasize the need for continued research into the genetic underpinnings of sleep physiology.

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