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Research Article

The Effect of Genetics on Sleep Disorders: A Review

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Abstract

Sleep is a phenomenon observed in the majority of animals. Given that humans dedicate approximately one third of their lives to sleep, it is crucial to study sleep disorders and their origins. Genetics is a significant factor influencing sleep and its disorders, but it has received relatively limited attention in research, leading to an air of uncertainty regarding its impact on sleep. However, advancements in molecular techniques have now made it possible to comprehend the connection between specific genes, their products, and the quantity and quality of sleep. Various approaches, such as family studies, twin studies, Genome-Wide Association Studies (GWAS), and investigations involving animals, particularly circadian rhythm studies in fruit flies, have provided answers to questions pertaining to sleep and genetics. This article examines the correlation between certain genes and sleep characteristics, their hereditary nature, the involvement of the HLA system in certain sleep disorders, the association between the immune system and sleep disorders like Parkinson's disease, and the role of the hypocretin molecule in sleep disorders.

Keywords: Sleep disorders, Genetics, Biological clock

Introduction

Sleep plays a vital role in human health as it serves to replenish the energy reserves in the brain that are depleted during periods of wakefulness [1]. Among its essential functions, one is the reduction of synaptic strength during deep sleep, also known as Slow Wave Sleep (SWS). This process is crucial because without it, the brain would lose its ability to acquire new knowledge and skills [2].

The behavior of sleep and wakefulness can be understood through the combined influence of two processes. The first is the circadian rhythm, which determines the optimal timing for sleep and is influenced by environmental cues, particularly light. The second is the sleep rhythm, which encompasses both the quality and quantity (duration) of sleep [2-4]. Sleep consists of different stages, including wakefulness, Non-Rapid Eye Movement (NREM) sleep, and Rapid Eye Movement (REM) sleep [2].

NREM sleep is characterized by the synchronization of EEG waves and is comprised of different stages. Stage N1 occurs during the transition between wakefulness and sleep, stage N2 is marked by specific EEG patterns known as sleep spindles and K complexes, and stage N3, also referred to as Slow Wave Sleep (SWS) or deep sleep, is characterized by high voltage activity in the lowest frequency range. On the other hand, REM sleep is distinguished by the lack of EEG synchronization and the presence of low-amplitude waves, along with the absence of muscle tone, irregular breathing patterns, and the occurrence of Rapid Eye Movements (REM) [1,2].

Sleep disorders encompass a group of neurological conditions that disrupt daily activities, leading to cognitive difficulties, impaired work performance, and decreased overall productivity, thus impacting general health [5]. These disorders are classified into four main groups: circadian rhythm disorders, hypersomnia, insomnia, and parasomnia. Circadian rhythm disorders can disrupt sleep patterns due to factors such as timing, environmental influ-

ences, social factors, or occupational demands. Additionally, some individuals may have a genetic predisposition to circadian rhythm disorders [4,6].

Recognizing the significance of sleep in maintaining our well-being, it is crucial to comprehend the genetic components associated with it in order to prevent and address sleep disorders. By examining the underlying causes of these disorders, we can utilize information from sleep EEG and explore the genetic influences on brain activity during sleep patterns, thereby identifying genetic factors involved [7,8].

Materials and Methods

The article was written utilizing the Google Scholar database. By employing the keywords "sleep disorders" and "genetics," a total of 31 relevant articles were retrieved. Out of these, 21 articles were selected for inclusion in the review article based on the quality of the research and the presence of distinct and discussable results.

Result

Research indicates that neuropeptides and neurotransmitter systems play a crucial role in regulating sleep. Notably, hypocretins or orexins are among the most significant neuropeptides in this domain, as their deficiency is linked to narcolepsy [9,10]. Additionally, other factors influencing the sleep-wake cycle include transcription factors like C-FOS, NGFI-A, and junB, which exhibit a substantial increase in activity within the cerebral cortex during wakefulness compared to sleep [11].

The influence of circadian clock genes, such as Clock and Per genes, on sleep behavior is also noteworthy. For instance, specific point mutations in the human clock gene (Per2) are associated with advanced sleep phase syndrome, while functional polymorphisms in the Per3 gene are linked to delayed sleep phase syndrome [12].

A notable and intriguing characteristic of numerous sleep disorders is their strong correlation with the Human Leukocyte Antigen (HLA) system. To date, at least four sleep disorders, including Kline-Lewin syndrome, RBD disorder, and narcolepsy, have been associated with polymorphisms in the HLA gene set. This observation suggests a potential interplay between sleep and the immune system, necessitating further research for a more comprehensive elucidation [13-16].

In regards to sleep disorders, studies indicate that only a small subset of them have a clearly defined genetic basis. Examples of such disorders include fatal familial insomnia, familial advanced sleep stage syndrome, and narcolepsy, which can be attributed to a single gene mutation [17].

Discussion

Sleep Disorders and Genetics

Sleep is primarily associated with cellular and molecular processes. Several sleep characteristics, including sleep duration, sleep onset latency, and insomnia, have a heritable component, although they are not governed by a specific gene or locus. Twin studies have been instrumental in investigating genes that may contribute to sleep and sleep disorders, as sleep latency, REM manifestations, and sleep cycle durations tend to be highly similar in identical twins [4].

Regarding the regulation of sleep and wakefulness cycles, it is evident that the loss or dimerization of nuclear proteins can impact the control of these periods. In fruit flies, Clock and cycle proteins, and in mammals, Clock and BMAL1 proteins, play significant roles in this process. Additionally, suppressor genes such as Per and Cryptochrome also contribute to sleep regulation. These findings highlight the importance of various proteins and genes within the biological clock pathways in governing sleep and wakefulness periods [9]. Furthermore, a recent study demonstrated that the deletion of the BMAL1/Mop3 gene can alter the sleep pattern [12].

The Relationship Between Genetics, Restless Legs Syndrome (RLS) and Parkinson's: During the daily EEG examination of patients with Restless Legs Syndrome (RLS) compared to the control group, certain changes were observed. These changes included an increase in the power of the delta wave and fast alpha wave, as well as a decrease in the power of the slow alpha wave [1]. In terms of genetics, a study has identified three gene loci associated with restless legs syndrome. These loci include MEIS1 on chromosome 2p14, multiple variants in BTBD9, and seven variants in a region containing MAP2K5 and SKOR1. The combination of these variants increases the risk of restless leg syndrome by 50% [7].

Drugs that target GABA receptors have demonstrated improvement in the symptoms of Restless Legs Syndrome (RLS). The episodic and unique nature of this syndrome suggests a possible connection between nerve ion channel genes and RLS. Various research studies have explored the genetic factors underlying RLS, but a conclusive confirmation of these factors has not yet been established. Additionally, there is some indication that RLS may be associated with chromosome 12q and spinal ataxia type 3, although the precise impact of these genes on RLS remains uncertain [11]. Based on the available studies, the current understanding is that RLS is caused by an imbalance in the circuits of the brain and spinal cord that integrate sensory input and control motor output [2]. Gender and age have also been identified as confirmed risk factors for RLS. Research has shown that women are affected by this condition twice as often as men, and the prevalence of RLS tends to increase with age. Studies on different families suggest that the disease follows an autosomal dominant mode of inheritance with high penetrance and variable expression of the responsible genes [10]. The prevalence and proportion of RLS in familial cases appear to vary widely based on the geographic origin of the studied population. However, a recent study briefly reported a 19.9% risk of the disorder among first-degree relatives and a 4.1% risk among second-degree relatives [18]. There is a connection between restless legs syndrome (RLS) and Parkinson's disease. Among a group of 126 patients diagnosed with Parkinson's, 7.9% of them also experienced RLS symptoms. In contrast, only 0.8% of the control group without Parkinson's exhibited RLS [1].

Genetics, Obstructive Sleep Apnea (OSA) and Serotonin: Research indicates that variations in the ApoE gene are associated with Obstructive Sleep Apnea (OSA). This gene is characterized by three alleles: ε3, ε2, and ε4. The presence of the ε4 allele increases the risk of developing OSA. Additionally, a recent study has linked vitamin D deficiency and changes in the VDBP (rs4588) and VDR (rs2228570, rs1544410) genes to the occurrence of OSA [4].

Studies conducted on rodents suggest that a deficiency in the enzyme monoamine oxidase A can contribute to sleep apnea, and elevated serotonin levels may influence this type of sleep disorder. Another article proposes that sleep apnea in children could lead to genetic alterations in circulating white blood cells. The results demonstrate that RNA extracted from peripheral white blood cells supports the presence of changes in functionally related gene clusters [15].

Genetic analyses conducted on families have revealed that certain genetic factors may play a role in the inheritance of this disorder. Furthermore, in African-American individuals, sample analyses suggest the existence of shared and non-shared genetic factors between OSA and obesity. Collectively, these analyses emphasize the significant role of genetic factors in understanding sleep disorders and related conditions [8].

The Relationship Between Genetics and Advanced Sleep Phase Syndrome (ASPS): ASPS has a strong familial association and follows an autosomal dominant pattern of inheritance. A specific point mutation has been identified in an ASPS family, affecting the circadian Per2 gene at the casein-epsilon kinase phosphorylation site [14]. The first gene mutation associated with familial ASPS was discovered in 2001 in one of the component genes of the circadian system, Per2. Per2 plays a positive role in the feedback loop function of BMAL1. This mutation alters a phosphorylation site within the internal CKI binding domain of Per2. However, it should be noted that most cases of familial ASPS are not caused by this particular mutation. Another missense mutation in the CKIdelta gene has recently been identified [12].

Scientists have found that ASPS has a familial subtype known as FASPS. Patients with FASPS struggle to stay awake during the desired waking hours and tend to wake up early. Generally, mutations in the PER2 (S662G) and CKIδ (T44A) genes are observed in individuals with FASPS. A common mutation is found in the CKIε binding site in hPER2 [4]. Research findings demonstrate that individuals with advanced sleep phase disorder exhibit specific alterations in their sleep and wake patterns. Compared to individuals with typical sleep patterns, their sleep patterns, body temperature, and melatonin hormone secretion occur approximately 3-4 hours earlier. Furthermore, studies indicate that the quality and duration of sleep in individuals with advanced sleep phase disorder are not significantly different from those of individuals with normal sleep patterns, as long as they are allowed to sleep during their desired times [6]. FASPS is closely tied to the body's natural circadian clock. The key components involved in the body's natural circadian clock system include CLOCK and BMAL1 transcription factors, PER1-3 and CRY1-2 proteins, as well as Casein Kinase (CK) 1, δ, and ε enzymes. Research on mice and mosquitoes has revealed that the loss of function in the hPER2 gene can disrupt the circadian cycle [16].

Delayed Sleep Phase Syndrome (DSPS)

Delayed Sleep Phase Syndrome (DSPS) is the opposite of Advanced Sleep Phase Syndrome (ASPS). It is primarily observed in young individuals and is characterized by a persistent delay in both waking up and falling asleep. People with DSPS experience a delay in their melatonin cycle. The MEL1A and AANAT genes have been implicated in this disorder, along with variations in the hPER3 gene. The PER3 protein forms heterodimers with PER1, PER2, CRY1, and CRY2, which then translocate to the nucleus and inhibit the activity of CLOCK/BMALL1. In a study, Four Haplotypes (H1-4) of the hPER3 gene were identified, and it was found that the polymorphisms present in H4 were associated with DSPS. Furthermore, the T3111C mutation in the CLOCK gene has been linked to DSPS [4].

This disorder may be caused by a delay in the melatonin cycle, which is observed in individuals with DSPS. Melatonin and its receptor protein are expressed in the suprachiasmatic nuclei, and a relationship has been demonstrated between the Melatonin Receptor Protein 1A (MEL1A) and asynchrony in the 24-hour sleep-wake rhythm. Additionally, a connection has been reported between DSPS and the arylalkylamine N-acetyltransferase gene, which is involved in the synthesis of melatonin [12].

From a Genetic Mutation to Fatal Family Insomnia!

The underlying cause of this degenerative brain condition is a specific point mutation occurring in codon 178 of the Prion Protein (PrP) gene, leading to the destruction of a particular thalamic nucleus. Familial Fatal Insomnia (FFI) affects both males and females equally and follows an autosomal dominant pattern of inheritance with high penetrance, ultimately resulting in death. In individuals affected by FFI, mutations are observed in the PRNP gene at positions 178 and 129 [15].

Does Genetics Affect Insomnia, the Most Common Form of Sleep Disorders, or Not?

This disorder is influenced by various psychological, social, hormonal, and genetic factors, and it affects approximately 20% of the adult population. Insomnia associated with major depressive disorder is characterized by normal sleep onset but frequent awakenings in the second half of the night and early morning awakening. There appears to be a genetic component to the relationship between sleep and depression, as research indicates that 30% of 8-year-old children and 11% of 10-year-old children exhibit both sleep disorders and depression [17].

Through the use of animal models and sleep deprivation studies, scientists have identified the Homer1a gene, which is expressed in individuals with a predisposition to sleep deprivation. Furthermore, adult patients who are homozygous for the clock gene genotype have a higher susceptibility to experiencing early, middle, and late insomnia [15].

In childhood insomnia, genetic factors also contribute, particularly when the disorder manifests at an early age. Having a family history of insomnia further increases vulnerability to the disorder, especially in cases of primary insomnia. For instance, a missense mutation in the GABA-A subunit has been identified, causing an alteration in a single amino acid and affecting the function of the GABA receptor. Interestingly, individuals with the clock genotype, known as CC patients, frequently experience difficulties in falling asleep (initial insomnia), staying asleep (intermediate insomnia), and waking up early (terminal insomnia) [12]. Unraveling the connection between genetics and narcolepsy: the crucial role of HLA and the autoimmune theory of the disease Narcolepsy is typically characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations [5]. In fact, narcolepsy displays the most significant HLA linkage known, with over 99% of narcolepsy patients carrying specific alleles in two related HLA loci, DQA1 and DQB1, specifically DQA1*01:02 and DQB1*06:02 [2]. Studies have indicated that narcolepsy, except for rare familial forms, is not a monogenic hereditary disorder but rather involves one or more environmental factors acting on a susceptible genetic background. In individuals with narcolepsy, orexin is not detected in the cerebrospinal fluid, and post-mortem examinations have revealed the destruction of orexin neurons in the hypothalamus of these patients.

Furthermore, genetic evidence indicates the involvement of an autoimmune process that specifically targets orexin neurons as a contributing mechanism to the disorder. Two key components of the immune system, Human Leukocyte Antigens (HLA) and T Cell Receptor (TCR), play a role in narcolepsy. Numerous studies have consistently demonstrated a strong association between narcolepsy and a specific MHC class II haplotype. In fact, 90 to 100% of narcoleptic patients with cataplexy exhibit the HLA DQA1*0102-DQB1*0602 haplotype [10]. Homozygotes of this allele have shown elevated levels of HLA-DQ mRNA and protein expression in their white blood cells, suggesting a potential functional role for this allele. Due to its association with HLA alleles, narcolepsy is believed to be an autoimmune disease [7].

Other Disorders

Sleep disorders typically involve a combination of genetic susceptibility, environmental influences, and interactions between these factors. The heritability of sleep disorders has been demonstrated in monozygotic twins, and unique genetic patterns in sleep electroencephalogram (EEG) provide valuable information for identifying genes involved in sleep regulation and genetic factors contributing to sleep disorders. Therefore, in the following discussion, we explore the relationship between genetics and various sleep disorders [19].

Research on sleepwalking has revealed a connection between the HLA-DQB1*05 subtype and this particular disorder. Additionally, studies conducted on identical twins have indicated a genetic association with sleep terrors [4].

When it comes to enuresis (bedwetting), family history is consistently cited as a significant etiological factor. It is primarily inherited through autosomal dominant transmission with a penetrance rate of approximately 90%. Four gene loci (8q, 12q, 12q, and 22q11) have been identified in relation to enuresis [15].

Genetic factors play a significant role in sleep disorders. Pathophysiological hypotheses suggest that Klein-Lewin Syndrome (KLS) involves dysfunction of the hypothalamus. While KLS is typically sporadic, there have been recent reports of two siblings with this syndrome. In an analysis of candidate genes in 30 KLS patients, it was found that the frequency of the HLA-DQB1*0201 allele of the human hypothalamic locus antigen was significantly elevated in KLS patients [8].

Molecular studies on primary insomnia are relatively limited, but one study documented a missense mutation in a patient with chronic insomnia. This mutation involves the substitution of the amino acid arginine with histidine at position 192 (R192H) in exon 6 of the gene responsible for encoding the β3 subunit of the GABAA receptor. This mutation leads to functional changes in the GABAA receptor under experimental conditions and is believed to impact sleep processes. The β3 subunit of the GABAA receptor is also thought to play a role in sleep [15].

In summary, genetics contribute to sleep disorders by influencing various aspects of sleep regulation and functioning, including hypothalamic dysfunction in KLS and genetic mutations affecting neurotransmitter receptors involved in sleep processes.

What is the Role of Genetics in Sleep Disorders: This characteristic is inherited according to a classical Mendelian dominant autosomal inheritance pattern. The mutation responsible for this disorder has been identified in the PER2 gene located on chromosome 2q. However, in other cases of advanced familial sleep phase syndrome, mutations in the PER2 gene are not the cause, suggesting genetic variation within the disorder. Delayed phase syndrome (DPS) refers to a persistent delay in sleep and wakefulness. Although DPS appears to be a diverse phenomenon, there have been hypotheses suggesting an association with HLA DR1 and the per gene [8]. Additionally, other studies have indicated that the CK1δ gene plays a crucial role in regulating the circadian clock. In vitro experiments have shown that mutations in this gene reduce the phosphorylation of cycle substrates, resulting in a lengthened circadian period in mosquitoes and a shortened circadian period in mice [16].

What is the Effect of Congenital Central Caudal Hypothyroidism (CCHS): Approximately 50% of patients with Congenital Central Hypoventilation Syndrome (CCHS) also have Hirschprung's disease, while around 20% have neuromuscular tumors. This condition is caused by a mutation known as an extended Polyalanine Repeat In The Homeobox (PHOX) 2B or PHOX2B gene. This gene is crucial for the proper development of central autonomic nerve relays, including all components of the autonomic nervous system [15].

Genome-Wide Association Studies (GWAS) for Sleep Duration: Recent research has uncovered two genes, namely CSNK2A2 and PROK2, that play a role in regulating the circadian clock and are associated with sleep duration. Additionally, a Single Nucleotide Polymorphism (SNP) in the PDE4D gene has been linked to sleep duration. Another study has identified an intragenic variant in ABCC9 that is also associated with sleep duration. Furthermore, two new genomic loci have been discovered, which are involved in regulating sleep duration [7].

Moreover, the most effective signaling pathways and molecules involved in sleep regulation have been identified. These include the PKA/CREB pathway, dopamine receptors, and cGMP kinase. Through detailed investigations, these studies have shed light on how multiple molecular regulators influence the timing and duration of sleep in different individuals [4].

What is the Effect of PER3 Gene on Sleep: The PER3 gene, also recognized as a sleep regulator, possesses a sequence of 54 nucleotides. The number of repetitions in this gene has an impact on its function, particularly influencing human sleep. Additionally, this gene plays a role in regulating circadian rhythm, and genetic studies indicate its involvement in the regulation of sleep homeostasis and sleep Electroencephalogram (EEG) patterns. Individuals who are homozygous for a longer repeat in this gene exhibit improvements in sleep following sleep deprivation, characterized by increased Slow-Wave Sleep (SWS) and decreased Rapid Eye Movement (REM) sleep [2]. Furthermore, research has demonstrated an association between Delayed Sleep Phase Syndrome (DSPS) and polymorphism in the Per3 gene, while Advanced Sleep Phase Syndrome (ASPS) is linked to a point mutation in the human clock gene Per2 [18].

Are the Immune System and Sleep Disorders Related: While it is challenging to identify a single common feature among sleep disorders, the research findings indicate an underlying connection between sleep and the immune system that remains largely unexplored. There is a possibility that the immune system influences brain activity and sleep, or vice versa, suggesting a close relationship between these two systems. Due to the complexity of sleep and sleep disorders in terms of their occurrence and regulation, multiple approaches are required to gain a deeper understanding of their molecular basis [14].

To summarize, unlike animal models, human narcolepsy is not simply a genetic disorder associated with hypocretin deficiency. Instead, it is a complex condition involving an unknown immune-mediated mechanism that interacts with a specific HLA haplotype and environmental triggers, leading to disruptions in other neurotransmission pathways [15].

Studies have also indicated that a particular genetic makeup (HLA mutation on chromosome 6) could heighten the vulnerability of hypocretin-containing neurons to immune-related assaults [18].

Association Between Parkinson's Disease and REM Sleep Disorder: Insufficient sleep and sleep disorders have significant negative impacts on various bodily systems, particularly in relation to cardiovascular diseases such as hypertension, insulin resistance, systemic inflammation, accumulation of visceral fat, and Parkinson's disease [1].

Research findings indicate an overlap in the genetic basis of Parkinson's disease and REM sleep disorder. This connection can serve as a foundation for future clinical investigations in this field [19].

Evaluation of Circadian Sleep Rhythms Using Biological and Genetic Markers: The investigation focused on examining the daily expression patterns of human clock genes—hPer1, hPer2, hPer3, hBmal1, and hClock—in whole blood cells as potential markers for detecting circadian rhythms. In individuals with a healthy sleep-wake cycle, mRNA expression levels of hPer1, hPer2, and hPer3 were found to be higher in the early morning and lower in the late afternoon. On the other hand, peak mRNA expression levels of hBmal1 and hClock occurred earlier than those of hPers. Additionally, hBmal1 exhibited rhythmic expression in the early morning and evening, while hClock did not display such patterns [20].

Furthermore, Four different Haplotypes (H1-4) of the hPER3 gene were identified, and it was observed that genetic changes associated with H4 were linked to disruptions in the sleep clock seen in Delayed Sleep Phase Syndrome (DSPS). Additionally, the T3111C mutation in the CLOCK gene has also been recognized as being associated with DSPS [4].

Circadian Rhythm and Internal Synchronization Phenomenon: Circadian sleep rhythm disorders can disrupt a person's sleep due to factors like environmental, social, or occupational schedules. Additionally, some individuals may have a genetic predisposition to such sleep circadian rhythm disorders. Research indicates that approximately 33% of variations in sleep quality and around 40% of variations in sleep patterns can be attributed to genetic differences [6].

Furthermore, studies reveal that individuals with regular sleep-wake cycles typically exhibit normal circadian rhythms of melatonin and cortisol. However, factors both internal and external, such as room temperature and clothing, as well as plasma concentrations of melatonin and cortisol, can influence the results of these assessments. Additionally, in humans, a phenomenon known as internal synchronization is observed, where individuals placed in temporal isolation experience lengthened sleep-wake cycles, while the circadian rhythm markers of body temperature, melatonin, and cortisol remain unchanged [20].

Conclusion

The current study aimed to explore the connection between genetic factors and sleep disorders. The results reveal the involvement of several genes, such as PER, Cryptochrome, BMAL1/MOP3, in governing the daily cycle. Furthermore, we discovered a close relationship between the immune system, HLA genes, and certain sleep disorders. However, many of the genetic associations with sleep disorders remain somewhat uncertain, and the precise mech-

anisms underlying these interactions have not been fully elucidated. Like numerous other studies, attaining more comprehensive insights necessitates further research and investigation.

Acknowledgement

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Conflict of Interest

None.

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