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Mini-review: Genetics of Common Types of Sleep Disorders

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Abstract. Sleep is of essential necessity to humans in regard to relaxation, regulation and promoting memory. As technology is swiftly developing, more and more sleep disorders are being classified and recognized. Nearly 100 kinds of sleep/wake disorders have been identified and they mainly fall into four groups: hypersomnia, insomnia, circadian rhythm disorders and parasomnias. The etiology of sleep disorders is complex and involves both genetic and environmental factors. By use of twin studies, pedigree analysis and model organisms, more and more genetic loci increasing susceptibility to sleep disorders are uncovered. In this Review, we describe genetic factors found linking to each type of sleep disorders. As people are gaining more and more knowledge about the genetic factors of sleep disorders, we can hopefully have more meaningful discoveries in this realm in the future.

Key words: Sleep disorders, classification, genetic factors.

INTRODUCTION

Sleep is defined as a periodically spontaneous and reversible resting state. Humans spend approximately a third of their day sleeping, which is of essential necessity to them in regard to relaxation, regulation and promoting memory. But most people ignore the importance of sleeping, and they don't regard their sleeping disorders as diseases. Undiagnosed and untreated sleep disorders can cause great trouble to both individuals and society. As technology is swiftly developing, more and more sleep disorders are being classified and recognized. Some are mainly related to the outside environment as well as the psychological states of people, others are related to genes. One sleep period is divided into two main phases, the Rapid Eye Movement (REM) phase when dreams occur, and the Non Rapid Eye Movement (NREM) phase without dreams.

Nearly 100 kinds of sleep/wake disorders have been identified and they mainly fall into four groups: hypersomnia, insomnia, circadian rhythm disorders and parasomnias. Hypersomnia refers to excessive abnormal daytime sleeping, while insomnia is related to difficulty in falling asleep at night. Circadian rhythm disorders are connected with biological clocks, and have the closest relationship with genetics. Parasomnias are complex behaviors in sleeping periods. Although the four primary types of diseases have almost completely different phenotypes, in some cases, the principles are quite similar.

HYPERSOMNIA

Hypersomnia should be taken seriously for it can severely affect people's daytime behaviors, resulting in accidents such as car crashes. There are two typical types of hypersomnia diseases.

Obstructive Sleep Apnoea (OSA)

OSA is the most common kind of hypersomnia, influencing 2-4% of the American population [1]. It is defined by recurrent reductions (hypopnoeas) or stoppage (apnoeas) in breathing during sleep as a result of pharyngeal airway

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narrowing or collapse [1]. Another kind of disease similar to OSA is Central Sleep Apnoea, in which patients totally lack respiratory effort during airflow attenuation, but it is much less common.

Several factors may increase the risk of getting OSA, including obesity, being male and being aged. People with OSA are also observed to have smaller pharyngeal airway, increased pharyngeal dilator muscle activity and retro-positioned maxillae and mandibles[1].

There has only been one genetic factor reported to be related to OSA by far, which is APOE ε4. Studies have shown that the presence of APOE ε4 allele doubles the risk of getting OSA, but the result is still controversial, and no direct link has been observed.

Narcolepsy

Narcolepsy is a rare disorder, characterized by the inclination of falling asleep during inappropriate time during the day. It represents the abnormalities of the wake/sleep generators [2]. Other symptoms include cataplexy, hypnagogic or hypnopompic hallucination, sleep paralysis, automatic behavior and disrupted nighttime sleep. Patients cannot keep the boundaries between sleep and wakefulness, and REM and NREM phases.

Recent studies have shown genetic factors causing narcolepsy. People have discovered that canine narcolepsy was caused by a mutation in the hypocretin (orexin) receptor 2 gene (Hcrt2) [3]. But narcolepsy in human is more sporadic, not caused by a single gene mutation. In the majority of the cases, patients with narcolepsy lose around 70000 hypothalamic neurons producing hypocretin [4]. Nearly all narcolepsy/hypocretin deficiency cases carry two specific and tightly linked HLA class II gene alleles: DQA1*01:02 and DQB1*06:02 [4]. Also, in the HLA class III region, the tumor necrosis factor-alpha (TNF-α) gene showed correlation with narcolepsy. Researchers examined the known single-nucleotide polymorphisms (SNPs) in the promoter region of TNF-α gene in 49 narcoleptic patients [5], and discovered a significant difference in the frequency of the genotype at position -857 between patients and controls [5]. Therefore, it is conceivable that the TNF-α with –857T was associated with narcolepsy independently of the strong association of DRB1*1501 with the disorder [5].

Apart from the possible genetic reasons, the onset of narcolepsy is also linked with environmental factors. Researchers have discovered that infection with H1N1 influenza virus in mice that lack B and T cells can lead to narcoleptic-like sleep–wake fragmentation and sleep structure alterations [6], for the infection targeted neurons that produce orexin/hypocretin.

INSOMNIA

Insomnia is the most prevalent sleep disorders in the population. It is not defined by total sleep time, but rather, by the inability to obtain sleep that is sufficiently long or “good enough” to result in feeling rested or restored the following day [2]. It may lead to depression, and vice versa. Many cases in insomnia have social or psychological reasons, but some are related to genetic and hormonal disorders, especially the secretion of melatonin.

Fatal Familial Insomnia (FFI)

In 1986, the Fatal Familial Insomnia was first discovered in a 53-year-old man who presented with progressive insomnia and dysautonomia. His dreamlike status, dysarthria, tremor, and myoclonus subsequently developed, leading to coma and death after nine months [7]. After that, his two sisters and many other relatives had died of similar symptoms [7]. Later, researchers used antibodies to prion protein (PrP) to perform dot and Western blot analysis, and discovered the Fatal Familial Insomnia is a prion disease with a mutation in codon 178 of the PrP gene [8].

Common Insomnia

In 256insomniacsinvestigated in a study conducted in 2005, 72.7% of the primary insomniacs and 43.3% of the psychiatric insomniacs were reported to have familial tendency [9]. Although the number may vary due to the difference in regions and peoples, it can be concluded that insomnia is somehow related to genetics.

Study has discovered that insomnia was related to 3111C/CLOCK gene polymorphisms [10]. Also, a mutation in β3 (R192H) of the GABAA receptor which constitutes the major inhibitory neuronal ion channels in the mammalian brain [11] was associated with insomnia. Besides these findings, the overexpression of hypocretin found in zebrafish also contributed to insomnia [12]. Some findings also indicated its relationship with several other loci, but these

mentioned above are the major ones. It can be seen that insomnia not only can be inherited, but also can be a result of incomplete neuronal development and improper hormone regulation.

The common type of insomnia is a consequence of many complex factors, including both environmental and genetic reasons. Future study should still be conducted in order to find out its relations with other possible triggers.

Restless Legs Syndrome (RLS)

Restless legs syndrome (RLS) is a frequent neurological disorder, characterized by an imperative urge to move the legs during night, unpleasant sensation in the lower limbs, disturbed sleep and increased cardiovascular morbidity, resulting in severe insomnia [13].

In a GWAS study, researchers found its relationship with three gene loci, namely MEIS1, MAP2K5 and LBXCOR1 [13]. Then, in samples collected in Iceland, researchers observed significant association with a common variant in an intron of BTBD9 on chromosome 6p21.2 [14]. Another study from a previous researcher provides evidence for an association of variants in the NOS1 gene and RLS, and suggests the involvement of the NO/arginine pathway in the pathogenesis of RLS [15].

It can be concluded that compared to the most common type of insomnia, RLS is more related to genetic reasons.

CIRCADIAN RHYTHM DISORDER

The study of circadian rhythm disorders has not aroused wide interests until recently. They are closely related to the biological clock mechanism in human bodies, and sometimes they have genetic triggers. There are six main types of circadian rhythm disorders, namely delayed sleep phase syndrome (DSPS), advanced sleep phase type (ASPS), irregular sleep-wake type (ISWT), free-running type, jet lag type and shift work type [16]. Among them, DSPS and ASPS are related to genes, jet lag type and shift work type are mainly due to environmental factors.

People with CRSD do not have normal sleeping or waking time. The most typical two types of CRSD are ASPS and DSPS. DSPS is the most common type of CRSD, making up about 83% of the diagnosis CRSD. In a random survey, 7 people out of 1525 have syndromes similar to DSPS. The free-running type is the second most common disorder, taking up 12%. ASPS and ISWT are relatively rarer, only accounting for 2% [16].

Mechanism of the Molecular Circadian Clock

The mechanism of the molecular circadian clock in human is a transcriptional negative feedback loop, which involves at least ten genes. In mammals, the clock genes are located in suprachiasmatic nuclei (SCN), which is thought to be the pacemaker of the circadian rhythm [17]. The cis-elements, such as E-box, RORE and D-box, can regulate downstream clock-controlled genes by control of the transcription process.

It starts when the protein CLOCK and BMAL1 bind to special DNA elements that have E-box and E'-box in the promoters of target genes. The binding activates the transcription of downstream genes Per and Cry, and their protein products PER and CRY will come back into the nucleus and inhibit the binding of CLOCK and BMAL1 with E-box [18].

According to Hoffmann's research, mice with mutations in Clock genes have less sleeping time than normal mice. Knockout of mouse Per1 and Per2 can result in totally chaotic sleeping pattern. Mutation or loss in Cry1, Cry2, Per1, Per3, CK1εmay lead to altered period length, in Clock or Per2 may lead to slowed down period length, and in Bmal1may lead to complete loss of circadian rhythmicity [17].

Advanced Sleep Phase Syndrome (ASPS)

ASPS indicates the abnormal behavior of people who go to sleep and wake up very early. It is a very rare disease, and only until 1999 have people revealed its relation with genes. Researchers discovered that ASPS has a family tendency (FASPS), so they conducted study on three of the affected families. They kept track of the patients' sleep logs, measured their core temperature and melatonin secretion, and finally came to the conclusion that ASPS has a strong relation with genes. Then in 2001, new studies found that ASPS was attributed to a missense mutation of a clock component hPER2. Affected individuals have a serine to glycine within the CK1ε binding region of hPER2 [19].

In 2005, new studies suggested a correlation between FASPS and CK1ε-T44A mutation. Two years later, researchers used mice and drosophila to conduct an experiment. They have already proposed that phosphorylation of

hPER2 S662 could facilitate the phosphorylation of other residues [20]. The transgenic mice carrying FASPS hPER2 S662G have a shorter period, while those carrying S662D mutation display opposite phenotypes. That is because the S662D mutation mimics the process of phosphorylation, resulting in a longer period. They also precluded the possibility that protein degradation attributed to these protein level differences [20]. Through their findings, it could be deduced that hPER2 S662 is not phosphorylated by CK1; instead, a phosphate at hPER2 S662 is required for CK1 to phosphorylate other residues in the peptide [20].

Delayed Sleep Phase Syndrome (DSPS)

It must be surprising to most people that difficulty going to bed and getting up is a genetic sleep disorder. In a study conducted in 2002, the screening of the entire coding region of the hClock gene with PCR amplification indicated a T3111C mutation possibly contributed to DSPS [21]. Later, a full screening of the hPer3 gene identified four haplotypes, respectively H1, H2, H3 and H4, among which the H4 haplotype was associated with increasing susceptibility to DSPS [22], which included G647, P864, 4-repeat, T1037, R1158 polymorphisms. What's more, the V647G variation altersCK1ε-induced phosphorylation of PER3 protein, leading to an abnormal circadian rhythm phenotype [23].

When screening for CK1ε genes, researchers detected a missense variation, S408N, which served as one of the postulated target residues for autophosphorylation [23]. CK1εwith S408N substitution showed higher enzyme activity compared to wild types, which was proved by experiments. Also, CK1ε with S408N displayed increased enzyme activity against PER3, so people suggested that CK1ε-induced phosphorylation of PER3 protein might play an important role [23] in regulating circadian rhythm.

PARASOMNIA

Parasomnias refer to the unpleasant behavioral phenomena that occur during sleep. The most common parasomnias are examples of "dissociated sleep states", representing the admixture of either REM or NREM sleep with wakefulness [2]. There are quite complex motor behaviors during sleep.

In clinical practice, parasomnias have found to run in families and co-occur; therefore several studies have looked into the genetic factors of parasomnias. A questionnaire in the 1990s indicated that parasomnias share common genetic backgrounds [24].

NREM Parasomnias

In NREM parasomnias, people tend to arise from slow-wave sleep, usually occurring during the first third of the sleep cycle [25]. Children are most likely to have parasomnias. There are three types of NREM parasomnias.

Confusional Arousals

Confusional arousals are often seen in children, with movements in bed, thrashing about and inconsolable crying. They are almost universal in children before the age of 5 years, becoming much less common in older childhood, and being fairly rare in adulthood [26].

Clinically, there appears to be a strong familial pattern in the cases of confusional arousals seen in families of deep sleepers. However, more detailed studies have not been published [26].

Sleepwalking

Sleepwalking is characterized by walking during sleep with partial to complete amnesia the next day [27]. It is very common in children in 11-12 years old, and has varying degrees calmness or agitation. DQB1 polymorphic amino acid might be more tightly associated than any single allele with sleepwalking [27].Also, familial occurrence in sleepwalking is common.

It is the most dramatic kind of arousal, with scream, panic and motor activities such as hitting a wall or running around [2]. One universal feature is inconsolability. They may cause damage to themselves or to the environment.

By conducting twin study, researchers have found sleep terror could be heritable. 390 pairs of monozygotic and dizygotic twins were involved in the study since their birth, and the result showed that the polychoric correlations were 0.63 for monozygotic and 0.36 for the dizygotic twins [28].There is a relatively higher relation between monozygotic twins than dizygotic twins, indicating that sleep terror is gene related.

REM Parasomnias

The best studied is the REM sleep behavior disorder (RBD), in which patients' somatic muscle atonia is lost, resulting in the acting out of dream mentation. They may also cause injuries to themselves or their bed partners [2].

The chronic form of RBD is either idiopathic or associated with neurological disorders. It is probably a harbinger for Parkinson's disease, and its high similarity with narcolepsy in the unclear boundaries between phases in sleep indicates its high incidence in patients with narcolepsy. A genetic study reported an association between the REM sleep parasomnia and HLA-DQ1 (DPB1*05 and 06) [29]. From previous statements, we can clearly see the similarities between the mutated genes that result in narcolepsy and REM parasomnias.

SUMMARY AND FURTHER DIRECTIONS

Sleep disorders, as indicated above, fall into four major categories of hypersomnia, insomnia, circadian rhythm disorders and parasomnias. Previous studies have probed into the genetic factors as well as environmental triggers of sleep disorders, and many groundbreaking discoveries have been made. Since the mechanism of sleep is still very complex, future researches on sleep disorders will surely go on.

For most cases in the past, researches on sleep disorders relied on the utilization of model animals. By analyzing the genes that affect the sleep behavior of animals such as mice, drosophilae and so on, scientists were able to figure out candidate genes that may result in human sleep disorders. As the CRISPER-Cas9 technology came out, knocking out the specific genes is easier than ever before. Therefore, we can find out new candidate genes related to sleep disorders by genome-wide screen.

What's more, researchers need to collect more human samples so as to have a deeper understanding of sleep disorders. There should be a clearer classification of diseases and a wider range of families involved as well. In the past, people used GWAS to find associated common SNP. Recently, next generation sequence (NGS) makes it possible to find out rare mutations that may link to diseases. More attention has been paid to the noncoding region of genes, hoping to find some relations with the diseases.

Upon today, sleep remains one of the least understood phenomena in biology—even its role in synaptic plasticity remains debatable [4]. We have made great discoveries in this mysterious realm, and undoubtedly, with the rapid development of instruments and technology, more and more unanswered questions will become clear to us.

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