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SLEEP DISORDERS: ARE THEY A GENETIC QUESTION?

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SUMMARY

Sleep disorders are commonly studied from the psychiatric and neurological point of view, leaving aside other aspects such as genetic component. Despite the limited literature regarding this field, different genetic variants have been proposed to be associated with sleep disorders. In this review, we summerize the experimental research that has brought to light the pivotal genetic influence in the development of these pathologies.

Key words: *genetics – psychiatry - genetic factors - sleep disorders*

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INTRODUCTION

Complex anatomical structures and sophisticated neurobiochemical processes are involved in the the sleep-wake rhythm. Sleep is an active process, capable of inducing profound changes in vegetative life such as heart rate, blood pressure, oxygen saturation, body temperature and so on, but also in life's relations, such as increasing aggression or decreasing perfomances after sleep deprivation. Biological, psychological and social factors can alter the physiological pattern of sleep, producing complex clinical pictures. In all organisms, a substantial portion of life is spent during sleep and its disruption has immediate negative health consequences (Mukherjee et al. 2015), leading to conditions defined "sleep disorders".

As for other psychiatric diseases such as bipolar disorders (Juli et al. 2012), eating disorders (Juli et al. 2014) and addiction disorders (Juli et al. 2015), sleep disorders have been evaluated through genetic studies in order to identify genetic factors that may influence the vulnerability to these complex disorders. In this review, we report the emerging insights on molecular genetic studies that, using the development of detailed human genome map, have already led to the identification of genetic factors in several sleep disorders.

CIRCADIAN RHYTHM DISORDERS

The circadian rhythm is the "internal body clock" that regulates the approximately 24-hour cycle of biological processes in animals and humans. Circadian rhythm disorders are disruptions in a person's circadian rhythm and include different conditions involving a misalignment between actual and desired sleep periods (Benjamin 2007). Day-night circadian rhythm is controlled by cells that are dependent on cryptochrome (CRY) and period (PER) genes activity which control CRY and PER protein levels (Viaterna et al. 2005, Bidaki et al. 2011). The most recognized circadian rhythm disorder is the Familial Advanced Sleep Phase Syndrome (FASPS) that is caused by mutations in human clock-related genes (Toh et al. 2001, Xu et al. 2005) and has an autosomal dominant pattern. The analysis of two pedigree populations indicated defects in phosphorylation of PER2 as the most common alteration and mutations in both PER2 and Casein Kinase 1 genes (CK1δ) (Sehgal and Mignot 2012). Circadian rhythm disorders have been investigated also in other organisms such as Drosophila and the Syrian hamster where mutations in the CK1ε kinase lead to reduction of PER phosphorylation that is critical for determining the sleep/wake period length (Sehgal and Mignot 2012). In addition, a genetic variant has been reported in the core clock gene CRYPTOCHROME 2 (CRY2) defined as an alanine to threonine replacement at amino acid residue 260 (A260T) (Hirano et al. 2016). However, a recent study reported an association between CRY1 variation and delayed sleep phase disorder (DSPD) (Patke et al. 2017).

NARCOLEPSY

Narcolepsy is characterized by involuntary "sleep attacks" that can occur while talking, standing, walking, eating and driving (Veatch et al. 2017, Zhang & Fu 2018). It is defined by excessive daytime sleepiness (EDS) and cataplexy but also by symptoms of dissociated rapid eye movement (REM) sleep (such as sleep paralysis and dream-like "hypnagogic" hallucinations at sleep onset) (Sehgal & Mignot 2012). This sleep disorder also occurs in dogs and mutation in the hypocretin (orexin) receptor 2 gene (Hcrtr2) is believed to be the cause (Lin et al. 1999). It has been demonstrated that narcolepsy is influenced by environmental factors and susceptible genes. In fact, close relatives have about 1-2% probability to develop the disease increasing by 20-40 fold respect to normal population (Bidaki et al. 2012). Human Leukocyte Antigen (HLA) and T cell receptor (TCR) variants have been implicated in the predisposition of narcolepsy (Sehgal & Mignot 2012). In particular, narcolepsy was associated with some HLA

alleles such as DR2/DQW1 (Hayduk et al. 1997), DR5 and DRB1*1501/DRB1*1503 (Mignot 1998), DQB1*0602 (Tafti et al. 2016, Mignot 2000). In addition, the role of HLA-alleles in the susceptibility of the disease has been documented in monozygotic twins with cataplexy (Hayduk et al. 1997). The TCR alpha gene (TCRA), involved in the immune response thereby interaction with peptide-buond HLA antigens, has been implicated in the susceptibility of narcolepsy; a polymorphism in one of its segment showed significant association in Caucasians and other ethnic groups (Hallmayer et al. 2009). Since HLA and TCR genes are involved in the immune response, it has been hypothesized that narcolepsy is caused by autoimmune attack of orexin neurons (Veatch et al. 2017).

Genome-wide association studies also identified polymorphisms in carnitine palmitoyltransferase 1B (CPT1B), a carnitine shuttle, and Choline Kinase B (CHKB) that metabolizes choline, associated with narcolepsy in Japanese sample (Sehgal & Mignot 2012, Miyagawa et al. 2008). On the other hand, it has been demonstrated the implication of purinergic receptors in narcolepsy in Caucasians as well as in multiple ethnic groups (Kornum et al. 2011). Because of its role in immune regulation, a polymorphism in the purinergic receptor gene decreases the receptor's expression in peripheral mononuclear cells associating with narcolepsy susceptibility (Sehgal & Mignot 2012). Genetic studies have been also performed in an autosomal recessive canine model of narcolepsy and in gene-targeted mice where the hypothalamic hypocretin (orexin) neuropeptide system was identified as the major pathway implicated in this pathology (Taheri 2004, Billiard 1994); in these patients hypocretin level in the cerebrospinal fluid (CSF) is low (Dauvilliers 2003). Furthermore, it has been demonstrated that Deberman/ Labrador dogs are affected by narcolepsy showing mutation in hypocretin receptor 2 (Lin et al. 1999).

INSOMNIA, HYPERSOMNIAS, PARASOMNIAS

Insomnia is characterized by difficulty in initiating and maintaining sleep, waking up too early, or sleep that is chronically non-restorative or poor in quality (American Academy of Sleep Medicine 2005, Bidaki et al. 2012). Its prevalence is about 10% to 50% in general population and 35% of people with insomnia have a positive family history. Insomnia runs in families and has higher concordance in monozygotic twins (Sehgal and Mignot 2012). It has been demonstrated that insomnia is often associated with major depressive disorder (Benjamin 2007) which seems to have a genetic explanation. In fact, twin studies showed that the association between sleep disorders and depression is 30% in 8-year-old twins and 11% in 10-year-old (Gregory et al. 2009).

Fatal Familial Insomnia (FFI) is a neuro-genetic disorder with an autosomal dominant pattern of inheritance. This pathology is characterized by mutation in codon D178N of prion protein (PrP) gene that was the first gene to be linked to human sleep disorder (Medori et al. 1992) and it is now believed to be the cause of thalamic nuclei degeneration (Bidaki 2012). It has been shown that this mutation is the result of change in aspartate location (Winkelmann 2008); patients with homozygote methionine in codon 129 show a shorter period of disease compared with those who have heterozygote valine-methionine in codon 129 (Bidaki 2012).

Idiopathic Hypersomnia, a poorly defined and heterogeneous phenotype, has shown a frequency of DQB1*0602 of 40% in its patients although hypocretin levels in cerebrospinal fluid are in normal range. As narcolepsy, a polymorphism located between CPT1B and CHKB is associated with hypersomnia in Japanese cohorts (Sehgal and Mignot 2012).

In addition, Kleine Levin syndrome (KLS), a disorder that affects adolescent males and disappears in adulthood, has been associated with genetic factors. It has been shown that 5 out of 105 KLS patients reported an affected family member. Furthermore, Arnulf et al. shown an HLA association with KLS but this data has not been demonstrated in other studies (Arnulf et al. 2008; Sehgal & Mignot 2012).

Among REM sleep features, sleep paralysis shows high concordance in monozygotic twins and an autosomal dominant transmission (Mignot, 1997). In Parkinson's disease it can occur REM sleep behavior disorder as an early sign of neurodegenerative disorder; a number of single gene defects and HLA-DR/DQ have been involved in the development of Parkinson's disease (Sehgal & Mignot 2012).

Non-REM sleep parasomnias such as sleepwalking, sleep talking, nocturnal enuresis, bruxism and night terrors have also genetic basis (Hublin et al. 2001, Sehgal & Mignot 2012). For istance, the rate of sleep walking in a child whose none of the parents are involved is 22% and if one or both of the parents are involved, this rate increased to 45% (Behram et al. 2000). In addition, an association between HLA O501 and DQ-B1 with sleep walking have been recently demonstrated (Abe & Shimakawa 1966, Hublin at al. 1997, Bidaki et al. 2012).

On the other hand, four gene locations including 8q, 12q, 12qh, and 22qu were found in nocturnal enuresis (Kaplan and Sadock 1998).

RESTLESS LEG SYNDROME (RLS)

Restless Leg Syndrome is characterized by an uncomfortable desire to move the lower limbs with periodic leg movements during the sleep. Regarding pathophysiological factors, it has been shown that reduced dopaminergic neuronal activity and iron deficiency in the brain are often present in RLS (Salas et al. 2010, Sehgal & Mignot 2012).

An autosomal dominant pattern has been suggested for Restless Leg Syndrome (Kimura & Winkelmann 2007) and more than half of the cases have a familiar pattern with risk of 3-6 fold more in close relatives (Bidaki et al. 2012). However, an high concordance (83%) has been reported in monozygotic twins (Sehgal & Mignot 2012). Recent genome-wide association studies revealed different transcription factors that affect spinal cord regulation of sensory perception and locomotor pattern generation interacting with brain iron homeostasis, as a developmental regulatory factors (Sehgal & Mignot 2012). For istance, MEIS1, a member of Hox transcriptional regulatory network that specifies motor neuron pool identity and thus the pattern of target-muscle connectivity within the spinal cord, has been considered as the most important RLS susceptibility gene. MEIS1 is expressed in dopaminergic neurons of the substantia nigra, spinal cord and red nucleus that regulates coordination of limb movement, all regions where it has been demonstrated lower iron levels in RLS cases (Sehgal & Mignot 2012). Winkelmann et al. shown that MEIS1 variants near exon 9, a region with high interspecies conservation, revealed the strongest association with RLS (Winkelmann et al. 2007). Subsequently, an additional study found an independent association in a region regulating MEIS1 expression (Winkelmann et al. 2011).

BTBD9 (BTB (POZ) domain containing 9) variants have also revealed association with RLS. Although little is known for BTBD9 function in mammals, it has been shown that in Drosophila proteins containing the BTB (POZ) domain have relevant roles in metamorphosis and limb pattern formation (Sehgal & Mignot 2012). Stefansson et al. shown single nucleotide polymorphism associations in an Icelandic cohort that were strongly bound to the presence of periodic limb movements such as repetitive cramping or jerking of the legs during sleep suggesting that this gene probably confers risk for the motor component of RLS (Stefansson et al. 2007, Li et al. 2017). Taken together, these data indicated that BTBD9 is a genetic determinant of limb movements during sleep (Zhang & Fu 2018).

However, two additional loci have been proposed by genome-wide association studies such as PTPRD (protein tyrosine phosphatase receptor type delta) locus that emerged through fine mapping of a significative signal in a linkage region on chromosome 9p (Schormair et al. 2008), and a large linkage disequilibrium block containing TOX3, a breast cancer susceptibility locus, and untranslated BC034767 all togheter associated with RLS pathogenesis (Winkelmann 2011).

Finally, linkage analysis in population based RLS cases and controls suggested a role for neuronal nitric oxide synthase (NOS1) through finemapping of a region on chromosome 12q (Winkelmann et al. 2008). Despite no mutations were detected in RLS1-linked family members nitric oxide synthase is a good candidate because of nitric oxide acts as an atypical neurotransmitter in the central nervous system with roles in pain perception, control of sleep-wake regulation and modulation of dopaminergic activity (Winkelmann et al. 2008, Sehgal & Mignot 2012).

OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME (OSAHS)

Obstructive Sleep Apnea is composed by periods of intermittent and functional obstruction of the upper airway collapse during sleep, resulting in decreases in arterial oxygen saturation which impairs ventilation and disrupts sleep (White 2005, Bidaki et al. 2012, Sehgal & Mignot 2012). Genetic studies have not led to consistently data for this complex phenotype using the apnea hypopnea index. However, an association between Apolipoprotein E allele e4 (APOE e4) and sleep apnea has been reported (Gottlieb et al. 2004) although samples differed by age, ethnicity and body mass index. It has been hypnotized that APOE e4 could predispose to sleep apnea thereby lower levels of choline acetyltransferase and reduced neuromuscular activation of the upper airway dilator muscles (Sehgal & Mignot 2012). On the other hand, one study in Japan shown an association between HLA-DR2 and OSAHS (Riha 2006) and an American study on narcoleptic population with OSAHS demonstrated that the frequency of HLA-DR2 sequence in such patients was higher than normal subjects (Guilleminault 1992, Bidaki et al. 2012). Furthermore, it has been proposed that epigenetic modifications may be crucial in pediatric obstructive sleep apnea (Perikleous et al. 2018). In particular, DNA methylation patterns has been implicated in the development of the disorder: forkhead Box P3 (FOXP3) DNA methylation levels were associated with inflammatory biomarkers and serum lipids, hypermethylation of the core promoter region of endothelial Nitric Oxide Synthase (eNOS) gene in OSA children were related with decreased eNOS expression. In addition, increased expression of pro-oxidant enzymes genes and decreased expression of anti-oxidant enzymes genes revealed the disturbances in oxygen homeostasis throughout neonatal period predetermined increased hypoxic sensing in adulthood (Perikleous et al. 2018).

CONCLUSIONS

Multiple lines of evidences have reported the genetic influence in developing sleep disorders, although not all studies have succeeded in confirming them. Certainly, additional studies with more selected models are needed to better clarify the role of genetic component in these pathologies and to provide a novel approach in the currently used therapeutic strategies.

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Contribution of individual authors:

Giada Juli conceived and drafted the manuscript;

Rebecca Juli collected the references and partecipated in the discussion;

Luigi Juli provided critical evaluation of and revised the manuscript. All authors read and approved the final manuscript.

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