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Review Article

Do genes matter in sleep?-A comprehensive update

Rajib Dutta*

MD Neurology, India

Abstract

Sleep is considered as a complex process in human beings and is least understood mechanism. Role of sleep in synaptic plasticity remains a debatable topic till date. Sleep is influenced by genetic background of the individual. EEG done in human sleep showed strong influence of genetic factors. A handful of familial analyses involving specific gene loci and twin studies has been done in this regard. In this review article focused discussion on genetic contribution to sleep phenotypes, twin and familial linkage studies and effect of genetic variation on sleep will be covered.

Introduction

Human being need to rest on a daily basis. Lack of rest leads to severe physical and psychological symptoms which can lead to behavioral inactivity. Pathobiology and molecular mechanisms involved in sleep is quite complex and least understood phenomenon according to many researchers. Sleep studies and researches has gained a lot of momentum in recent years. The main reason is role of genetic background which can disrupt sleep and thereby causing several types of sleep disorders reported in literature till date [1].

Variation of sleep phenotypes, their intraindividual stability as well as familial aggregation of certain sleep related disorders has drawn a lot of attention recently. Human sleep EEG showed evidence that it is dependent on genetic background of the individual in question which led many to think that human EEG is highly heritable trait in human beings [2,3]. Heritability of sleep traits is controlled by genetic polymorphism and regulation [4-8]. Relation of sleep with age, gender, environment still needs to be elicited in ongoing studies. Molecular processes and function that produce the need to sleep both remain understudied [9,10].

Major advances in the recent years comprise the identification of brain structures, neurotransmitters and several other molecules regulating sleep and common understanding among clinicians and researchers that it is quite a common treatable phenomenon which when unaddressed can cause severe psychosomatic and cognitive symptoms that can affect quality of life in individuals irrespective of age, gender and other confounding factors [11-14].

More Information

*Address for Correspondence: Rajib Dutta, MD Neurology, India, Email: rajibdutta808@gmail.com

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Abbreviations: EEG: Electroencephalogram; PSG: Polysomnogram; REM: Rapid Eye Movement; NREM: Non Rapid Eye Movement; AD: Autosomal Dominant; AR: Autosomal Recessive; RLS: Restless Leg Syndrome; SNP: Single Nucleotide Polymorphisms; VNTR: Variable Number Tandem Repeat; MAO: Monoamine Oxidases; COMT: Catechol-O-Methyltransferase; TNF: Tumor Necrosis Factor; BDNF: Brain-Derived Neurotrophic Factor; SLC: Solute Carrier Family 6 Member 3; ADA: Adenosine deaminase; PRNP: Prion Protein Gene; GNAZ: Guanine Nucleotide-binding protein G(z) subunit alpha

Previously twin studies has reported higher concordance of sleep habits, e.g. sleep duration and quality in monozygotic (MZ) than in dizygotic (DZ) twins, even when exposed to different environmental situation with an estimated heritability of 30%-44% [15-19]. Pittsburgh Sleep Quality Index (PSQI) is usually used to investigate subjective sleep quality [20]. Zung, et al. performed the first polysomnogram in MZ showing temporal sleep patterns in terms of sleep stages [21]. Genetic background contributes heavily on numerous sleep traits like sleep duration, quality, onset latency, efficiency and wake after sleep onset, REM/NREM sleep characteristics, stage changes, diurnal preference, behavioral reaction due to sleep loss, insomnia and several sleep related disorders like restless leg syndrome [22-25].

NREM sleep is found consistently to be under strong genetic control in humans and animal models as compared to REM sleep [26-28]. REM sleep amount was found to be significantly

correlated in MZ twins, 95% heritable in some studies, with conflicting results from other studies [21,23,25,29], sleep onset latency in MZ only [29], sleep efficiency and wake after sleep onset [18,19,24,29,30], stage changes and frequency profiles also in MZ [4,31], diurnal preference [19,32,33], neurobehavioral reaction to sleep loss [24], disorders like insomnia [19,34,35], RLS [36,37], sleep talking, bruxism, enuresis [38-40].

In terms of familial and linkage studies certain sleep-related diseases show high familial risk and specific modes of transmission, loci and certain molecules.

Familial Advanced Sleep Phase Syndrome (FASPS)

It shows an AD pattern of inheritance, characterized by persistent early evening sleep onset and early morning awakening. Although the complaint of awakening earlier than desired is relatively common, particularly in older adults, extreme advance of sleep phase is rare. hPer2, CK1ε, and CK1δ has been associated with this syndrome complex [41,42]. The circadian rhythms of sleep propensity and melatonin secretion are regulated by a central circadian clock, most importantly the suprachiasmatic nucleus of the hypothalamus along with body core temperature. Reid, et al. used measures of sleep onset and offset, dim light melatonin onset, Horne-Ostberg morningness - eveningness questionnaire and clinical interviews in a 32 member family with ASPS [43].

Autosomal semi-dominant mutations in rodents with fast or slow biological clocks (i.e. short or long endogenous period lengths; tau) are associated with phase-advanced or delayed sleep-wake rhythms, respectively [44]. A known missense mutation (bp2106 A/G) in hPer2 was checked in 2 Japanese families. None of the tested subjects possessed the missense mutation and there was no significant linkage between affected subjects with hPer2 region by 2-point mapping and by direct sequencing of 23 exons of hPer2, supporting the possibility of genetic heterogeneity [45]. Phosphorylation of PER proteins regulates their stability as well as their subcellular localization. Vanselow, et al. have identified 21 phosphorylated residues of mPER2 including Ser 659, which is mutated in patients suffering from FASPS. Phosphorylation at Ser 659 results in nuclear retention and stabilization of mPER2, whereas phosphorylation at other sites leads to mPER2 degradation in oscillating fibroblasts [46].

Restless Legs Syndrome (RLS)

Diagnostic criteria of RLS is quite simple [47]. Mode of inheritance can be AD, AR and few cases are not clear. AD type comprises of 5 types of RLS (1-5), sequenced to long and short arm of chromosome [48-52,53-58]. Liebetanz, et al. showed fine-mapping of an AD locus in a family of Bavarian origin with intrafamilial heterogeneity with RLS3 [59]. Desautels, et al. examined 276 individuals from 19 families using a selection of markers spanning the identified candidate interval on chromosome 12q. Results also suggested the presence of heterogeneity in RLS as linkage was formally excluded across the region in 6 pedigrees. Significantly higher periodic leg movements during sleep indices were observed for all probands with RLS from linked families showing AR pattern of inheritance of RLS1 [60], unclear inheritance pattern in RLS2(12q,14q) and related to several other molecules like MEIS1.

Sarayloo, et al. used human cell lines to conduct a RNA-Seq study. MEIS1, acts as a regulator of the expression of many other genes and some of the genes affected by its expression level are linked to pathways previously reported to be associated with RLS. Cells where MEIS1 expression was either increased or prevented, bone mineral absorption was the principal dysregulated pathway. The mineral absorption main pathway genes, HMOX1 and VDR are involved in iron metabolism and response to vitamin D, respectively. Same enrichment of the mineral absorption pathway in postmortem brain tissues of RLS patients showed a reduced expression of MEIS1. Expression of genes encoding metallothioneins (MTs) was observed to be dysregulated across the RNA-Seq datasets generated from both human cells and tissues in their study. MTs are highly relevant to RLS as they bind intracellular metals, protect against oxidative stress and interact with ferritins which manage iron level in the central nervous system. While MTs have been implicated in the pathogenesis of neurodegenerative diseases such as Parkinson's disease this was the first study showed the molecular association with RLS [61,62].

RLS-linked genetic signal has been mapped to an intronic regulatory element within MEIS1. This element plays a role in the ganglionic eminences of the developing forebrain, with the RLS risk allele related to a reduced activation of the enhancer part. Ganglionic eminences play an important role in the development of genetic susceptibility to RLS. Some rare variants within MEIS1 alone are sufficient to suppress MEIS1 function in neural development, providing further evidence of the importance of neurodevelopmental processes in the pathological mechanism of MEIS1 in RLS. Salminen, et al. 2019 reported heterozygous MEIS1 inactivation in mice causing hyperactivity at the onset of the inactive period, consistent with human RLS. These mice related animal study also revealed an effect of MEIS1 on the dopaminergic system at both the spinal and supraspinal level thereby suggesting complex pathomechanistic process [63], BTBD9, MAP2K5, LBOXCOR1, DMT1 [64-68]. Recently Tilch, et al. has updated the genetic profile of RLS by mutation load analysis previously not reported [69]. TOX3 gene variant could be associated with painful restless legs [70].

Primary Nocturnal Enuresis (PNE)

Nocturnal enuresis, or nightly bedwetting in children more than seven years of age affects about 10% of seven-year-old

children, with a wide range of frequencies between populations. From the age of seven there is a spontaneous cure rate of 15% per year, such that few remain affected even after the age of 16 years. Two types of nocturnal enuresis exists: type I (PEN1, primary) with at least three nightly episodes in children above seven years, where the child has always had the disorder and type II (secondary) where the child has been dry for at least six months, but enuresis has recurred. Reports from a danish family population, in which 17 families were examined, eleven of these family had type I nocturnal enuresis (PEN1) that appeared to follow an AD mode of inheritance with penetrance almost above 90%. Strong evidence of linkage with the DNA polymorphisms D13S291 and D13S263 was found. Multipoint analysis indicated that these markers flank the disease locus at chromosome 13q13-q14.3 as reported by Eiberg, et al. [71-73]. Arnell, et al. found a region around D12S80 on chromosome 12q that showed a positive two point lod score in six of the families among sixteen of them. Ratio of males to females was 3:1, indicating sex linked or sex influenced factors [74].

Linkage analysis revealed 6 families with dominant primary nocturnal enuresis around the aquaporin-2 (AQP2) water channel locus. PNE is ameliorated by desmopressin, AQP2 expression is increased by desmopressin and AQP2 is essential for concentrating urine. Deen, et al. in their study reported no mutation in the AQP2 coding, the AQP2 gene is excluded as a candidate for autosomal dominant PNE in these families in which the disease co-segregates with chromosome 12q [75]. Eiberg, et al. in their research used total genome scan and multipoint analysis and mapped PNE to chromosome 22 between the markers D22S446 and D22S343 with a multipoint lod score of 4.51.GNAZ has a transducin function in eye and brain and is an obvious candidate gene on chromosome 22q11 for PNE [76].

Brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are neurotrophins which affects maturation of the nervous system. Delayed neuronal maturation has been suggested as a pathogenetic mechanism in primary monosymptomatic nocturnal enuresis (PMNE). Neurotrophin gene polymorphisms did not significantly contribute to the development of PMNE, but urine levels of neurotrophin gene products were higher in PMNE [77]. Dopamine D4 receptor (DRD4) promoter (-616; rs747302) has been associated with primary nocturnal enuresis (PNE). Yu, et al. reported C-allele carriers were associated with a higher AS (Arousal from Sleep), decreased GMV (Grey Matter Volume) and FCD (Functional Connectivity Density) in the pregenual anterior cingulate cortex. Children with PNE carrying the C-allele exhibit decreased GMV and FCD in the thalamus however, controls who participated in the studies carrying the C allele exhibit increased FCD in the posterior cingulate cortex. Thus this genetic variation of the DRD4 locus may give a genetic susceptibility of the DRD4 -616 C allele to PNE [78,79]. Fatouh, et al. reported PNE can be in part linked to reversed ADH circadian rhythm which may be linked to chromosome 22 [80]. The association between 5HTR2A gene polymorphisms and polysymptomatic NE was reported by Wei, et al. suggesting that genetic variations at 5HTR2A may influence NE treatment response [81].

Genetic variations affecting sleep phenotypes include several genes, modifications like SNP, missense mutation, VNTR, insertion/deletion variant, SNPs in promoter and coding region, missense mutation in signal peptide, SNP in 5′UTR. Specific genes are described below:

CLOCK: A transcription-translation feedback loop serves as the basic mechanism for the clock machinery in the suprachiasmatic nucleus (SCN) to control circadian rhythmic city. The PER and CRY proteins, in turn, act as negative regulators of CLOCK/BMAL1 activity by forming a repressor complex with casein kinase (CK) 1ε (encoded by the CSNK1E gene) and CK1δ (CSNK1D) [52,59]. Besides their function in circadian rhythmicity, clock genes have also been found to influence sleep variables. Supporting evidence comes from animal models showing that knockout of BMAL1 and NPAS2 and double knockout of Cry1 and Cry2 lead to abnormalities in sleep homeostasis in animal model [82-84]. In 1998, Katzenberg, found a T3111C polymorphism in the 3′ UTR of CLOCK associated with diurnal preferences, in that carriers of the C-allele are more often evening- type. In a Japanese sample, the highest eveningness was likewise found in C/C homozygous subjects, along with significantly delayed sleep onset, shorter sleep duration, and higher daytime sleepiness compared with either heterozygous or homozygous T- allele carriers [85-93].

SLC6A3(DAT): In humans, a VNTR polymorphism in the 3′ UTR of the DAT encoding gene SLC6A3 leads to less DAT in the striatum in individuals homozygous for the long 10-repeat allele as compared with carriers of the 9 repeat allele. According to the available animal data, 10/10 carriers are more sensitive to caffeine generally, as well as to its effect on reducing SWS rebound after sleep deprivation, which was found more pronounced in 10- repeat homozygotes [94-98].

MAOA: Monoamine oxidase (MAO) A and B are encoded on the X- chromosome and catalyze the degradation of serotonin and melatonin. Females carrying an allele conferring higher activity due to a variable number tandem repeat (VNTR) polymorphism in the MAO- A promoter region are at higher risk of developing RLS. The less active allele seems to confer susceptibility to depression and poor sleep quality. Koch, et al. proposed an association of a VNTR in intron 1 of the MAOA gene and a dinucleotide repeat in intron 2 of the MAOB gene with the occurrence of narcolepsy with cataplexy. MAO- A and - B inhibitors are capable of reducing symptoms of narcolepsy such as cataplexy and abnormal REM sleep [99-102,103-106].

ADA: Adenosinergic neurotransmission is suspected to play a major role in the regulation of sleep and wakefulness and their homeostasis in mice and humans. Retey, et al. found

an increase in slow wave sleep (SWS) during an undisturbed night in ADA* 1–2 carriers resembling the effects of one night of sleep deprivation [107]. This was further accompanied by higher delta power in NREM sleep, which is a marker of sleep need [108-112].

BDNF: Evidence in the recent past suggested increased sleep slow waves after sleep deprivation is a reflection in plastic synaptic processes, and that brain-derived neurotrophic factor (BDNF) is causally involved in their homeostatic regulation. The functional Val66Met polymorphism of the gene encoding pro-BDNF causes impaired activity-dependent secretion of mature BDNF protein. Bachmann, et al. reported about the contribution of BDNF to the regulation of sleep slow wave oscillations and variation in neuronal plasticity modulates NREM sleep intensity in humans [113-124].

PRNP: FFI (Fatal Familial Insomnia) is characterized by disrupted sleep, i.e., loss of sleep spindles and slow wave sleep, and impaired sleep stage organization, as well as progressive reduction of sleep time. Reduced metabolism in thalamic and limbic regions and degeneration of thalamic nuclei has been identified. A missense mutation, a G- to -A transition at codon 178, leads to substitution of aspartate for asparagine. Two Italian affected kindred revealed an underlying point mutation in the prion protein (PrP) gene (PRNP) on chromosome 20. Creutzfeldt– Jakob disease (CJD) is characterized by the same mutation and accumulation of protease- resistant prion protein plaques, but differs from FFI regarding a polymorphism at codon 129, which is common and leads to either incorporation of a methionine or valine and further to protein isoforms differing in size and glycosylation pattern. While in FFI- affected individuals the mutated allele encodes for methionine, those with CJD express valine on the mutated PRNP allele [125-130].

ADORA: Common genetic variation of ADORA2A is an important determinant of psychomotor vigilance in rested and sleep-deprived state. It also modulates individual responses to caffeine after sleep deprivation. Role for adenosine A (2A) receptors in the effects of prolonged wakefulness on vigilant attention and the sleep EEG [131]. Role of adenosine A2A receptors for sleep in humans, suggest that a common variation in ADORA2A contributes to subjective and objective responses to caffeine on sleep [132].

COMT: A sexual dimorphism and a strong effect of COMT genotype on severity of narcolepsy exists. Women narcoleptics with high COMT activity fell asleep twice as fast as those with low COMT activity during the multiple sleep latency test (MSLT) while the opposite was true for men. COMT genotype also strongly affected the presence of sleep paralysis and the number of REM sleep onsets during the MSLT [99]. Dopaminergic mechanisms contribute to impaired waking functions after sleep loss [133]. The Val158Met polymorphism of COMT modulates the effects of modafinil on the NREM sleep EEG in recovery sleep after prolonged wakefulness. The sleep EEG changes induced by modafinil markedly differ from those of caffeine, showing that pharmacological interference with dopaminergic and adenosinergic neurotransmission during sleep deprivation differently affects sleep homeostasis [134,135].

TNFA: Three SNP of the TNFA promoter and one adjacent microsatellite was investigated by Wieczorek, et al. These results point towards an etiological influence of TNFA alleles in narcolepsy and support previous findings suggesting genetic heterogeneity and differences in pathophysiological characteristics of HLA-DR2 positive and negative narcolepsy [136]. TNF-alpha with 857T was associated with narcolepsy independent of the strong association of DRB1*1501 [137].

PER3: Polymorphism in the PER3 promoter associates with diurnal preference and delayed sleep phase disorder [138-140]. PER3 VNTR polymorphism was not associated with individual differences in neurobehavioral responses to PSD (Partial Sleep Deprivation), although it was related to one marker of sleep homoeostatic response during PSD. PER3 does not contribute to the neurobehavioral effects of chronic sleep loss [141]. PER3 polymorphism differentially influences the effects of sleep deprivation on executive and non-executive function in the early morning. These effects appear to be mediated through homeostatic sleep pressure [142,143]. Individual phase differences in PER3 expression during a constant routine correlate with sleep timing during entrainment. PER3 expression in leukocytes represents a useful molecular marker of the circadian processes governing sleep-wake timing [93].

TNFR2: In a Japanese case control study it was found TNFR2 is likely associated with the susceptibility to narcolepsy. Relationship of TNFR2 and TNF-alpha with the susceptibility to narcolepsy indicates the possibility that an additive effect on the susceptibility to the disorder lies between TNFR2-196R and TNF-alpha (-857T) alleles [144]. Chen, et al. reported increased TNF-α level was associated with narcolepsy in our patients, and that chronic inflammation due to various factors might have led to the increased TNF-α levels found in their patients [145].

HCRT: Hypocretin loci do not contribute significantly to genetic predisposition, however cases of human narcolepsy are associated with a deficient hypocretin system [146]. Hypocretin-specific CD8+ T cells was detected in the blood and cerebrospinal fluid of several patients in a study with narcolepsy [147]. Selective hypocretin receptor 2 agonist (YNT-185) has been shown to ameliorate symptoms of narcolepsy in murine models [148].

GABRA (GABA A receptors): A missense mutation was found in the gene of the beta3 subunit nucleotide polymorphism in a patient with chronic insomnia [149]. Pharmacogenetic experiments are currently leading to an understanding of the circuit mechanisms in the hypothalamus by which zolpidem and similar compounds induce sleep at

α2βγ2-type GABAA receptors [150]. GABA receptors undergo dynamic and differential changes in the wake-active Orx neurons and the sleep-active MCH neurons as a function of and homeostatic adjustment to their preceding activity and sleep-wake state [151].

HTR2A (5-HT2A receptor): Serotonin (5-HT) 5-HT2A receptor (5-HT2AR) and 5-HT2C receptor (5-HT2CR) in the central nervous system are implicated in a range of normal behaviors (e.g., appetite, sleep) [152]. Job stress and 5-HTR2A receptor gene polymorphisms are associated with sleep quality in physicians. Subjects with high job stress level or/and the -1438G/A GG genotype were more likely to report poor sleep quality, and furthermore, their combination effect on sleep quality was higher than their independent effects [153]. Polymorphisms of 5-HT 2A receptor gene and obstructive sleep apnea was shown in metanalysis [154,155]. Joëlle Adrien in one animal study showed the role of serotonin transmission in mice model [106].

SLC6A4 (5-HTT): Tryptophan improved objective sleep efficiency and objective wake after sleep onset irrespective of allelic variation in one study [156]. Tryptophan augmentation may be a valuable treatment strategy for sleep impairments related to genetic deficiencies in 5-HT functioning. A metanalysis demonstrated that 5-HTR-1438 "A" and 5-HTTVNTR "10" alleles were significantly associated with OSAS. The "S" allele of 5-HTTLPR and the "GG" genotype of LEPR conferred protection against OSAS in line with some other researches [157-160].

Discussion

Sleep as we see is the most complex biological process in human beings. In this article genes associated with sleep is being reviewed in details.MZ are more affected than DZ as evident from the twin studies. Disorders associated with sleep genetics include insomnia, breathing disturbances during sleep (i.e., sleep apnea), movement disorders during sleep (i.e., Restless leg syndrome, Periodic leg movements) and sleep-wake state dissociation disorders (i.e., narcolepsy, Rapid Eye Movement (REM) sleep Behavior Disorder, sleep walking).

Familial and linkage studies also hinted at several diseases like FASPS, RLS, and PNE. Pattern of inheritance can be AD/AR or of unclear origin. Several involved molecules and loci are reported among studies. Genes, modification at cellular level like SNP, VNTR, and missense mutations are also reported in literature and every gene modification can lead to different phenotypic trait related to sleep. Neurotransmitters like adenosine, dopamine, serotonin, GABA are involved along with individual effect and complex interaction among them related to neuroanatomical circuit. Molecules like MAO, COMT, TNF, BDNF, Prion protein, orexin, hypocretin are involved in sleep disorders associated with gene interaction. Circadian CLOCK genes are also reviewed in this article.

Conclusion

Genetics of sleep are still studied because it is considered as a very complex mechanism in humans. Sleep phenotypes and sleep disorders are controlled by individualised genetic factors. Mechanism of sleep function and pathophysiology behind it is controlled from molecular to organismic behavioral level. Sound sleep is important for proper functioning of individual. Improper sleep can lead to unnecessary stress and can be harbinger of diseases like hypertension, diabetes mellitus etc. and decreased neurocognitive status. Various genes are responsible for sleep disorders however if any single gene involved is not known yet. Sleep studies are quite complicated and even PSG may not be able to pick the diagnosis at initial stage. Genetic sequencing may be of great help in subset of population when diagnosis is not clear. Further studies are required in form of basic and translational research which will involve linking of various disorder phenotypes to normal mechanisms regulating the most basic biological substrates.

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