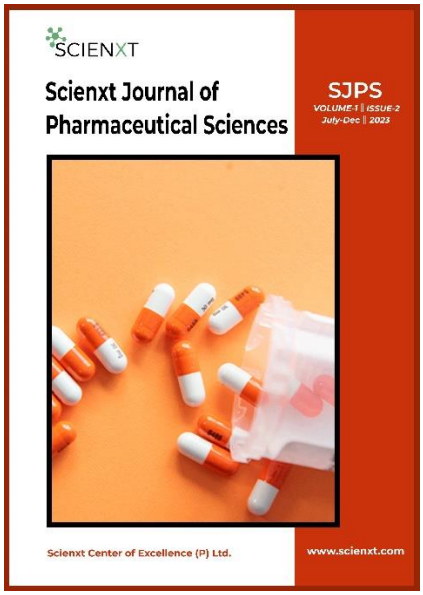

Scienxt Journal of Pharmaceutical Sciences
Year-2023 || Volume-1 || Issue-2 || July-Dec || pp. 59-74

Significance of sleep: Pharmacogenomics perspective

[*1]Rajavarman Kittu *, [2]Anuja Mishra
[1, 2]Bioinformatics Department, Prema's life sciences Pvt Ltd, New Delhi, India

**Corresponding Author: Rajavarman Kittu*
Email: k.rajavarman52@gmail.com

Abstract:

Sleep is being more impact in order to gain the energy of the body. There are several genes like CLOCK, BMAL1 (or ARNTL), PERIOD (PER1, PER2, and PER3), and cryptochrome 1 and 2 (CRY1 and CRY2) are additional genes implicated in the sleep-wake cycle. The pharmacogenomics were through the genome-wide association study about the sleeping disorder. Pharmacogenetics is a promising approach to enhancing the efficacy and acceptability of existing medicines. Here we are discussing the significance of sleep and pharmacological prospects to be overlooked in order to gain confidence.

Keywords:

Pharmacogenomics, Pharmacogenetics, wakefulness, Kleine-Levin syndrome, Circadian rhythms

1. Introduction :

The human brain is hard wired complicated neurology system, which is very difficult to study and understand. The brain being responsible for multiple reactions including biochemical process regular basis. The biochemical pathways are the key factors in neuros role. The activation and de-activation of certain specific genes in specific pathways gives hope for both activeness and under performance respectively.

Sleep is a very important physiological aspect for all living organisms. Having a good and sound sleep helps to maintain good physical and psychological well beingness. In many cases, not every individual gets to sleep for a defined period of time (6-8 hrs for men and 8-10 hrs for women). These kind of cases does not relate only to increasing work stress but due to multiple inherited genetic factors, different behavioural pattern and environmental factors. The way genes are responsible are for individual's traits in the same way genes play a major role when controlling the "sleep-wakes cycle" of an individual. The patients and Factors involved in sleep disorders are shown in diagram [Fig. 1].

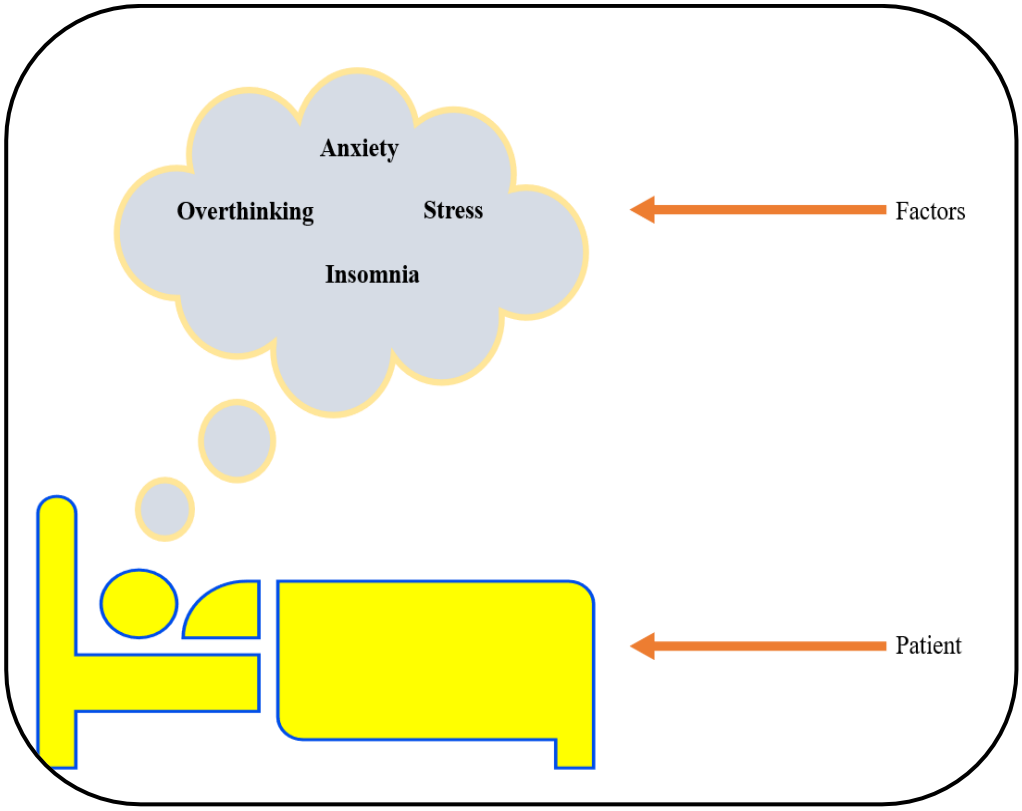

Figure. 1: Patients and respective factors

Stress levels may induce genes having impact on quality and duration of sleep. Stress-related stimulation of specific neurons appears to pave the way for sleep issues, such as trouble falling asleep, remaining asleep or falling back to sleep. The words referring to "early bird" or "night

owl" describes not only sleep patterns but also the genetic affect. From the studies of fruit-flies, scientist was able to explain how short sleepers remain short-sleepers across the generation as compared to long and normal sleepers. Many studies have also shown involvement of mutations in fragmented sleep patterns or genes controlling the circadian clock.

2. Review of literature:

Circadian rhythm: The body's internal clock, known as circadian rhythm, controls the body's 24-hour cycle of sleep and wakefulness. Because the area of the brain that responds to light controls circadian rhythm, alertness often peaks during the day and declines at night. Circadian rhythms not only synchronize to light-dark cycles but also plays regulates different physiological processes include heart rate, body temperature, and metabolism. Two basic mechanisms regulate the circadian rhythm: the internal biological clock system and the environment. The suprachiasmatic nucleus, often known as the SCN [Master clock], is a cluster of about 20,000 nerve cells that controls the body's biological clocks. This SCN is located in the hypothalamus region of brain which uses daylight signals to distinguish between alertness and sleepiness. Melatonin, also known as sleep hormones are controlled by SCN receptors. Apart from hormone production, SCN also regulates metabolism and synchronizes local clock found connective tissue, muscles, lungs to which works independently of the master clock. The age and the total sleep amount needed per day is listed below [Table. 1]

Table. 1: Age and respective total sleep amount per day

Age	**Total sleep amount per day**
0-3 months	14-17 hours
4-12 months	12-16 hours, including naps
1-2 years	11-14 hours, including naps
3-5 years	10-13 hours, including naps

6-12 years	9-12 hours
13-18 years	8-10 hours
18-61 years	7 hours or more per night
61-64 years	7-9 hours
64+	7-8 hours

Any changes in the normal circadian rhythms can give rise to complicated sleep patterns resulting in different sleep disorders. There are up to 80 identified sleep disorders, which affect about 70 million of Americans per say. Some of the most often identified sleep disorders, such restless legs syndrome, as well as some of the rarest, like Kleine-Levin syndrome, have a strong genetic association. Numerous research investigations have demonstrated a strong hereditary link with restless legs syndrome. A hormone and a neurotransmitter name dopamine present in brain controls the muscle movements and iron has an effect on dopamine's synthesis and action. A shortage of iron in the brain and dopamine malfunction seems to be the root causes of restless legs syndrome. Up to 50% of individuals with RLS have a family member who also has the condition. The kleine-levin syndrome which mostly affects the adolescent males shows disrupted behaviour. It is characterised by phases of excessive drowsiness, changes in mood and personality, extremely high calorie intake, irritability, and unrestrained sexual behaviour. The brain's hypothalamus and thalamus, which are where these behaviours are controlled, may be dysfunctional, leading to symptoms. Over the course of a decade, Kleine-Levin episodes often become less frequent and may perhaps stop altogether by adulthood. The interplay of sensitive genes with specific environmental factors may result in Kleine-Levin syndrome. Apart from these syndrome other most commonly seen sleep disorders include insomnia, sleep waking, sleep paralysis, Nocturnal Bruxism, Sleep apnea may contain the genes linked to the sleep-wake cycle and circadian rhythms. Longevity, lower levels of stress, and a robust metabolism are all associated with a normal circadian cycle. Circadian rhythms regulate sleep and wake cycles via detecting light signals. The wake state and alertness are brought on by light, which enters the eye through the retina and travels through a neuronal pathway to the SCN. The master clock instructs the brain to create melatonin, which causes tiredness and encourages sleep, as the sun sets and there is less light. Lack of sleep can intensify the circadian

rhythm's normal peaks causing sensations of drowsiness and alertness to be accentuated. The functioning of vital body systems as well as energy and fitness levels are all significantly influenced by circadian rhythms, according to research. Circadian rhythm irregularities have been connected to long-term illnesses like depression, obesity, and sleep difficulties. According to research, night shift employees are more likely to be obese, develop diabetes, and have accidents. The blue light emitted by screens on mobile devices, laptops, tablets, and televisions inhibits melatonin generation and is a significant cause of irregular heartbeat. The body's metabolism has a close relationship with the circadian cycle. In the past ten years, scientists have learned that circadian rhythms play a role in controlling the energy levels in cells. This may clarify how disturbed sleep patterns might make people more hungry, which can result in weight gain, obesity, and other metabolic issues. Studies of traits seen in monozygotic and dizygotic twins can offer important insights into genetic transmission. More advanced methods, including segregation analysis and genome-wide linkage studies, can be used to evaluate heritability in families, which is defined as the percentage of variance in a phenotype, trait, or disease that can be attributed to genetic influence. Population-based, case-control, genome-wide association studies (GWASs) have recently shed light on previously unidentified genetic loci, including the genetic implications in sleep disorders. It is possible to categories various gene alleles (risk variations) based on how frequently they occur and how much of an impact they have on a phenotype, trait, or illness. Risk variations can have effects on a specific phenotype, trait, or disease that range in size from small (increased risk by a factor of 0.1) to huge (increased risk by a factor of >100). They can be rare (allele frequency 1%) to common (allele frequency >5%).The basic stages are listed as below [Fig. 2].

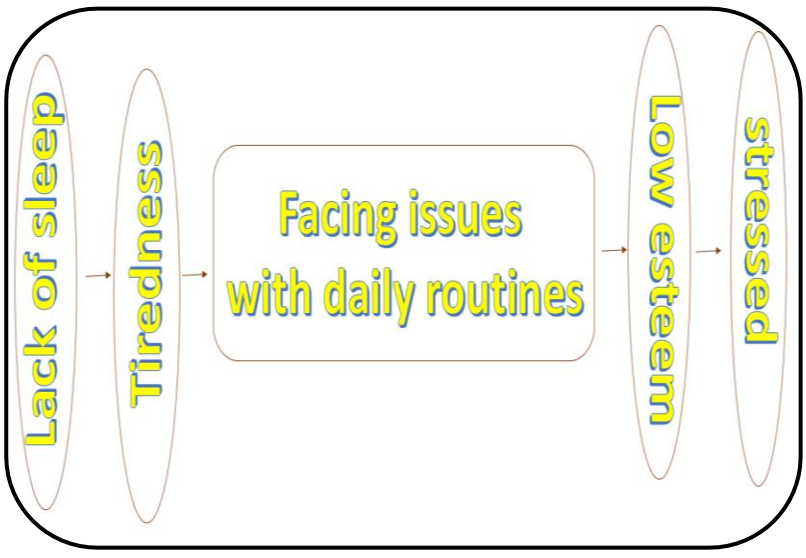

Figure. 2: Different stages

Similar EEG frequencies have been seen in monozygotic twins compared to dizygotic twins or unrelated control patients in EEG pattern analyses, which indicates a strong genetic component.

Sleep is regulated by a variety of genes many of which are yet unknown. One of the earliest sleep characteristics discovered in both animal models and humans that has had its molecular basis deciphered is circadian rhythm.

CLOCK, a gene on chromosome 5 that codes for the CLOCK protein, was the first gene associated with the circadian rhythm to be identified from the studies done on Drosophila melanogaster (Fruit Fly). The genes BMAL1 (or ARNTL), PERIOD (PER1, PER2, and PER3), and cryptochrome 1 and 2 (CRY1 and CRY2) are additional genes implicated in the sleep-wake cycle. The CLOCK/BMAL1, PER, and CRY proteins made by these genes form a feedback loop that contributes to the circadian clock's molecular underpinnings. The CLOCK protein and the BMAL1 protein, which is the result of the BMAL1 gene forms a dimer inside the cell's suprachiasmatic nucleus (SPN). The PER1, PER2, and PER3 genes, which code for the PER1, PER2, and PER3 proteins, as well as the CRY gene, which codes for the CRY protein, are increased in transcription by CLOCK/BMAL1. The PER and CRY proteins are transferred from the nucleus into the cytoplasm and a PER/CRY dimer is created. The CLOCK/BMAL1 dimer receives negative feedback from the PER/CRY dimer over the course of 24 hours, which inhibits its own transcription. There are more feedback loops to control the sleep-wake cycle. The genes for casein kinase 1 (CK1 or CSNK1E) create proteins that control the PERIOD protein. The genes NR1D1 (formerly known as REV-ERB) and ROR1 produce the distinct proteins REV-ERB and ROR1, which are transcribed in the SPN and appear to control BMAL1. Additionally, CRY has proteins that control its expression.

Genome-Wide Association Studies, Candidate Gene, Linkage have been able to find identify alleles or loci associated with different sleep disorders. A summary describing genes associated to sleep disorders is given below [Table. 2]

Table. 2: sleep disorders, genes corresponding to with comments

Sleep Disorder	Associated Gene, Loci, SNP	Comments
RLS (Restless legs syndrome)/PLMS	RLS1-5	Complex transmission, autosomal dominant with incomplete penetrance; identified in familial

(periodic limb movements in sleep)		linkage studies in people of different countries; no associations with the dopamine system or iron metabolism have been reported.
	MEIS1	Based on GWAS and confirmed in numerous studies, MEIS1 is connected to the development of motor neurons.
	BTBD9	According to GWAS, the allele is linked to PLMS without RLS and lower ferritin levels.
	MAP2K5/SKOR1 (LBXCOR1)	Gene related to dorsal horn sensory pathway development, according to GWAS.
	PTPRD	Two SNPs related to neural development, according to GWAS.
Narcolepsy/cataplexy	DQB1 and DQA1; primary allele DQB1*0602	HLA class II allele; impact seen in many racial/ethnic groups; high prevalence (90%) in cataplexy-accompanied narcolepsy.

Narcolepsy/cataplexy	T-cell receptor α	Based on GWAS, the T-cell receptor on lymphocytes interacts with HLA class I and II antigens, including the DQB1*0602 allele, which was separately discovered in different ethnic groups.
Fatal familial insomnia	Single point mutation in prion gene	Point mutations at codon 129 and position 178 of the prion protein gene
Familial advanced sleep phase syndrome	HPER2	Candidate gene sequencing was used to identify autosomal dominant transmission.

3. Immune system & sleep:

Numerous systems are involved in the intricate regulation of sleep. Numerous cytokines that are essential to the immune system's response to infection have been identified to affect and control sleep. Additionally, new research has revealed that the duration and quality of sleep is crucial for the immune system. Short sleep periods seem to have an impact on the immune system, are linked to changes in the system, and may raise the risk of clinical infections. Both positive and negative feedback loops regulating nonrapid eye movement (NREM) sleep involve many cytokines and other substances. The majority of the data points on the cytokines IL-1β and TNF-α. Both IL-1β and TNF-α have diurnal patterns in the brain and cerebrospinal fluid; the highest concentrations of IL-1β and TNF-α are detected during periods of sleep. If administered to rabbits or other animal models, such as mice, rats, and cats, both IL-1β and TNF-α increase sleep, specifically NREM sleep. The amount of time spent sleeping overall is increased, and the REM, NREM, and waking cycles occur as they should. NREM sleep is reduced by substances that inhibit or impede the action of IL-1β or TNF-α. Examples include

antibodies against IL-1β or TNF, soluble cytokine receptors, and a chemical known as short interfering RNA that specifically targets IL-1 and TNF.

Animals lacking the cytokine receptors exhibit less sleep. Prostaglandin E2 and corticotropin-releasing hormone are examples of substances known to disrupt NREM sleep, and they also inhibit the synthesis of IL-1β and TNF. The compounds IL-4, IL-10, IL-13, and transforming growth factor-β are also known to suppress IL-1β or TNF, as well as NREM sleep.

There is evidence that IL-1β and TNF activate nuclear factor-B (NF-κB), a protein involved in DNA transcription, however the exact mechanism by which these two cytokines increase NREM sleep is not entirely understood. The same substances that stop NF-κB activity also stop sleep. For instance, it is well known that NF-B activity and NREM sleep are both inhibited by IL-4, IL-10, and the glucocorticoids. Additionally, there is proof that exogenous injections of IL-1β or TNF-α may cause the clinical signs of sleep deprivation, such as drowsiness, exhaustion, cognitive decline, and increased pain sensitivity. Increased brain and circulation levels of IL-1β and TNF-α are linked to clinical disorders like sleep apnea, chronic fatigue, rheumatoid arthritis, and chronic fatigue found with chronic inflammation. Clinically available TNF inhibitors, such as etanercept, have been shown to lessen the weariness associated with rheumatoid arthritis and the sleepiness associated with sleep apnea in several exciting case studies.

The majority of investigations have discovered an immune response that is non-specifically activated, as seen by rising leukocyte and monocyte counts as well as rising levels of cytokines like IL-6 and TNF. The effects of moderate sleep loss have also been linked to increases in IL-1β and IL-17. Lack of sleep is linked to lowered immunological response, including reduced T-cell cytokine production. Based on studies from nearly 57,000 people, shorter sleep durations are linked to a higher risk of pneumonia than those who sleep for eight hours or longer. Normal sleep improves response to hepatitis A vaccine, however one night of sleep deprivation worsens it. In spite of accounting for other factors, shorter sleep duration as evaluated by actigraphy in healthy persons was linked to a compromised IgG response to hepatitis B surface antibody and a failure to reach the threshold for clinical protection from the hepatitis B vaccine. In addition, lack of sleep may affect the effectiveness of the influenza vaccine.

4. Pharmacogenomics and sleep:

For uninterrupted health, cognitive function, and quality of life, a good quality sleep is essential. Disorders of sleep-wake cycle are the third most common brain disorders which costs Europe about €800 billion annually. Although understanding of the unique neurotransmitter nuclei and neuronal pathways that regulate and maintain wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep is growing, current pharmacotherapy is still largely based on symptomatic treatments, and many patients do not benefit from the therapeutics that are currently available. Therefore, new methods are required to specifically and efficiently treat disorders of sleep-wake cycle. Pharmacogenetics is a promising approach to enhancing the efficacy and acceptability of existing medicines. The Pathway of circadian rhythm is shown below in diagram [Fig. 3].

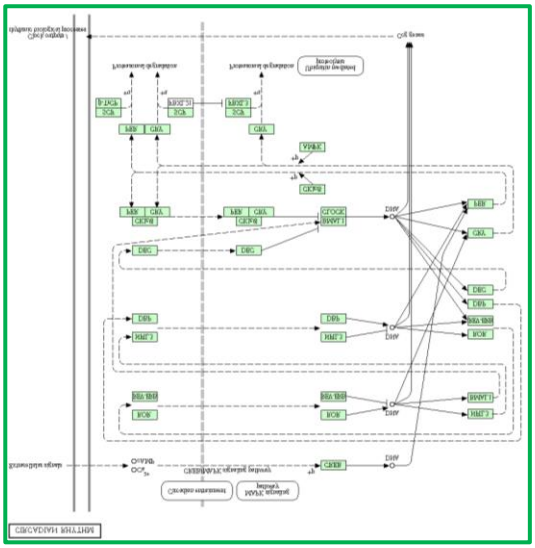

Figure. 3: The circadian rhythm pathway

The FDA has approved the use of low-dose doxepin [8], a TCA having a high affinity for the H1 receptor, to treat insomnia. Patients with major depressive disorder (MDD) with comorbid insomnia experience better sleep after taking the antidepressant mirtazapine, which has 5-HT and His antagonistic characteristics. RBD is currently first-line-treated with BZD clonazepam. The TCA imipramine, which is FDA-approved for depression and paediatric enuresis, and clonazepam are additional medications for treating night terrors and somnambulism. Pharmacogenetic techniques seek to distinguish responders from non-responders and minimise toxicity and adverse medication effects by elucidating genetically determined interindividual variability in drug responses. Single nucleotide polymorphisms (SNPs), insertions/deletions, copy number variations and variable-number-tandem-repeat (VNTR) polymorphisms in genes that control the pharmacokinetics and/or pharmacodynamics (e.g., enzymes, ion channels, receptors, immune molecules) of drugs are some of the sources of genetic variation [Table. 3]

Table. 3: The drugs, genes with relevant variants corresponding to it rsid listed

Drug	**Gene**	**Variant**	**SNP-ID**	**Prevalence**	**Drug response phenotype relevant for sleep**
Caffeine	CYP1A1/CYP1A2	NA	rs2470893	9	Habitual caffeine consumption
	CYP1A1/CYP1A2	NA	rs2472297	6.6	Habitual caffeine consumption
	CYP1A2	c.-9-154C>A	rs762551	NA	Caffeine metabolism
	AHR	NA	rs4410790	46.7	Habitual caffeine consumption
	AHR	NA	rs6968865	45.7	Habitual caffeine consumption
	ADA	c.22G>A	rs73598374	5.1	Disturbed sleep
	ADORA2A	c.1976T>C	rs5751876	44.2	Disturbed sleep; improved attention
	SLC6A3	VNTR	rs28363170	NA	Recovery sleep EEG after sleep deprivation
Methylphenidate	SLC6A3	VNTR	rs28363170	NA	Therapeutic dose
	COMT	c.472G>A	rs4680	36.9	Therapeutic dose
Methamphetamine	SLC6A3	VNTR	rs28363170	NA	Risk of psychosis and abuse
	COMT	c.472G>A	rs4680	36.9	Risk of psychosis and abuse
Modafinil	SLC6A3	VNTR	rs28363170	NA	Recovery sleep EEG after sleep deprivation
	COMT	c.472G>A	rs4680	36.9	Improved well-being and cognitive function after sleep loss; recovery sleep

					EEG; effective dose in narcolepsy and treatment of methamphetamine dependence
l-dopa	COMT	Unknown	NA	NA	Therapeutic dose in RLS
Pramipexole	SLC22A1	c.1386-2964C>A	rs622342	25.9	Therapeutic dose; survival time with l-dopa [9]
	DRD2/AKNN1	Taq1A	rs1800497	32.5	Treatment discontinuation
	DRD3	c.25G>A	rs6280	48.6	Therapeutic dose in PD
	DRD3	c.1006+400G>A	rs4646996	44	Treatment discontinuation
Ropinirole	DRD2/AKNN1	Taq1A	rs1800497	32.6	Treatment discontinuation
	DRD3	c.1006+400G>A	rs4646996	44	Treatment discontinuation
Diphenhydramine	CYP2D6	Number of gene copies	NA	NA	Paradoxical excitation
Chlorpheniramine and promethazine	CYP2D6	Number of gene copies and various alleles	NA	NA	Sleepiness (adverse effect)
Doxepin	CYP2D6	Number of gene copies and various alleles	NA	NA	Therapeutic dose; intoxication
	CYP2C19	Various alleles	NA	NA	Therapeutic dose in MDD patients
Mirtazapine and	CYP2D6	Number of gene	NA	NA	Therapeutic dose; sleepiness (adverse effect)

esmirtazapine		copies and various alleles			
	CYP2C19	Various alleles	NA	NA	Therapeutic dose in MDD patients
	HTR2A	c.-998G>A	rs6311	44.5	Sleep improvement in MDD patients
Zolpidem	CYP2C19	Various alleles	NA	NA	Pharmacokinetic variables
	CYP3A4	Various alleles	NA	NA	Pharmacokinetic variables
Lorazepam	UGT2B7	Unknown	NA	NA	Prolonged sedation
Gabapentin	SLC22A4	c.1507C>T	rs1050152	13.4	Renal clearance
Melatonin	CYP1A2	c.-9-154C>A	rs762551	37	Melatonin metabolism
	MTNR1A	c.-386A>G	rs2119882	47	Insomnia symptoms in schizophrenia
Agomelatine	CYP1A2	Haplotype	rs762551, rs2470890, rs2472304	37.0, 23.6, 23.8	Therapeutic dose
Ketanserin	HTR1B	c.371T>C	rs130060	0.3	Receptor binding
	HTR2A	c.102C>T	rs6313	44.1	Receptor binding

5. Discussion and conclusion:

The best technique to determine why many people do not respond well to the currently available wake-promoting drugs or sleeping medicines is to use a pharmacogenetic approach. The development of novel medicines relies heavily on the preclinical and clinical human pharmacogenetics of interindividual variations in response to sleep-wake altering drugs. A growing number of genetic variations that influence exposure and sensitivity to medications

that target the neurochemistry of sleep-wake control and the pathophysiology of sleep-wake disorders are known to vary drug response phenotypes, as shown in above table. Studies in mice lacking the relevant genes can be a powerful addition to human pharmacogenetics to support the significance of these genetic variants for tailored sleep-wake medication.

6. References:

(1) Brummett BH, Krystal AD, Ashley-Koch A, Kuhn CM, Züchner S, Siegler IC, Barefoot JC, Ballard EL, Gwyther LP, Williams RB., Sleep Quality Varies as a Function of 5-HTTLPR

(2) Herzog ED, Takahashi JS, and Block GD (1998). Clock controls circadian period in isolated suprachiasmatic nucleus neurons. Nature neuroscience 1, 708–713. [PubMed: 10196587]

(3) Welsh DK, Logothetis DE, Meister M, and Reppert SM (1995). Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. Neuron 14, 697–706. [PubMed: 7718233]

(4) https://sleepopolis.com/education/genetics-of-sleep/

(5) Asif N, Iqbal R, Nazir CF. Human immune system during sleep. Am J Clin Exp Immunol. 2017 Dec 20; 6(6):92-96. PMID: 29348984; PMCID: PMC5768894.

(6) Besedovsky L, Lange T, Born J. Sleep and immune function. Pflugers Arch. 2012 Jan; 463(1):121-37. doi: 10.1007/s00424-011-1044-0. Epub 2011 Nov 10. PMID: 22071480; PMCID: PMC3256323.

(7) 7. https://www.genome.jp/pathway/hsa04710

(8) Katwala J, Kumar AK, Sejpal JJ, Terrence M, Mishra M. Therapeutic rationale for low dose doxepin in insomnia patients. Asian Pac J Trop Dis. 2013 Aug; 3(4):331–6. doi: 10.1016/S2222-1808(13)60080-8. PMCID: PMC4027305

(9) Schmidt MH, Koshal VB, Schmidt HS. Use of pramipexole in REM sleep behavior disorder: results from a case series. Sleep Med. 2006 Aug; 7(5):418-23.

(10) Sebastian C. Holst, ∗ Amandine Valomon, ∗ and Hans-Peter LandoltSleep Pharmacogenetics: Personalized Sleep-Wake Therapy. Annu. Rev. Pharmacol. Toxicol. 2016. 56:577–603.

(11) Wennberg J, Gittelsohn Small area variations in health care delivery. Science. 1973 Dec 14;182(4117):1102–8.

(12) Paradise JL, Bluestone CD, Bachman RZ, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. N Engl J Med. 1984 Mar 15;310(11):674–83

(13) Dooling KL, Shapiro DJ, Van Beneden C, et al. Overprescribing and inappropriate antibiotic selection for children with pharyngitis in the United States, 1997-2010. JAMA Pediatr. 2014 Nov;168(11):1073–4.

(14) Bathala S, Eccles R. A review on the mechanism of sore throat in tonsillitis. J Laryngol Otol. 2013 Mar;127(3):227–32.

(15) Paradise JL, Bluestone CD, Colborn DK, et al. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. Pediatrics. 2002 Jul;110(1 Pt 1):7–15.

(16) Baugh RF, Archer SM, Mitchell RB, et al. Clinical practice guideline: tonsillectomy in children. Otolaryngol Head Neck Surg. 2011 Jan;144(1 Suppl):S1–30.

(17) Paradise JL, Bluestone CD, Colborn DK, et al. Adenoidectomy and adenotonsillectomy for recurrent acute otitis media: parallel randomized clinical trials in children not previously treated with tympanostomy tubes. JAMA. 1999 Sep 8;282(10):945–53.

(18) Park JG, Ramar K, Olson EJ. Updates on definition, consequences, and management of obstructive sleep apnea. Mayo Clin Proc. 2011 Jun;86(6):549–54. quiz 54-5.

(19) Beebe DW. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. Sleep. 2006 Sep;29(9):1115–34.

(20) Teo DT, Mitchell RB. Systematic review of effects of adenotonsillectomy on cardiovascular parameters in children with obstructive sleep apnea. Otolaryngol Head Neck Surg. 2013 Jan;148(1):21–8.

(21) Walz PC, Schroeder JW Jr. Pediatric polysomnography for sleep-disordered breathing prior to tonsillectomy: a guideline review. Pediatr Ann. 2013 Oct;42(10):188–94.