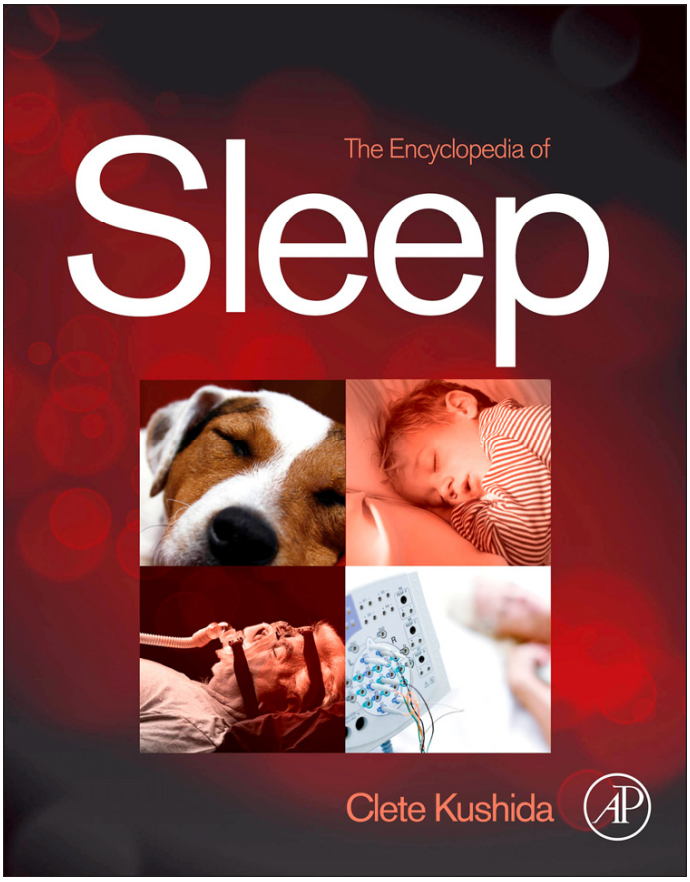

Landolt H.-P. (2013) Genetic Effects. In: Kushida C. (ed.) The Encyclopedia of Sleep, vol. 1, pp. 251-256. Waltham, MA: Academic Press.

Genetic Effects

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Glossary

Candidate gene: A gene for which evidence exists that it is causing or contributing to a particular phenotype (e.g., a disease or condition).
Forward genetics: Search for a gene or a set of genes responsible for a particular trait or phenotype.
Genome-wide association (GWA) study: Experimental approach comparing the complete deoxyribonucleic acid (DNA) of individuals with a phenotype (e.g., a disease or condition) to the DNA of individuals without the phenotype.
Heritability: Proportion of phenotypic variation in a population, which can be explained by genetic variation among the individuals.
Quantitative trait locus (QTL): Region of DNA associated with a particular trait. Sequencing the regions of DNA contributing to the trait may identify candidate genes determining the phenotype.
Reverse genetics: Search for the specific phenotype caused by a given genetic variation.
Single nucleotide polymorphism (SNP): Small genetic change or variation occurring within a person's DNA sequence. The prevalence of SNPs in the human population is on average more than 1%.
Trait: Distinct variant of a single feature or quantifiable measurement of an organism that may be inherited, due to environmental influences, or be determined by genetic and nongenetic factors. A measurable trait is the product of many molecular and biochemical processes.

Sleep–Wake Regulation

Sleep is an active process, which is finely and reliably regulated. According to the widely accepted two-process model of sleep regulation, the interaction of a homeostatic *Process S* and a circadian *Process C* regulates the daily alternation of wakefulness and sleep, as well as variations in sleep structure and the sleep electroencephalogram (EEG). The sleep–wake-dependent Process S keeps track of 'sleep propensity' or 'sleep need': it accumulates during wakefulness and dissipates during sleep. The duration of slow wave sleep (SWS) and the preponderance of EEG δ/θ oscillations in non-rapid eye movement (NREM) sleep (and also in rapid eye movement (REM) sleep) reliably reflect the duration of prior wakefulness. When compared to baseline sleep, SWS is prolonged and δ/θ-activity is enhanced in recovery sleep after sleep deprivation. By contrast, activity in the spindle frequency range is typically reduced after sleep loss. Opposite changes occur in sleep and sleep EEG after excess sleep such as after a daytime nap. Process C is largely independent of wakefulness and sleep: it determines the daily phases of high and low propensity for sleep, including REM sleep, and wakefulness. Particular experimental protocols (e.g., forced desynchrony protocols) are required to analyze the distinct contributions of homeostatic and circadian components to sleep propensity and sleep architecture.

Characteristic Brain Oscillations in Wakefulness and Sleep

Quantification of the EEG in wakefulness and sleep is among the most important methods to study sleep–wake regulation. Distinct brain oscillations, together with information obtained from an electrooculogram (EOG) and an electromyogram (EMG), characterize the occurrence and cyclic alternations of wakefulness, NREM sleep, and REM sleep. Rested wakefulness is characterized in many individuals by regular α (~9–12 Hz) and higher (i.e., β and γ) EEG activity. Decreasing α and increasing θ (~5–9 Hz) oscillations with closed eyes and the occurrence of slow eye movements herald the transition into NREM sleep. When NREM sleep is more superficial, the EEG is characterized by phasic events representing sleep spindles (~12–16 Hz, σ-frequency range) and K complexes. In deep NREM sleep (SWS), high-amplitude slow waves (0.5–2 Hz, δ-frequency range) are most prevalent. By contrast, REM sleep is identified by low-amplitude θ, α, and β oscillations, rapid eye movements, and atonia in antigravity muscles.

Evidence for Trait-Like Individual Differences in Sleep, Sleep EEG, Sleep Duration, Diurnal Preference, and Sleep Timing

Genetic Bases of Sleep Phenotypes

Rapidly accumulating evidence demonstrates that many aspects of sleep and sleep–wake regulation reflect trait-like individual differences. Each of these aspects is probably under the control of multiple genes, which may interact, and are also influenced by environmental and other factors (e.g., age).

Heritability of Sleep

Already, the first sleep studies in monozygotic (MZ) twins revealed almost complete concordance in the temporal sequence of sleep stages. Subsequent work demonstrated that in particular those sleep variables that most reliably reflect sleep need are under tight genetic control. They include the duration of NREM sleep stages, especially SWS, and the density of rapid eye movements in REM sleep. For example, it has been estimated that 95% of the variability in REM density can be

Encyclopedia of Sleep, (2013), vol. 1, pp. 251-256

explained by overall genetic effects. Not only twin studies but also multiple recordings in the same individuals demonstrate the trait-like nature of sleep variables. Thus, the *intra*-individual similarity and the interindividual variation in NREM and REM sleep characteristics are stable, robust, and substantial, suggesting that sleep structure is genetically determined.

Heritability of Sleep EEG

The EEG in NREM and REM sleep differs largely among individuals, yet is impressively constant across multiple recordings in the same individual, both in view of absolute power values as well as the shape of the spectra. Much like a fingerprint, different statistical methods demonstrated that multiple nights of single individuals can be separated from the nights of other members of a study sample, only based on the EEG in NREM and REM sleep. The robust between-subject variation and the high within-subject stability indicate that strong genetic influences shape individual sleep EEG profiles, in particular in δ, θ, α, and σ frequencies. This notion is supported by analyses of the spectral composition of the sleep EEG between MZ and dizygotic (DZ) twin pairs. The within-pair concordance in spectral power in the 2–13 Hz range in NREM sleep is significantly higher in MZ twins than in DZ twins. α/σ frequencies appear to reflect particularly strong genetic influences. Heritability in this frequency range may be as high as 96%.

Heritability of Habitual Sleep Duration

Sufficient sleep is necessary for subjective well-being and optimal daytime performance, yet even healthy people differ widely in how much sleep they need. Common habitual sleep durations may range from 5 to 10 h. Either short or long sleep is often observed in different families, suggesting a genetic influence on sleep duration. Indeed, twin studies suggest that ~20–40% of the interindividual variation in sleep duration is caused by genetic factors. Because sleep length in the general population shows a perfect normal distribution, it can be expected that apart from possible rare mutations with large effects, multiple genetic polymorphisms with small effects modulate sleep duration.

Heritability of Diurnal Preference and Sleep Timing

The timing of the peaks and troughs of daytime alertness and the timing of nocturnal sleep (i.e., diurnal preference) are highly variable among healthy individuals. Some of us go to sleep when others wake up. Self-rating scales show normal distribution along an 'eveningness–morningness' axis, indicating the contribution of additive, small effects of multiple genes in combination with the environment. Studies in large numbers of MZ and DZ twin pairs and population- and family-based cohorts have revealed roughly 50% heritability for diurnal preference and 22–25% for habitual bedtime.

Genetic Dissection of Sleep and Circadian Rhythms

Forward Genetics in Mice

Forward genetic techniques have been successfully employed to genetically dissect sleep and sleep regulation in mice. Because QTLs typically underlie continuous traits, this approach has been a method of choice to study the genetics of the sleep EEG. It was found that a QTL on mouse chromosome 14 determines the contribution of δ (1–4 Hz) activity to the EEG in NREM sleep. Subsequent forward, molecular, and reverse genetic work identified retinoic-acid receptor-β (*Rarb*) as the underlying gene. Also with the QTL approach, one single gene was identified on chromosome 5 that is tightly linked to different frequencies of θ oscillations in REM sleep. Fine mapping revealed short-chain acyl-coenzyme A dehydrogenase (*Acads*) as the candidate gene. Finally, a QTL for the increase of δ-power after sleep deprivation was found on chromosome 13, and referred to as δ-power-sleep-1 (*Dsp1*). Further studies of different laboratories identified *Homer1a* as a potentially credible candidate gene for *Dsp1*.

Forward Genetics in Humans

Forward genetic approaches in humans include family-based linkage studies and GWA studies. For example, family studies revealed that the circadian disorder, familial advanced sleep phase syndrome (FASPS), is associated with mutations in the clock genes *PERIOD2* (*PER2*) and *CASEIN KINASE 1 DELTA* (*CK1δ*). Aiming at identifying novel 'sleep genes' and discovering novel sleep regulatory pathways, GWA studies of sleep and sleep EEG are currently being conducted in different sleep centers throughout the world. This approach has successfully identified genes related to sleep-associated disorders such as restless leg syndrome and narcolepsy, yet no published results of normal sleep are currently available.

Reverse Genetics in Humans

Reverse genetics in humans examines the impact of candidate genes, for which evidence exists that they are implicated in sleep and sleep–wake regulation. With this method, individuals with distinct genotypes of known SNPs are prospectively studied in the laboratory. This approach precludes the discovery of novel 'sleep genes,' but helps to understand the consequences of distinct polymorphism for sleep physiology. The studies that are currently available demonstrate that single genes can profoundly modulate sleep and sleep EEG phenotypes.

Molecular Components of Sleep Homeostasis and Circadian Clock

Candidate Genes

Apart from looking for disease genes underlying sleep and circadian rhythm disorders, the growing knowledge about the molecular bases of sleep homeostasis and circadian clock mechanisms have provided obvious rationales for the search for associations between candidate genes and 'sleep' and 'circadian' phenotypes in healthy individuals.

Neurochemistry of Sleep Homeostasis

The neurochemical bases underlying sleep homeostasis remain poorly understood. Nevertheless, it is widely accepted that adenosine, nitric oxide, prostaglandin D_2, tumor necrosis

factor, interleukin-1, and growth-hormone-releasing hormone are importantly involved in the regulation of NREM sleep duration and intensity. Especially with regard to adenosine, compelling and converging evidence has accumulated over the past years to support a primary role for this neuromodulator and its receptors in homeostatic sleep regulation.

Adenosine Formation and Metabolism

Adenosine serves as a building block for adenosine triphosphate (ATP). When ATP is metabolized for energy production due to increased energy demand, adenosine levels increase. Intracellularly, adenosine is formed from adenosine monophosphate (AMP) by cytosolic 5′-nucleotidase. The nucleoside is metabolized to AMP by adenosine kinase, to inosine by adenosine deaminase (ADA), or to *S*-adenosyl homocysteine (SAH) by *S*-adenosyl homocysteine hydrolase (SAHH). Extracellularly, adenosine is produced through ecto-nucleotidases-mediated hydrolysis of released adenine nucleotides, especially ATP. These enzymes dephosphorylate adenine nucleotides to AMP, which by the terminal enzymatic step is hydrolyzed by ecto-5′-nucleotidase to adenosine. Recent insights indicated that astrocytes importantly contribute to adenosine-mediated modulation of neural transmission. Adenosine is transported through plasma and intracellular membranes by specialized nucleoside transporters.

Adenosine Receptors

There are four types of well-characterized G-protein-coupled adenosine receptors, referred to as A_1, A_{2A}, A_{2B}, and A_3 receptors. It is thought that A_1 and A_{2A} receptors are most likely those that mediated physiological effects of adenosine on sleep. Thus, adenosine may increase sleep by reducing excitatory neurotransmission through binding to inhibitory A_1 receptors, which are widely expressed throughout the central nervous system. Stimulation of these receptors opens several types of K^+ channels, inhibits adenylate cyclase through activation of G_i proteins, and inactivates transient voltage-dependent Ca^{2+} channels. Alternatively, it is possible that adenosine disinhibits sleep-active cells in basal forebrain and ventrolateral preoptic (VLPO) area of the hypothalamus through presynaptic reduction of gamma-aminobutyric acid (GABA) release, and actively excites distinct VLPO neurons through postsynaptic activation of A_{2A} receptors. Stimulation of this receptor subtype increases adenylate cyclase activity through activation of G_s (or G_{olf} in striatum) proteins, induces the formation of inositol phosphates, and activates protein kinase A. Lesions of the VLPO result in a significant initial decrease in sleep. Suggesting that adenosinergic mechanisms are involved, preliminary data show that mice with A_{2A} receptor loss-of-function have reduced sleep and reduced responses to sleep deprivation and the wake-promoting effects of the adenosine receptor antagonist, caffeine.

Molecular Circadian Clock Mechanisms

Compared to sleep homeostasis, the molecular components of the mammalian circadian clock are much better understood. The circadian system is organized in a hierarchy of central and peripheral oscillators. The master clock is located in the suprachiasmatic nuclei of the anterior hypothalamus, and coordinates the outputs of independent peripheral oscillators at the organismal level to a coherent rhythm. At the molecular level, both central clock mechanisms and peripheral oscillators consist of a network of transcriptional/translational negative-feedback loops with a delay between transcription and negative feedback that drives rhythmic expression patterns of genes whose protein products are necessary for generation and regulation of circadian rhythms. Important clock-related genes include the transcription regulators *CLOCK*, *BMAL1*, *PER1-3*, *CRY1-2*, and other genes.

Gene Polymorphisms Modulating Sleep, Sleep EEG, Habitual Sleep Duration, Diurnal Preference, and Sleep Timing in Healthy Humans (Table 1)

22G>A Polymorphism of Adenosine Deaminase (*ADA*) Gene

Forward genetic studies in inbred mice have revealed that a genomic region comprising the gene encoding the adenosine-metabolizing enzyme adenosine deaminase (*Ada*) modifies the rate at which NREM sleep need accumulates during wakefulness. Moreover, local pharmacological inhibition of Ada increases the extracellular adenosine concentration and the duration of deep NREM sleep in rats. In humans, the *ADA* gene is located on chromosome 20 and encodes two electrophoretic variants of ADA, referred to as ADA*1 and ADA*2 (SNP-ID number: rs73598374). The ADA*2 variant results from a guanine-to-adenine transition at nucleotide 22, which is translated into an asparagine-to-aspartic acid substitution at codon 8. The heterozygous ADA*1-2 (G/A) genotype shows reduced catalytic activity of ADA when compared to homozygous individuals carrying the ADA*1 (G/G) genotype. Consistent with the findings in animals and supporting an important role for adenosine in regulating sleep intensity, human individuals with the G/A genotype have more SWS than subjects with the G/G genotype. Moreover, this polymorphism is associated with enhanced EEG δ-activity (primarily within the ~0.75–2 Hz range) in NREM sleep.

1976>TC Polymorphism of Adenosine A_{2A} Receptor (*ADORA2A*) Gene

Adenosine is an endogenous agonist at A_1, A_{2A}, A_{2B}, and A_3 receptors, but for the effects on sleep and the sleep EEG, the A_1 and A_{2A} receptors may be primarily important. The effects of polymorphic variants of the A_1 receptor gene have not yet been studied. With respect to the A_{2A} receptor gene (*ADORA2A*) located on chromosome 22, a common synonymous 1976T>C variation (SNP-ID number: rs5751876) is linked to a 2592C>T_{ins} polymorphism in the 3′-untranslated (UTR) region of *ADORA2A*. This genetic variation may modulate receptor protein expression. It was found that the 1976T>C polymorphism contributes to individual sensitivity to the effects of caffeine on sleep, but also affects EEG activity in all vigilance and sleep states. In case-control studies, spectral power in the θ/α-range (~7–10 Hz) is invariably higher in subjects with the C/C genotype than in subjects with the T/T genotype. These findings may suggest that genetically increased

Table 1 Single nucleotide polymorphisms of candidate genes modulating sleep and circadian phenotypes in healthy humans

Gene	*Chromosome location*	*SNP-ID (major/minor alleles)*	*Estimated allele frequencies*	*Main suggested genotype-dependent differences*
ADA	20q13.12	rs73598374 (G/A)	94:6	– More SWS in G/A versus G/G – Elevated <5 Hz activity in G/A versus G/G in NREM sleep
ADORA2A	22q11.23	rs5751876 (C/T)	60:40	– Elevated ~7–10 Hz activity in C/C versus T/T in NREM – Sleep, REM sleep, and wakefulness
COMT	22q11.21	rs4680 (G/A)	51:49	– Elevated ~11–13 Hz activity in G/G versus A/A in NREM – Sleep, REM sleep, and wakefulness
CLOCK	4q12	rs1801260 (T/C)	73:27	– Increased evening preference in C/C versus T-allele carriers
PER1	17p13.1	rs2735611 (T/C)	82.5:17.5	– Increased morning preference in C-allele carriers
PER2	2q37.3	rs2304672 (C/G)	84:16	– Increased morning preference in G-allele carriers
PER3	1p36.23	rs57875989 del (3031–3084 nt)	66:34	– More SWS in $PER3^{5/5}$ versus $PER3^{4/4}$ – Elevated 1–2 Hz activity in NREM sleep and 7–10 Hz activity in REM sleep in $PER3^{5/5}$ versus $PER3^{4/4}$
AA-NAT	17q25.1	rs4238989 (G/C)	51:49	– Preferred late/short sleep in C-allele carriers

Gene: National Center for Biotechnology Information (NCBI) gene symbol. SNP-ID number: Single nucleotide polymorphism reference number. Allele frequencies may vary considerably among different ethnic populations. Values refer to published data from mainly white populations (except the values for *AA-NAT*, which are derived from a Japanese population).

A_{2A} receptor-mediated signal transduction enhances EEG θ/α-activity in vigilance/sleep state-unspecific manner.

544G>A Polymorphism of Catechol-*O*-Methyltransferase (*COMT*) Gene

Preclinical studies show that binding of adenosine to A_{2A} receptors affects dopamine release in the cerebral cortex. The enzyme catechol-*O*-methyltransferase (*COMT*) plays an important role for the breakdown of cortical catecholamines. The human *COMT* gene is also located on chromosome 22, and contains a functional 544G>A polymorphism that alters the amino acid sequence of COMT protein at codon 158 from valine (Val) to methionine (Met) (SNP-ID number: rs4680). Individuals homozygous for the Val allele have more COMT protein in postmortem brain tissue than individuals with two Met alleles. Moreover, individuals homozygous for the Val allele show higher COMT activity and lower dopaminergic signaling in prefrontal cortex than Met/Met homozygotes. Sleep variables and the sleep EEG response to sleep deprivation do not differ between male carriers of Val/Val and Met/Met genotypes. By contrast, the variation in the *COMT* gene is associated with consistently lower EEG activity in the α-range in NREM sleep, REM sleep, and wakefulness in Val/Val homozygotes when compared to Met/Met homozygotes (particularly in 11–13 Hz band). This difference is present in baseline and recovery nights after sleep deprivation, and persists after administration of the stimulant modafinil. By contrast, the polymorphism profoundly affects the efficacy of modafinil to improve impaired well-being and cognitive functions after prolonged wakefulness.

Polymorphisms of Circadian Locomotor Output Cycles Kaput (*CLOCK*) Gene

A rare proline-to-arginine amino acid change at codon 385 of the transcription factor hDEC2 was recently associated with short sleep in a family-association study. On the other hand, tightly controlled studies of the temporal profiles of nocturnal melatonin and cortisol levels, body temperature, and subjective sleepiness suggest that the circadian pacemaker programs a longer biological night in physiological long sleepers (habitual sleep duration >9 h) than in physiological short sleepers (habitual sleep duration <6 h). Thus, genetic differences in clock genes may contribute to the large variation in habitual sleep duration. Indeed, the distinct combination of two gene variants (SNP-ID numbers: rs12649507 and rs11932595) of the canonical clock gene 'circadian locomotor output cycles kaput' (*CLOCK*) located on chromosome 4 was recently proposed to associate with long sleep (>8.5 h) in two independent European populations.

Concerning circadian aspects of sleep, it was first studied whether a rare genetic variation of *CLOCK* affects diurnal preference in middle-aged adults. It was suggested that homozygous C-allele carriers of the 3111T>C polymorphism (SNP-ID number: rs1801260) have increased evening preference for mental activities and sleep, with delays ranging from 10 to 44 min when compared to individuals carrying the T-allele. This SNP may affect the stability and half-life of messenger RNA and, thus, alter the protein level that is finally translated. Nevertheless, while similar results to the first study were found in a Japanese population, newer reports in European and Brazilian samples failed to confirm the association between genetic variation in *CLOCK* and diurnal preference.

2434T>C Polymorphism of Period1 (*PER1*) Gene

Mouse Per1 and Per2 are importantly involved in maintaining circadian rhythmicity, and possible associations between variation in these genes and diurnal preference were also investigated in humans. Screening for missense mutations and functional or synonymous polymorphisms in promoter, 5′- and 3′-UTR, and coding regions of the *PERIOD1* (*PER1*) gene located on chromosome 17 in volunteers with extreme diurnal preference and patients with delayed sleep phase syndrome (DSPS) initially remained unsuccessful. By contrast, the distribution of the T and C alleles of a silent 2434T>C polymorphism in exon 18 of PER1 (SNP-ID number: rs2735611) was

found to differ between extreme evening and morning types. More specifically, the frequency of the C-allele was roughly half in subjects with extreme evening preference (12%) compared with subjects with extreme morning preference (24%). This polymorphism may be linked to another functional polymorphism or directly affect *PER1* expression at the translational level.

111C>G Polymorphism of Period2 (*PER2*) Gene

A missense mutation in the human *PER2* gene on chromosome 2 currently provides the most striking example of a direct link between genetic variation in a clock gene and changed circadian rhythms. Linkage analyses in families afflicted with FASPS revealed associations with functional polymorphisms of *PER2* that cause altered amino acid sequences in regions important for protein phosphorylation, and a mutation in the protein kinase CK1δ. The subsequent finding that CKIδ can regulate a circadian period through Per2 in a transgenic mouse model expressing the human FASPS mutation provided further evidence that this gene is importantly involved in the mechanisms of circadian rhythm regulation in humans. In accordance with these findings, a 111C>G polymorphism located in the 5′-UTR of *PER2* (SNP-ID number: rs2304672) modulates diurnal preference in healthy volunteers. Thus, the G-allele is significantly more prevalent in subjects with extreme morning preference (14%) than in individuals with extreme evening preference (3%). Computer simulation predicted that the G-allele has different secondary RNA structure than the C-allele, and that the two transcripts may be differently translated.

Variable Number Tandem Repeat Polymorphism of Period3 (*PER3*) Gene

A 54-nucleotide sequence in the coding region of the clock gene *PERIOD3* (*PER3*) located on human chromosome 1 is repeated in either four or five units (SNP-ID number: rs57875989). The repeated segments are translated into numerous potential phosphorylation sites and may alter post-translational modification and stability of PER3 protein. Homozygous carriers of the long-repeat genotype fall asleep more rapidly and show more SWS than homozygous 4-repeat individuals. In addition, in recovery sleep after sleep deprivation, REM sleep is reduced in $PER3^{5/5}$ individuals compared to $PER3^{4/4}$ homozygotes. Not only sleep architecture, but sleep EEG profiles are affected by this polymorphism. The carriers of the $PER3^{5/5}$ genotype have higher EEG activity in the δ-range (1–2 Hz) in NREM sleep and in the θ/α-range (7–10 Hz) in REM sleep when compared to the $PER3^{4/4}$ genotype. Moreover, the increase in a central EEG derivation in slow-wave energy (i.e., power within 0.5–4.5 Hz accumulated over all epochs of stage 2–4 sleep in the first two NREM sleep episodes) after acute sleep restriction is slightly elevated in adults carrying the $PER3^{5/5}$ genotype compared to $PER3^{4/5}$ and $PER3^{4/4}$ allele carriers.

The variable number tandem repeat (VNTR) polymorphism of *PER3* also appears to modulate morning and evening preference. In European and Brazilian populations, the 5-repeat allele was associated with morning preference, whereas the 4-repeat allele was more prevalent in subjects with evening preference.

Finally, the decline of performance on cognitive tasks testing executive functions after one night without sleep may be more rapid in $PER3^{5/5}$ individuals than in $PER3^{4/4}$ individuals. Taken together, this VNTR may alter the dynamics of sleep homeostasis and through its interaction with the circadian system differentially affect performance impairment during prolonged wakefulness.

Polymorphisms of Arylalkylamine *N*-Acetyltransferase (*AA-NAT*) Gene

The gene encoding arylalkylamine *N*-acetyltransferase (*AA-NAT*) is located on human chromosome 17. This enzyme plays a key role in melatonin biosynthesis and may, thus, be important for diurnal preference and circadian rhythm disturbances. Comparison between a Japanese population of 50 outpatients diagnosed with DSPS and 161 unrelated healthy controls suggested that the frequency of a seldom occurring threonine allele at codon 129 is significantly higher in patients than in controls. However, this association was not confirmed in a Brazilian population where virtually no allelic variation at this position was found. In a small study conducted in Singapore, it was suggested that a commonly occurring, silent −263G>C polymorphism of *AA-NAT* (SNP-ID number: rs4238989) modulates sleep timing and sleep duration among healthy students.

See also: **Background:** Concepts of Fatigue, Sleepiness, and Alertness; Neurotransmitters and Neuropharmacology of Sleep/Wake Regulations; Normal Human Sleep; **Chronobiology of Sleep:** Molecular and Genetic Bases for the Circadian System; Sleep Homeostasis; **Critical Theoretical and Practical Issues:** Future of Sleep Research; **Extrinsic Factors Affecting Sleep Loss/Deprivation:** Effects of Light and Temperature on Sleep in Adults and the Elderly; **Features, Factors, and Characteristics of CRSD:** Circadian Rhythm Sleep Disorder: Genetic and Environmental Factors; **Instrumentation and Methodology:** Overview of Objective Tests to Assess Excessive Sleepiness; **Intrinsic Factors Affecting Sleep Loss/Deprivation:** Age and Individual Determinants of Cognitive Effects of Sleep Loss; Biochemical Correlates of Prolonged Wakefulness; Changes in Gene Expression; Electroencephalographic and Neurophysiological Changes; Homeostatic and Circadian Influences; **Pharmacology of Sleep:** Basic Pharmacologic Mechanisms of Sleep; Endogenous Sleep-Promoting Substances; **Sleep and the Nervous System:** Neurochemistry of Sleep; **Sleep Deprivation/Fragmentation Paradigms:** Acute Sleep Deprivation; Partial and Sleep-Stage-Selective Deprivation.

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