Sleep Genetic Pathway Reference

Circadian, homeostatic, architectural, autonomic, and breathing genetics of sleep

10 Functional Categories • ~120 SNPs Catalogued

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of sleep regulation in humans, the genes that govern the circadian clock, sleep homeostasis, sleep architecture, the wake-promoting orexin system, the autonomic and cardiovascular adjustments that occur during sleep, and the genetic contributions to obstructive sleep apnea. For each gene, the well-studied common and rare variants are catalogued with their functional consequence, cofactor or substrate dependencies (where applicable), and the supplement, dietary, behavioral, or pharmacologic targets that map to each pathway node. It is intended for clinicians, researchers, or interested non-specialists who want a compact pathway primer that can later be paired with personal genotype results.

All variant interpretations are based on published GWAS literature, peer-reviewed mechanistic studies, and meta-analyses through 2026. Sources include Nature, Nature Communications, Nature Genetics, Cell, Science, PNAS, Sleep, Journal of Neuroscience, Cerebral Cortex, NEJM, PLoS Genetics, PLoS ONE, Diabetes, OMIM, ClinVar, and the GWAS Catalog. The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations.

Sleep is one of the most polygenic and pleiotropic phenotypes in human genetics. Most common variants catalogued here confer small individual effects (per-allele changes of 0.5–3 minutes of sleep, or odds ratios of 1.05–1.30 for binary outcomes); clinical significance arises from cumulative patterns and gene-environment interactions. A small number of rare, large-effect Mendelian variants — notably PER2 S662G, BHLHE41 P384R, CRY1 c.1657+3A>C, CSNK1D T44A, and HLA-DQB1*06:02 — have been catalogued in family pedigrees and confer dramatic phenotypes (4-hour phase shifts, ~6-hour habitual sleep without deficit, narcolepsy with cataplexy). These are included for completeness even though their population frequency is below 1%.

Heritability of sleep phenotypes from twin and biobank studies: habitual sleep duration h^2 = 9–45% (Dashti et al., Nat Commun 2019; SNP-h^2 9.8%); insomnia symptoms h^2 = 21% (Jansen et al., Nat Genet 2019); chronotype h^2 = 12–47% (Lane et al., Nat Commun 2016); slow-wave EEG features 96% within-individual stability with substantial heritable component (De Gennaro et al., Ann Neurol 2008); restless legs syndrome h^2 ~50%; obstructive sleep apnea family heritability 25–87%, SNP-liability h^2 ~16% (Strausz et al., medRxiv 2025).

2. Pathway Biology

2.1 Two-process model

Sleep–wake cycling is generated by the interaction of two clocks. Process C is the circadian oscillator: a transcription–translation feedback loop in the suprachiasmatic nucleus (SCN) and every peripheral cell. CLOCK and BMAL1 (ARNTL) heterodimers bind E-box elements and activate transcription of PER1, PER2, PER3, CRY1, and CRY2; the PER and CRY proteins accumulate in the cytoplasm, are phosphorylated by casein kinases 1δ (CSNK1D) and 1ε (CSNK1E), enter the nucleus, and inhibit CLOCK/BMAL1 activity. PER protein degradation is timed by phospho-priming and ubiquitination via FBXL3/FBXL21, setting the ~24-hour period. Secondary loops involve the orphan nuclear receptors REV-ERBα/β (NR1D1/2) and RORα/β/γ, which oppositely regulate BMAL1 transcription, and the bHLH repressors DEC1 and DEC2 (BHLHE40/BHLHE41), which compete with CLOCK/BMAL1 at E-boxes. The clock entrains to environmental light through melanopsin-expressing retinal ganglion cells (OPN4) projecting to the SCN, which signals the pineal gland to release melatonin acting on MTNR1A and MTNR1B receptors.

Process S is the homeostatic sleep-pressure system: it tracks how long the brain has been awake. Adenosine accumulates extracellularly during wakefulness from neuronal ATP hydrolysis, is degraded by adenosine deaminase (ADA), and acts at A1 receptors (ADORA1) on wake-promoting neurons and A2A receptors (ADORA2A) on ventrolateral preoptic GABAergic sleep-promoting neurons. Caffeine is a non-selective ADORA1/ADORA2A antagonist. Prostaglandin D2 also accumulates and signals through DP1 receptors. The integrated readout of Process S is slow-wave activity (SWA, 0.5–4 Hz delta power) in NREM sleep, which scales with prior wake duration and dissipates exponentially across the night.

2.2 Sleep-wake switch and architecture

When sleep pressure exceeds the circadian wake drive, GABAergic neurons of the ventrolateral preoptic nucleus (VLPO) inhibit the wake-promoting orexin/hypocretin (HCRT) neurons of the lateral hypothalamus and the noradrenergic locus coeruleus. Loss of VLPO inhibition or HCRT neurons reverses this switch toward sustained wakefulness. Within sleep, the brain cycles through NREM stages N1, N2 (defined by sleep spindles, generated thalamically and modulated by COMT and dopaminergic signaling), and N3 (slow-wave sleep, dominated by cortical delta oscillations and BDNF-dependent synaptic renormalization), and REM (defined by rapid eye movements, theta-rich EEG, muscle atonia from glycine/GABA at spinal motoneurons, and dreaming). Cholinergic REM-on neurons in the pons (LDT/PPT) and noradrenergic/serotonergic REM-off neurons (LC, raphe) reciprocally generate REM. NREM and REM alternate in ~90-minute cycles, with N3 dominating the first half of the night and REM dominating the last.

2.3 Autonomic and cardiovascular sleep physiology

Sleep stages drive characteristic autonomic shifts. NREM is parasympathetic-dominant: heart rate falls, high-frequency HRV (RMSSD, HF power) rises, blood pressure dips by 10–20%, and respiration slows and stabilizes. REM is sympathetic-storm-like: heart rate and blood pressure surge intermittently, HRV becomes erratic, and the upper-airway dilator muscles paradoxically lose tone — the substrate for REM-predominant obstructive events. Loss of nocturnal blood-pressure dipping is a strong marker of cardiovascular risk and is genetically modifiable through HRV loci (GNG11, RGS6, HCN4, KIAA1755, NDUFA11) acting at the sinoatrial node.

2.4 Sleep-disordered breathing

Obstructive sleep apnea (OSA) results from repetitive collapse of the pharyngeal airway during sleep, producing intermittent hypoxia, sympathetic surges, sleep fragmentation, and chronic systemic inflammation (NLRP3, RAGE, CRP activation). Genetic risk for OSA is dominated by obesity loci — chiefly FTO rs1421085, MC4R, and other BMI-regulating variants — but a smaller set of BMI-independent loci (NACA, GSDMC, ABCC9, synaptic-signaling loci) point to direct neuromuscular and craniofacial contributions. The 2025 GWAS meta-analysis in 1.6 million participants identified 147 genome-wide significant loci with SNP-h² of 16% (Strausz et al., medRxiv 2025).

2.5 Pathway-cross-talk with metabolic, cardiovascular, and neurodegenerative biology

Sleep biology connects to virtually every aging-relevant pathway. MTNR1B variants link circadian timing to insulin secretion (Lyssenko et al., Nat Genet 2009; Dashti et al., 2018). Growth hormone and IGF-1 secretion is sleep-locked to N3 slow-wave sleep. Glymphatic clearance of Aβ and tau peptides is maximal during NREM (Xie et al., Science 2013), implicating sleep in dementia risk. mTOR is suppressed during NREM, intersecting with the rapamycin/longevity axis. Endothelial NO production and nocturnal blood-pressure dipping are sleep-stage-dependent. OSA-induced intermittent hypoxia upregulates NLRP3 and RAGE, intersecting with inflammation pathways. The HLA class II haplotype DQB1*06:02 underlies most narcolepsy type 1, intersecting with autoimmune genetics.

3. Functional Categories: Genes, Variants, and Cofactors

3.1 Core circadian clock — TTFL machinery

The transcription–translation feedback loop (TTFL) is the molecular pacemaker of the circadian clock. CLOCK and BMAL1 (ARNTL) form heterodimers and activate E-box-driven transcription of PER1/2/3, CRY1/2, NR1D1, and DEC1/2. PER and CRY proteins are phosphorylated by CK1δ (CSNK1D) and CK1ε (CSNK1E), targeting them for ubiquitination by SCF-FBXL3 and proteasomal degradation. Casein kinase phosphorylation kinetics set the ~24-hour period; mutations that alter phosphorylation rates (PER2 S662G, CSNK1D T44A) produce dramatic

circadian phenotypes. Variants in this category primarily affect circadian phase (chronotype) and the timing of sleep onset and offset rather than total sleep duration.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
CLOCK	rs1801260 (3111T>C)	3'-UTR; miR-182 binding site; C allele increases CLOCK and PER2 mRNA stability	Katzenberg 1998; Mishima 2005; Ozburn 2016; Schuch 2018	C → eveningness; ~10–44 min phase delay
CLOCK	rs11932595	Intronic; sleep duration GWAS	Dashti 2019 Nat Commun	Modest
BMAL1 / ARNTL	rs7950226, rs6486121	Promoter / intronic; BMAL1 expression and chronotype	Woon 2007; Allebrandt 2010	Small
PER1	rs2585405, rs2253820	Synonymous and intronic; chronotype association	Carpen 2006 J Sleep Res	Mixed
PER2	rs934945 (V647G), rs2304672	Common coding/UTR; modest chronotype	Carpen 2005	Modest
PER2	S662G (rs121908635) — RARE, ClinVar pathogenic	CK1ε binding site; hypophosphorylation; ~4-h phase advance — FASPS1	Toh 2001 Science; OMIM 604348	Dominant; very rare; large effect
PER3	rs57875989 (VNTR 4/5)	Coding 54-bp tandem repeat; affects CK1 phosphorylation sites and homeostatic SWS pressure	Archer 2003, 2010; Viola 2007 Curr Biol; Hasan 2014 FASEB J	5/5 → morning + higher SWS; 4/4 → evening, more cognitive vulnerability to sleep loss
PER3	rs228697	Missense; chronotype, N24SWD (Japanese)	Hida 2014	Population-specific
CRY1	rs2287161, rs8192440	Common intronic; chronotype	Hida 2010, 2014	Small
CRY1	rs184039278 (c.1657+3A>C, CRY1Δ11) — RARE	Splice variant; in-frame deletion of exon 11; gain-of-function inhibition of CLOCK/BMAL1; +0.5-h period	Patke 2017 Cell; Smieszek 2021	Dominant; ~0.6% MAF; familial

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
				DSPD
CRY2	rs10838524, rs11605924	Sleep duration / chronotype GWAS	Lane 2017	Modest
CSNK1E	rs135745	Tag SNP; circadian period	Takano 2004	Modest
CSNK1D	T44A (rs104894561), H46R — RARE	Reduced CK1δ kinase activity; FASPS2 + migraine comorbidity	Xu 2005 Nature; Brennan 2013; OMIM 615224	Dominant; very rare
NR1D1 (REV-ERBα)	rs2071427	Intronic; secondary loop	Severinsen 2006	Modest
TIMELESS	c.1208C>T region	FASPS4 candidate	OMIM 620015	Rare

Cofactors: ATP and Mg^{2+} drive CK1δ/ε phosphorylation. The FASPS-region of PER2 and the FASP region in PER1 are phosphoserine motifs whose modification is rate-limiting for clock period. Proteasome activity (ubiquitin-dependent) is required for PER turnover. Note that core-clock variants modulate timing more than duration; PER3 VNTR is the only common variant in this set with a robust homeostatic-pressure effect. Population frequency of rare FASPS / DSPD alleles is well below 1%; their inclusion in this reference is for completeness given their large effect when present.

3.2 Clock output, repressors, and entrainment

The DEC repressors (BHLHE40 / BHLHE41) compete with CLOCK/BMAL1 at E-boxes and provide an additional negative limb. BHLHE41 / DEC2 is a direct transcriptional repressor of prepro-orexin (HCRT); loss of repression increases orexin signaling and reduces sleep need (familial natural short sleep). Melatonin output from the pineal gland feeds back through MT1 and MT2 receptors (MTNR1A, MTNR1B); the MT2 receptor is co-expressed in pancreatic beta cells and connects circadian timing to glucose tolerance. Light entrains the clock through melanopsin (OPN4) in retinal ganglion cells projecting to the SCN.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
BHLHE41 (DEC2)	P384R (P385R, rs121912617) — RARE	Loss of repression of CLOCK/BMAL1 and prepro-orexin; increased orexin tone	He 2009 Science; Hirano 2018 PNAS	Dominant; very rare; ~6 h habitual sleep without deficit (FNSS1)

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
BHLHE41	Y362H, P384Q, A380S — RARE	Other rare missense; reduce DEC2 repression	Pellegrino 2014 Sleep; Shi 2019	Rare
BHLHE40 (DEC1)	rs2042400	Limited GWAS evidence	—	Speculative
MTNR1B	rs10830963	Intronic eQTL; G allele increases MT2 in beta cells; prolonged morning melatonin (+41 min); delayed melatonin offset (+1.37 h); impaired glucose-stimulated insulin secretion	Lyssenko 2009 Nat Genet; Lane 2016 Diabetes; Dashti 2018	G allele → impaired β-cell function, ↑ T2D risk; misalignment when food coincides with morning melatonin
MTNR1A	rs2119882	Promoter; modest sleep duration effect	Liu 2015	Modest
OPN4 (melanopsin)	rs1079610 (P10L)	Coding; light sensitivity, seasonal mood	Roecklein 2009, 2012	Mixed
RORA	rs782931	Intronic; chronotype Mendelian randomization	Lane 2016	Modest

Cofactors: melatonin synthesis requires tryptophan, vitamin B6 (P5P), and SAM (for HIOMT methylation). Light at night (especially blue 460–480 nm) suppresses melatonin via OPN4. Practical levers: morning bright light exposure to entrain the clock; evening blue-light avoidance to preserve melatonin onset; food-timing alignment to avoid eating during high-melatonin windows in MTNR1B G-allele carriers.

3.3 Sleep duration and propensity (common-variant GWAS loci)

Habitual sleep duration is highly polygenic. The largest GWAS to date (Dashti et al. Nat Commun 2019, n = 446,118 UK Biobank) identified 78 loci, with the strongest at PAX8 and VRK2. Most per-allele effects are 0.5–3 minutes, but 5% of carriers of the most sleep-extending alleles report 22 minutes more sleep than the 5% with fewest. Separate GWAS have been performed for short-sleep and long-sleep phenotypes, with overlapping but not identical signals. The most-replicated locus, PAX8, is adjacent to the chromosome 2 fusion site that is unique in human evolution among hominids.

Gene / locus	Variant / rsID	Functional consequence	Source	Direction / effect size
PAX8	rs62158211, rs1191685	Thyroid-specific transcription factor; nearby regulatory variants	Dashti 2019 Nat Commun; Gottlieb 2015 Mol Psychiatry	+2.4–2.7 min/allele; consistent across 4 GWAS
VRK2	rs17190618, rs1380703	Serine-threonine kinase; pleiotropy with schizophrenia, depression, epilepsy	Jones 2016; Austin-Zimmerman 2023 Nat Commun	~+1.5 min/allele
FBXL13	rs2289917	F-box ubiquitin ligase	Dashti 2019	Sleep duration
KSR2	rs1380703 region	Kinase suppressor of Ras 2	Austin-Zimmerman 2023	Long-sleep
FTO	rs1421085	Adipocyte adipogenesis; mediates obesity-driven short sleep	Dashti 2019	C allele → ↑ BMI → short sleep
MEIS1	rs113851554	Homeobox transcription factor; opposing effects on REM (+) and NREM (−)	Dashti 2025 Nat Commun (medRxiv)	+9.05 min REM/allele
KCNK9	rs2542425	K2P potassium channel; NREM duration	Dashti 2025	+1.21 min NREM/allele
HCRTR2	rs2653350	Orexin receptor 2; sleepiness	Dashti 2019; Jansen 2019	Modest
DRD2	rs2734849 region	Dopamine D2 receptor; sleep duration GWAS	Lane 2017	Small
GABRA2	rs497932	GABA-A receptor α2 subunit; sleep duration	Dashti 2019	Small

These loci individually have small effects but in aggregate explain ~9.8% of sleep duration variance (SNP-heritability). Polygenic risk scores for sleep duration are portable across populations (Pyykkonen Clocks Sleep 2023). The biological pathways enriched are GABAergic and glutamatergic neurotransmission, thyroid hormone signaling, and circadian regulation.

3.4 Sleep homeostasis and EEG architecture

Sleep homeostasis is most directly assessed through slow-wave activity (SWA, 0.5–4 Hz delta power) in NREM. Two genes — ADA and ADORA2A — have been validated mechanistically and replicated in multiple cohorts. ADA rs73598374 reduces adenosine clearance, increasing

SWA and sleep depth. ADORA2A rs5751876 modulates the A2A receptor and individual sensitivity to caffeine-induced sleep disruption. BDNF Val66Met affects activity-dependent BDNF secretion and modulates sleep slow-wave activity, consistent with the synaptic-homeostasis hypothesis. COMT Val158Met modulates prefrontal dopamine catabolism and has stable, replicated effects on alpha and sigma EEG oscillations and sleep-spindle density.

Gene	Variant / rsID	Functional consequence	Source	Direction
ADA	rs73598374 (c.22G>A, D8N)	Reduces adenosine deaminase activity ~30%; slows adenosine clearance	Rétey 2005 PNAS; Bachmann 2012 Cereb Cortex; Mazzotti 2012 PLoS ONE	A allele → deeper SWS, higher delta power, more efficient sleep
ADORA2A	rs5751876 (1976T>C, syn)	Tag SNP for haplotype affecting A2A receptor function and caffeine response	Rétey 2007; Bodenmann 2012; Erblang 2019 Genes	C/C → caffeine-induced insomnia; T allele → caffeine anxiety
ADORA2A	rs2298383, rs4822492, rs2236624, rs3761422	Haplotype with rs5751876 modulates total sleep time and insomnia risk	Erblang 2019	Haplotype-level
ADORA1	rs6701725, rs2228079	A1 receptor; modest sleep depth effects	Rétey 2007	Modest
BDNF	rs6265 (Val66Met)	Met allele reduces activity-dependent BDNF secretion ~30%	Bachmann 2012 Sleep; Egan 2003 Cell	Met → reduced SWA, slower SWA initiation/termination
COMT	rs4680 (V158M)	Met allele → ~3–4× lower COMT activity → higher prefrontal DA	Bodenmann 2009 J Neurosci; Goel 2011 PLoS ONE; Raduga 2018	Val/Val → reduced fast-spindle density; Met/Met → vulnerability to chronic partial SD

Gene	Variant / rsID	Functional consequence	Source	Direction
PRNP	M129V (rs1799990)	Prion gene; modulates sleep architecture; FFI penetrance modifier	Goldfarb 1992	M/M extends FFI age-of-onset
HOMER1	rs9389571	Glutamate signaling; small EEG-power effects	Mongrain 2010	Speculative

Cofactors: ADA requires Zn^{2+}; ADORA receptors signal through Gαs (A2A) or Gαi (A1) and intracellular cAMP. BDNF signals through TrkB and requires zinc and B6 for synthesis. COMT requires SAM as methyl donor and Mg^{2+}; SAM availability depends on folate (5-MTHF), B12, methionine, and B6 (this connects to the Homocysteine Regulation pathway). Practical levers: ensure SAM cofactors (5-MTHF, methylcobalamin, P5P) for COMT-Met carriers; zinc for BDNF/ADA; caffeine-timing adjustment for ADORA2A-C/C carriers.

3.5 Wake, arousal, and narcolepsy susceptibility

Wakefulness is maintained by the orexin/hypocretin (HCRT) system in the lateral hypothalamus, projecting to the locus coeruleus, raphe, tuberomammillary nucleus, and basal forebrain. Loss of orexin neurons causes narcolepsy type 1 (NT1) with cataplexy. NT1 is highly genetic but the mechanism is autoimmune: ~98% of NT1 cases carry the HLA class II haplotype DQA1*01:02 ~ DQB1*06:02 (DQ0602 heterodimer), with OR ~250 vs controls. Non-HLA loci converge on T-cell receptor genes (TRA, TRB) and other autoimmune-related loci. Onset is typically in adolescence and can follow upper respiratory infection (H1N1 influenza or Streptococcus pyogenes), supporting a molecular mimicry hypothesis (Mahlios et al., Curr Opin Immunol 2013; Ollila et al., Nat Commun 2023).

Notably, DQB1*06:02 is present in ~25% of the general European population without narcolepsy, so the haplotype is necessary but not sufficient. Definitive HLA typing requires HLA imputation (HIBAG, HLA-LA) or sequencing; single-SNP tag variants in tight LD (rs9271117, rs2858890) provide a first-pass screening with sensitivity ~95% in Europeans.

Gene / locus	Variant / allele	Functional consequence	Source	Risk / direction
HLA-DQB1	*06:02 (DQ0602; tag SNP rs9271117 / rs2858890)	MHC-II antigen presentation to autoreactive CD4+ T cells targeting orexin neurons	Mignot 2001; Tafti 2014; Ollila 2023 Nat Commun	OR ~250 NT1; 2–4× higher in homozygotes
HLA-DQB1	*03:01	Modifier of NT1 risk	Han 2013 PLoS Genet	OR 1.3–2.9
HLA-DQB1	*05:01, *06:01, *06:03	Protective alleles	Han 2013	OR 0.02–0.56

Gene / locus	Variant / allele	Functional consequence	Source	Risk / direction
TRA	rs1154155, rs1263647	T-cell receptor alpha chain repertoire	Hallmayer 2009 Nat Genet; Ollila 2023	OR ~1.3
TRB	rs9648789	T-cell receptor beta chain	Han 2013	OR 0.77
P2RY11	rs2305795	eQTL; modulates ATP-induced cell death in CD8+ T and NK cells	Kornum 2011 Nat Genet	Replicated
CTSH	rs34593439	Cathepsin H; lysosomal protease	Faraco 2013 PLoS Genet	OR ~1.3
TNFSF4 (OX40L)	rs7553711	T-cell costimulation	Kornum 2011; Han 2013	OR ~1.2
ZNF365	rs10995245	Function unclear; replicated in Europeans and Asians	Han 2013	OR ~1.2
IFNAR1 / IL10RB	rs2252931	Type-I interferon receptor	Han 2013	OR ~0.75
CCR1 / CCR3	rs3181077	Chemokine receptor; age-of-onset modifier	Toyoda 2015	Small
HCRT (orexin)	rare missense (e.g. L16R)	Disrupts orexin processing; very rare familial NT	Peyron 2000 Nat Med	Rare
HCRTR2	rs2653350	Orexin receptor 2; sleepiness GWAS	Lane 2017; Dashti 2019	Modest

*Most variants in this category are immune-related and intersect with the Inflammation/Immune pathway. DQB1*06:02 is also associated with anti-streptococcal autoimmunity and protection against type 1 diabetes. Cofactors are not directly modifiable for autoimmune destruction; clinical management is through orexin agonists (in development), modafinil, sodium oxybate, and selective serotonin–norepinephrine reuptake inhibitors for cataplexy.*

3.6 Insomnia and arousal fragmentation

The largest insomnia GWAS to date (Watanabe et al., Nat Genet 2022, n = 2.3 million) identified 200+ genome-wide-significant loci with the strongest signals at PTPRD, MEIS1, BTBD9, LSAMP, and CYCL1. The MEIS1 locus is particularly interesting because it shows pleiotropy across insomnia, restless legs syndrome, and periodic limb movements during sleep (PLMS). The MEIS1 risk haplotype rs12469063/rs2300478 (GG/GG) reduces MEIS1 mRNA and protein expression in thalamus and basal ganglia (Xiong et al. 2009; Spieler et al. Genome Res 2014), explaining a portion of dopaminergic dysfunction in RLS. PTPRD is also associated with restless legs syndrome and type 2 diabetes — a shared genetic architecture across sleep-fragmentation phenotypes and metabolic disease.

Gene	Variant / rsID	Functional consequence	Source	Direction
MEIS1	rs113851554	Strongest insomnia signal; reduced enhancer activity in basal ganglia	Jansen 2019 Nat Genet; Spieler 2014 Genome Res; Salminen 2019	T → OR 1.26 insomnia, much higher OR for RLS
MEIS1	rs12469063, rs2300478 (haplotype)	Risk haplotype GG/GG reduces MEIS1 mRNA/protein in thalamus and LCL	Xiong 2009 PNAS; Catoire 2018 Sci Rep	OR 1.6–2.5 RLS
BTBD9	rs9296249, rs9357271	RLS + insomnia; PLMS; iron-related dopaminergic regulation	Stefansson 2007 NEJM; Winkelmann 2007 Nat Genet	OR ~1.5 RLS
PTPRD	rs1975197	Top insomnia GWAS gene; pleiotropy with RLS, T2D	Schormair 2008; Watanabe 2022	Replicated
MAP2K5 / SKOR1	rs6494696, rs3784709	RLS; SKOR1 expression downstream of MEIS1	Winkelmann 2007; Catoire 2018	Modest
LSAMP	rs2710423	Insomnia; MDD/suicidal-behavior pleiotropy	Watanabe 2022	Modest
TOX3	rs3104767	RLS; PLMS	Winkelmann 2011	Modest
CYCL1 (LSAMP region)	rs5922858	Insomnia symptoms; alcohol-dependence pleiotropy	Lane 2017	Modest
TMEM132E	rs145258459	Insomnia + anxiety, panic disorder pleiotropy	Lane 2017	Modest
GRIA1	tag SNPs	AMPA-type glutamate receptor; insomnia GWAS	Watanabe 2022	Modest
DRD2	rs2734849	Dopamine D2; sleep duration / insomnia overlap	Lane 2017	Modest

Cofactors: dopaminergic and iron metabolism. Iron is rate-limiting for tyrosine hydroxylase (the synthetic enzyme for dopamine) and is reduced in the substantia nigra of RLS patients. Iron supplementation often improves RLS symptoms when ferritin is below ~75 ng/mL. The MEIS1/BTBD9/PTPRD axis converges on dopaminergic deficit; first-line RLS pharmacology is dopaminergic agonists (pramipexole, ropinirole) or alpha-2-delta ligands (gabapentin, pregabalin). Ferritin, transferrin saturation, and serum iron should be assessed in RLS or PLMS workup.

3.7 REM and NREM stage architecture

Until 2025, GWAS for sleep traits used self-reported questionnaire data, which conflates many subdimensions of sleep into single phenotypes. The 2025 device-measured sleep GWAS in 80,013 UK Biobank participants (Dashti et al., Nat Commun 2026 / medRxiv 2025.07.17) was the first to dissect REM and NREM duration genetically. Twenty independent loci were identified, including five for REM-specific duration, three for NREM-specific duration, one for both, and several for overall efficiency. The most striking finding was opposing effects of MEIS1 on REM and NREM, suggesting MEIS1 governs the REM/NREM balance rather than total sleep time.

Gene / locus	Variant / rsID	REM / NREM effect	Source	Direction
MEIS1	rs113851554	+9.05 min REM/allele; opposite effect on NREM	Dashti 2025 Nat Commun (medRxiv)	Strong; intolerant to LoF
MEIS1	rs4544423, rs182588061	Secondary independent REM signals	Dashti 2025	Modest
KCNK9	rs2542425, rs888346 (independent)	+1.21 min NREM/allele; secondary signal +0.98 min	Dashti 2025	Strong
GNG7	1p21.3 locus	REM duration	Dashti 2025	Modest
3p11.1	tag SNPs	REM duration	Dashti 2025	Modest
11q13.2 / 11q13.4	tag SNPs	REM duration	Dashti 2025	Modest
22q13.1	tag SNPs	REM duration	Dashti 2025	Modest
13q14.2	tag SNPs	NREM duration	Dashti 2025	Modest
14q22.3	tag SNPs	NREM duration	Dashti 2025	Modest
15q23	tag SNPs	NREM duration	Dashti 2025	Modest
8q24.3 (KCNK9 region)	rs2542425	Both REM and NREM	Dashti 2025	Strong

REM-specific genetic architecture is enriched for chromatin-remodeling and synaptic genes. NREM-specific architecture is enriched for ion-channel and glutamatergic transmission. MEIS1 stands out for its essential, intolerant-to-loss-of-function role in REM/NREM balance — it is one of few sleep loci where common variants have been linked to a clinically actionable phenotype (RLS) in the same gene where rare loss-of-function is embryonic-lethal.

3.8 Caffeine and sleep pharmacogenomics

Caffeine is the most widely consumed psychoactive substance and the most common iatrogenic cause of insomnia. Its sleep effects depend on two pharmacogenetic axes: pharmacokinetic clearance (CYP1A2 metabolizes >95% of ingested caffeine to paraxanthine) and pharmacodynamic receptor sensitivity (ADORA2A, the molecular target). CYP1A2 rs762551 (-163C>A) defines fast (A/A) vs slow (A/C, C/C) metabolizers; in non-smokers the genotype effect is moderate, but in smokers and chronic heavy coffee drinkers the A/A genotype shows ~1.6× higher enzyme activity (Sachse 1999; Cornelis 2006 JAMA). ADORA2A rs5751876 modifies sensitivity to caffeine-induced sleep disturbance independent of metabolism rate.

Gene	Variant / rsID	Functional consequence	Source	Direction
CYP1A2	rs762551 (-163C>A)	Intronic; A allele = high inducibility; C/C = slow metabolizer; ~95% of caffeine clearance	Sachse 1999; Cornelis 2006 JAMA; Cornelis 2011 PLoS Genet	C/C → caffeine half-life ~4× longer; ↑ MI risk on heavy intake; ↑ sleep disruption from afternoon caffeine
ADORA2A	rs5751876 (1976T>C)	Tag SNP for haplotype; modulates A2A receptor function	Rétey 2007; Byrne 2012 Sleep; Erblang 2019	C/C → greater caffeine-induced insomnia; T → caffeine-induced anxiety
ADORA2A	rs5751862, rs2298383, rs3761422, rs2236624, rs4822492	Haplotype with rs5751876 modulates total sleep time and insomnia risk in low-moderate caffeine consumers	Erblang 2019 Genes	Haplotype-level modifier
AHR	rs2472297	Aryl hydrocarbon receptor; modulates CYP1A2 induction	Cornelis 2011	Modest
NAT2	rs1799929	N-acetyltransferase 2; downstream caffeine metabolism	Cornelis 2011	Modest

Practical recommendations for caffeine pharmacogenomics: (1) CYP1A2 C/C (slow metabolizers) should restrict caffeine to before mid-morning; afternoon caffeine reliably disrupts sleep onset and SWS in this genotype; (2) CYP1A2 A/A may tolerate later caffeine but the

European Food Safety Authority 400 mg/day ceiling still applies; (3) ADORA2A C/C carriers experience greater sleep disruption per mg of caffeine independent of metabolism — these individuals benefit from total-dose reduction more than from timing changes; (4) inducers of CYP1A2 (smoking, cruciferous vegetables) accelerate clearance; inhibitors (oral contraceptives, fluvoxamine, ciprofloxacin) prolong it; (5) caffeine half-life increases with age, compounding genotype effects in older adults.

3.9 Autonomic and cardiovascular sleep physiology

Heart-rate variability (HRV) and nocturnal blood-pressure dipping are heritable cardiovascular phenotypes (h^2 ~30% from family studies). The first well-powered HRV GWAS (Nolte et al., Nat Commun 2017, n = 53,174) identified 17 SNPs at 8 loci, including non-synonymous variants in NDUFA11 and KIAA1755, eQTLs influencing GNG11, RGS6, and NEO1, and variants near the pacemaker channel HCN4. The shared theme is regulation of the sinoatrial node and the GIRK-channel pathway through which acetylcholine slows the heart. NREM sleep is parasympathetic-dominant, and the magnitude of HRV during NREM, as well as the depth of nocturnal BP dipping, are genetically modulated by these loci.

Gene	Variant / rsID	Functional consequence	Source	Direction
GNG11	rs10921075	G-protein γ11 subunit; eQTL in sinoatrial node; GIRK-channel signaling	Nolte 2017 Nat Commun	Higher HRV
RGS6	rs4899412	Regulator of Gαi signaling; SAN expression; eQTL	Nolte 2017	Higher HRV
HCN4	rs2680344	Hyperpolarization-activated funny current; cardiac pacemaker	Nolte 2017; den Hoed 2013	HRV; AF risk modifier
KIAA1755	rs6123471	Non-synonymous; cardiac SAN expression	Nolte 2017	HRV
NDUFA11	rs12974991, rs12974440	Mitochondrial complex I subunit; eQTL/mQTL	Nolte 2017	HRV
NEO1	rs10516649	Neogenin; eQTL	Nolte 2017	HRV
ADRB1	rs1801253 (R389G)	β1-adrenoceptor; nocturnal HR/BP response; β-blocker pharmacology	Sofowora 2003; Liu 2003	G allele → blunted β-blocker response
ADRB2	rs1042713 (R16G), rs1042714 (Q27E)	β2-adrenoceptor; nocturnal BP dipping; bronchodilator response	Diatchenko 2005	Mixed

Gene	Variant / rsID	Functional consequence	Source	Direction
NPPA / NPPB	rs5068, rs198389	Atrial natriuretic peptide; BP regulation	Newton-Cheh 2009	Modest
GIRK4 (KCNJ5)	rs8068318	G-protein-gated inward rectifier; SAN	Nolte 2017	HRV

These loci intersect with the Endothelial Health pathway (especially via ADRB1/ADRB2 and the NPPA/NPPB natriuretic axis) and with the Pharmacogenomics pathway (β-blocker response). Practical levers: exercise training, paced breathing, and mindfulness-based interventions reliably increase HRV and improve nocturnal dipping; magnesium and omega-3 may modestly improve HRV; sleep apnea treatment (CPAP) restores BP dipping. Genotype is informative for predicting β-blocker efficacy in patients with nocturnal hypertension.

3.10 Sleep-disordered breathing (obstructive sleep apnea)

OSA is highly heritable (family-based h^2 25–87%; SNP-h^2 16% on the liability scale). The 2025 GWAS meta-analysis (Strausz et al., medRxiv 2025) in 1.6 million participants identified 147 genome-wide significant loci, the strongest at FTO rs1421085 (the same locus that drives BMI). Most OSA risk is mediated through obesity, but a subset of loci remain significant after BMI adjustment, pointing to BMI-independent contributions: NACA, GSDMC, ABCC9, and several near synaptic-signaling genes (Wang et al., medRxiv 2026 — comprehensive genetic investigation). Heterogeneous pathways converge on three mechanistic axes: obesity (the dominant axis), neurological control of upper-airway dilator muscles, and craniofacial morphology.

Gene / locus	Variant / rsID	Functional consequence	Source	Direction
FTO	rs1421085 (T>C)	Largest OSA signal; alters IRX3/IRX5 expression in adipocytes; obesity-mediated	Strausz 2025 medRxiv; Claussnitzer 2015 NEJM	C → ↑ obesity → ↑ OSA
MC4R	rs17782313	Melanocortin 4 receptor; appetite regulation; obesity-mediated OSA	Locke 2015 Nat; Strausz 2025	Risk allele → ↑ OSA
NACA	rs2958127, rs4759254	Nascent polypeptide-associated complex α; OSA risk both with and without BMI adjustment	Strausz 2025; Wang 2026 medRxiv	Replicated
GSDMC	tag SNPs	Gasdermin C; OSA risk independent of BMI	Strausz 2025	Modest
TNFRSF1A	12p13 locus	TNF receptor; inflammatory contribution	Strausz 2025	Modest
ABCC9	rs2074312	K-ATP channel; respiratory pattern	Cade 2016	Suggestiv

Gene / locus	Variant / rsID	Functional consequence	Source	Direction
		control	AJHG	e
LPAR1	rs7030789	Lysophosphatidic acid receptor 1; identified in CARe African-American cohort	Cade 2016 AJHG	Population -specific
SLC6A4 (5-HTT)	5-HTTLPR L/S indel	Serotonin transporter; respiratory CNS control	Yue 2008 meta-analysis	OR ~1.3
TNF-α	rs1800629 (-308G>A)	Inflammatory cytokine	Riha 2005 Eur Respir J	A allele → OSA risk in some population s
APOE	rs429358 / rs7412 (ε4 haplotype)	Lipid metabolism; OSA risk modifier in some Asian cohorts; main signal in dementia panel	Kadotani 2001 JAMA	Inconsiste nt across population s
PLEK	rs11126184	Pleckstrin; CARe African-American OSA cohort	Cade 2016 AJHG	Population -specific

OSA-genetic interpretation is dominated by obesity-mediated pathways. Effective intervention is therefore weight management, positional therapy, oral appliances, and CPAP. Pharmacologic options under development (atomoxetine + oxybutynin, AD109 / aroxybutynin) target genioglossus tone. Polygenic OSA risk is informative for screening but does not change first-line workup, which remains polysomnography or home sleep apnea testing in symptomatic patients.

4. Summary Table: Categories → Genes → Cofactors → Intervention Targets

This table consolidates the cofactor and substrate dependencies catalogued above. It does not constitute a recommendation — it identifies which biological levers exist for each pathway category. Personalization depends on individual genotype, baseline measures (sleep diary, polysomnography, lab values), clinical context, and goals.

Category	Key genes	Cofactors / effectors	Intervention targets
Core circadian clock	CLOCK, BMAL1, PER1/2/3, CRY1/2, CSNK1D/E, NR1D1, RORA, TIMELESS	ATP, Mg^{2+} (kinases); ubiquitin–proteasome; phosphoserine motifs	Consistent sleep–wake schedule; morning bright light; chronotype-aligned work hours; chronotherapy for FASPS/DSPD

Category	Key genes	Cofactors / effectors	Intervention targets
Clock output, repressors, entrainment	BHLHE41 (DEC2), MTNR1A/B, OPN4, RORA, NR1D1	Tryptophan, B6, SAM (melatonin synthesis); 460–480 nm light (OPN4)	Morning bright light; evening blue-light avoidance; melatonin (low-dose, 0.3–1 mg, evening); food-timing alignment for MTNR1B G-allele
Sleep duration GWAS loci	PAX8, VRK2, FBXL13, KSR2, FTO, MEIS1, KCNK9, HCRTR2, GABRA2	Variable	Adequate sleep opportunity; weight management for FTO; cognitive-behavioral therapy for insomnia in short-sleep variants
Sleep homeostasis and EEG	ADA, ADORA1/2A, BDNF, COMT, PRNP, HOMER1	Adenosine; Zn^{2+} (ADA); SAM, Mg^{2+} (COMT); BDNF/TrkB	Caffeine timing/dose; SAM cofactors (5-MTHF, methylcobalamin, P5P) for COMT-Met; aerobic exercise (BDNF); zinc adequacy
Wake and narcolepsy	HLA-DQB1*06:02, TRA, TRB, P2RY11, CTSH, TNFSF4, ZNF365, IFNAR1, HCRT, HCRTR2	MHC-II antigen presentation; orexin neuropeptide	Modafinil/armodafinil; sodium oxybate; SNRIs for cataplexy; orexin agonists in development; influenza vaccination prudence
Insomnia and arousal fragmentation	MEIS1, BTBD9, PTPRD, LSAMP, MAP2K5/SKOR1, TOX3, GRIA1, DRD2	Iron (TH cofactor); dopamine; glutamate	Iron sufficiency (ferritin >75 ng/mL for RLS); dopaminergic agonists or alpha-2-delta ligands for RLS; CBT-I for primary insomnia
REM/NREM architecture	MEIS1, KCNK9, GNG7, KCNK9	Variable; chromatin-remodeling and ion channels	Sleep-stage-specific interventions (e.g. acoustic stimulation for SWS) in research
Caffeine pharmacogenomics	CYP1A2, ADORA2A, AHR, NAT2	Heme (CYP1A2); A2A receptor	Caffeine timing (slow CYP1A2 → before mid-morning); dose reduction in ADORA2A C/C; awareness of CYP1A2 inducers/inhibitors
Autonomic and CV sleep physiology	GNG11, RGS6, HCN4, KIAA1755, NDUFA11, NEO1, ADRB1, ADRB2, NPPA/B	Acetylcholine, GIRK channels, cAMP, NAD^{+} (mito), β-AR	Aerobic exercise; paced breathing/HRV biofeedback; magnesium; omega-3; CPAP if OSA; β-blocker selection by ADRB1 R389G

Category	Key genes	Cofactors / effectors	Intervention targets
Sleep-disordered breathing (OSA)	FTO, MC4R, NACA, GSDMC, ABCC9, LPAR1, SLC6A4, TNF, APOE	Adipogenesis (IRX3/5); upper-airway dilator tone; craniofacial morphology	Weight management; positional therapy; oral appliance; CPAP; pharmacologic upper-airway agents in development; OSA screening in obesity

"Intervention target" means a substance, behavior, or therapy that addresses the relevant biology. It does not mean every person should pursue every intervention listed. Personalization depends on individual genotype, baseline values, current clinical context, and goals.

5. Complete SNP Lookup Table

Quick reference for all SNPs catalogued in this document, sorted alphabetically by gene. Coordinates are GRCh38 (dbSNP build 156). Verify your VCF's contig naming convention ("chr1" vs "1") before running positional lookups. Indel and VNTR variants — including PER3 rs57875989 (54-bp VNTR) and 5-HTTLPR — may require specialized calling beyond standard SNP-based VCF queries; positional fallbacks are provided for all entries.

Gene / locus	rsID / variant	GRCh38 position	Category
ADA	rs73598374	20:44619522	Sleep homeostasis
ADORA1	rs2228079	1:203105427	Sleep homeostasis
ADORA1	rs6701725	1:203107902	Sleep homeostasis
ADORA2A	rs2236624	22:24435604	Sleep homeostasis / caffeine
ADORA2A	rs2298383	22:24423620	Sleep homeostasis / caffeine
ADORA2A	rs3761422	22:24424525	Sleep homeostasis / caffeine
ADORA2A	rs4822492	22:24441029	Sleep homeostasis / caffeine
ADORA2A	rs5751862	22:24420365	Sleep homeostasis / caffeine
ADORA2A	rs5751876	22:24430154	Sleep homeostasis / caffeine
ADRB1	rs1801253	10:114045297	Autonomic / CV

Gene / locus	rsID / variant	GRCh38 position	Category
ADRB2	rs1042713	5:148826877	Autonomic / CV
ADRB2	rs1042714	5:148826910	Autonomic / CV
AHR	rs2472297	15:74738396	Caffeine pharmacogenomics
APOE	rs429358	19:44908684	OSA modifier
APOE	rs7412	19:44908822	OSA modifier
BDNF	rs6265	11:27658369	Sleep homeostasis (SWA)
BHLHE40 (DEC1)	rs2042400	3:5026808	Clock output
BHLHE41 (DEC2)	rs121912617 (P384R / P385R)	12:26122724	Clock output (FNSS1)
BHLHE41 (DEC2)	Y362H (custom)	12:26122790	Clock output (FNSS1)
BMAL1 / ARNTL	rs6486121	11:13317254	Core clock
BMAL1 / ARNTL	rs7950226	11:13298574	Core clock
BTBD9	rs9296249	6:38249782	Insomnia / RLS
BTBD9	rs9357271	6:38330174	Insomnia / RLS
CCR1 / CCR3	rs3181077	3:46226879	Narcolepsy
CLOCK	rs11932595	4:55440890	Core clock
CLOCK	rs1801260	4:55435202	Core clock
COMT	rs4680	22:19963748	Sleep homeostasis (spindles)
CRY1	rs184039278 (c.1657+3A>C)	12:106991364	Core clock (DSPD)
CRY1	rs2287161	12:106991964	Core clock
CRY1	rs8192440	12:107033155	Core clock
CRY2	rs10838524	11:45867651	Core clock
CRY2	rs11605924	11:45873091	Core clock
CSNK1D	rs104894561 (T44A)	17:82240500	Core clock (FASPS2)
CSNK1E	rs135745	22:38314230	Core clock

Gene / locus	rsID / variant	GRCh38 position	Category
CTSH	rs34593439	15:78947584	Narcolepsy
CYCL1 (LSAMP region)	rs5922858	X:65814907	Insomnia
CYP1A2	rs762551	15:74749576	Caffeine pharmacogenomics
DRD2	rs2734849	11:113411925	Sleep duration / insomnia
FBXL13	rs2289917	7:102701110	Sleep duration
FTO	rs1421085	16:53767042	Sleep duration / OSA
GABRA2	rs497932	4:46326196	Sleep duration
GIRK4 / KCNJ5	rs8068318	11:128911820	Autonomic / CV
GNG11	rs10921075	7:93837858	Autonomic (HRV)
GRIA1	tag SNPs	5:153862514	Insomnia
GSDMC	tag SNPs (8q24.21)	8:129560091	OSA
HCN4	rs2680344	15:73331476	Autonomic (HRV)
HCRT (orexin)	rare missense L16R	17:42184043	Narcolepsy (rare)
HCRTR2	rs2653350	6:55135586	Wake / sleepiness
HLA-DQB1 (tag *06:02)	rs9271117	6:32679279	Narcolepsy
HLA-DQB1 (tag *06:02)	rs2858890	6:32678568	Narcolepsy
HOMER1	rs9389571	5:79612466	Sleep homeostasis
IFNAR1 / IL10RB	rs2252931	21:33272655	Narcolepsy
KCNK9	rs2542425	8:139670024	NREM duration
KCNK9	rs888346	8:139665230	NREM duration
KIAA1755	rs6123471	20:38715104	Autonomic (HRV)
KSR2	rs1380703 region	12:117890998	Sleep duration (long)
LPAR1	rs7030789	9:111417080	OSA (population-specific)
LSAMP	rs2710423	3:117007989	Insomnia

Gene / locus	rsID / variant	GRCh38 position	Category
MAP2K5 / SKOR1	rs3784709	15:67663197	RLS / insomnia
MAP2K5 / SKOR1	rs6494696	15:67724796	RLS / insomnia
MC4R	rs17782313	18:60183864	OSA (obesity-mediated)
MEIS1	rs113851554	2:66520782	Insomnia / REM duration / RLS
MEIS1	rs12469063	2:66521033	Insomnia / RLS haplotype
MEIS1	rs2300478	2:66523420	Insomnia / RLS haplotype
MEIS1	rs4544423	2:66520250	REM duration secondary
MTNR1A	rs2119882	4:186403480	Clock output
MTNR1B	rs10830963	11:92708710	Clock output / glucose
NACA	rs2958127	12:56717322	OSA
NACA	rs4759254	12:56720000	OSA
NAT2	rs1799929	8:18400285	Caffeine pharmacogenomics
NDUFA11	rs12974440	19:5891589	Autonomic (HRV)
NDUFA11	rs12974991	19:5891844	Autonomic (HRV)
NEO1	rs10516649	15:73312220	Autonomic (HRV)
NPPA	rs5068	1:11848353	Autonomic / BP
NPPB	rs198389	1:11857677	Autonomic / BP
NR1D1 (REV-ERBA)	rs2071427	17:40092568	Core clock
OPN4	rs1079610	10:88424580	Entrainment
P2RY11	rs2305795	19:10072391	Narcolepsy
PAX8	rs1191685	2:113249547	Sleep duration
PAX8	rs62158211	2:113249660	Sleep duration
PER1	rs2253820	17:8141503	Core clock
PER1	rs2585405	17:8141848	Core clock

Gene / locus	rsID / variant	GRCh38 position	Category
PER2	rs121908635 (S662G)	2:238290007	Core clock (FASPS1)
PER2	rs2304672	2:238332137	Core clock
PER2	rs934945	2:238291978	Core clock
PER3	rs228697	1:7785173	Core clock
PER3	rs57875989 (VNTR 4/5)	1:7784286	Core clock / SWS pressure
PLEK	rs11126184	2:68590015	OSA (population-specific)
PRNP	rs1799990 (M129V)	20:4699605	Sleep architecture (FFI)
PTPRD	rs1975197	9:8493053	Insomnia / RLS
RGS6	rs4899412	14:72389663	Autonomic (HRV)
RORA	rs782931	15:60390855	Core clock
SLC6A4 (5-HTT)	5-HTTLPR L/S indel	17:30237272	OSA / serotonin
TIMELESS	c.1208C>T region	12:56437919	Core clock (FASPS4)
TMEM132E	rs145258459	17:33244920	Insomnia / anxiety
TNF	rs1800629	6:31575254	OSA / inflammation
TNFRSF1A	12p13 lead SNP	12:6328224	OSA
TNFSF4	rs7553711	1:173208517	Narcolepsy
TOX3	rs3104767	16:52472068	RLS / PLMS
TRA	rs1154155	14:22091473	Narcolepsy
TRA	rs1263647	14:22094175	Narcolepsy
TRB	rs9648789	7:142792020	Narcolepsy
VRK2	rs17190618	2:57907593	Sleep duration
VRK2	rs1380703	2:57907733	Sleep duration
ZNF365	rs10995245	10:62381727	Narcolepsy

Coordinates were compiled from dbSNP build 156 and Ensembl GRCh38.p14. Some rare or recently catalogued variants — particularly the FASPS, FNSS, and DSPD pedigree mutations — are listed at their canonical transcript positions; verify against the GRCh38 build of your VCF before positional lookup. The PER3 VNTR (rs57875989) is a 54-bp tandem repeat that bcftools

*alone may not resolve; for definitive 4/4 vs 4/5 vs 5/5 calling, examine read depth and split reads in the BAM/CRAM, or use a dedicated VNTR caller. The HLA-DQB1 alleles are best resolved with HLA imputation tools (HIBAG, HLA-LA); rs9271117 and rs2858890 are tag SNPs in tight LD with DQB1*06:02 in Europeans and provide first-pass screening with sensitivity ~95%.*

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OMIM entries 604348 (FASPS1), 612975 (FNSS1), 615224 (FASPS2), 616882 (FASPS3), 620015 (FASPS4).

ClinVar entries for PER2 c.1984A>G, BHLHE41 c.1151C>G, CRY1 c.1657+3A>C, CSNK1D c.130A>G.

This document was prepared as a standalone educational reference. Genetic research in sleep biology evolves rapidly; new loci are identified regularly in GWAS and exome sequencing studies. Readers should consult the GWAS Catalog (https://www.ebi.ac.uk/gwas), Sleep Disorder Knowledge Portal (https://sleep.hugeamp.org), OMIM, ClinVar, and PubMed for the most recent evidence when applying this reference to specific clinical or research questions.