The genetic and molecular regulation of sleep: from fruit flies to humans
Supplementary Tables

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Supplementary Table 1. Twin studies with heritability estimates for sleep phenotypes (% of variance explained by genetic effects)

Ref	Study type	Major Findings
By questionnaire		
Partinen et al., Sleep 6:179, 1983[1]	Finnish twin pairs (2238MZ, 4545DZ):	heritability of both duration of sleep and sleep quality ~ 44%, sleep apnea ≥50%
Heath et al., Sleep 13:318, 1990[2]	Australian twin pairs (1800MZ, 2010DZ)	heritability of sleep quality 32%, sleep time ~42%, sleep duration 40%, insomnia complains 32-36%, sleepiness 39%
McCarren et al., Sleep 17 :456, 1994[3]	Vietnam era veteran twins	heritability of sleep-onset insomnia 28%, sleep-maintenance insomnia 42%
Carmelli et al., J Sleep Res 10:53, 2001[4]	World War II male veteran twin pairs (818MZ, 742DZ)	heritability of subjective sleepiness (Epworth Sleepiness scale, ESS) 38% (most likely due to genetic susceptibility to sleep apnea)
Vink et al. Chronobiol Int 18:809, 2001[5]	Dutch twin family study	heritability of morningness/eveningness 44-47%
Carmelli et al., Sleep 27:917, 2004[6]	World War II male veteran twin pairs (68MZ, 54DZ)	heritability of sleep disordered breathing ~36%
Watson et al., Sleep 29:645, 2006[7]	Washington State twin pairs (1042MZ, 828DZ; 32-year old):	heritability of insomnia 57%, sleepiness 38%, obesity 73%; additive genetic effects found for insomnia/obesity and insomnia/sleepiness
Luciano et al., Sleep 30: 1378, 2007[8]	Australian twin pairs (1799MZ, 2009DZ):	heritability of coffee-attributed sleep disturbance ~ 40%; main source of genetic variance unrelated to a general sleep-disturbance factor
Koskenvuo et al., J Sleep Res 16;156, 2007[9]	Finnish twin pairs (2836MZ, 5917DZ):	heritability of morningness/eveningness 50% (12% additive, 38% due to dominance)
By EEG analysis		
Linkowski et al., J Sleep Res 8 (Suppl.1):11, 1999[10]	Belgian twin pairs (45MZ, 46DZ)	heritability of SWS duration 50%
Ambrosius et al. Biol Psych 64:344-8, 2008[11]	German twin pairs (35MZ, 14DZ)	Significant genetic influence for SWS duration, REM sleep duration, NREM spectral power within the alpha (8-12Hz) and low sigma (13-14Hz) range, and in the 2-13Hz range (using 1hz frequency bins)
De Gennaro et al., Ann of Neurol 2008, in press[12]	Italian twin pairs (10MZ, 10DZ)	heritability of EEG power spectrum in NREM sleep (8-16Hz) 96%

Supplementary Table 2. Studies in flies and mice using reverse and forward genetics to show effects of single candidate genes on sleep. Fly studies are indicated in blue, forward genetic studies in bold.

Gene	Major findings	Ref
Circadian regulation		
Clock mutant mice (partial deletion of the Clock protein)	~ 18% less total sleep/24h (due to less NREM sleep) Same % of total sleep recovered after sleep deprivation; normal increase in delta activity after sleep deprivation; ~50% smaller increase in REM sleep after sleep deprivation	13
Dbp (albumin D-binding protein) KO mice	More sleep during the night (trend, ns), ~25% less REM sleep during the light period; no change in total sleep duration and sleep homeostasis	14
Cry 1, 2 (cryptochrome 1 and 2) double KO mice *Cry 1* KO mice *Cry 2* KO mice	~20% increase in NREM sleep/24h (due to more sleep at night); higher NREM delta activity in baseline; smaller increases relative to wild-type mice in sleep duration (5 vs 33%) and delta activity (134 vs 170%) after sleep deprivation Normal sleep amount and sleep regulation Normal sleep amount and sleep regulation	15 16 16
mPer1, mPer2, mPer3 (Period 1,2,3) KO mice *mPer1/ mPer2* double KO mice	Altered 24h distribution of sleep; no change in total sleep duration or sleep homeostasis	17 18
Bmal1 (brain and muscle ARNT-like protein 1) KO mice	<15% increase in NREM sleep/24h; sleep fragmentation; slightly smaller homeostatic response after sleep deprivation	19
*Npas2 (*neuronal PAS domain protein 2) KO mice	Less NREM sleep only in the second half of the dark period; smaller increase in NREM duration (males only) and in delta activity after sleep deprivation	20 21
Prok2 (prokineticin 2) KO mice	~20% less total sleep/24h (due to less NREM sleep in the light phase, but REM sleep is increased); smaller increase in delta activity and REM sleep after sleep deprivation	22
Related to neurotransmitters/neuropeptides		
Adora1 (adenosine A1 receptor) KO mice	Normal 24h sleep/waking amounts; normal response to sleep deprivation Normal increase in waking after caffeine	23 24
Adora2a (adenosine A2A receptor) KO mice	Daily sleep/waking amounts not reported; no increase in sleep after infusion of adenosine A2A receptor agonist Preliminary evidence of no increase in NREM sleep after sleep deprivation No increase in waking after caffeine	25 26 24
*nAchR-a4 (*nicotinic acetylcholine receptor alpha 4 subunit) knock in mice	Increased brief awakenings	27
*nAchR-b2 (*nicotinic acetylcholine receptor beta *2* subunit) KO mice	Normal sleep/waking amounts; longer duration of REM sleep episodes; fewer microarousals in baseline and after sleep deprivation Decreased arousal from sleep after episodic hypoxia	28 29
*Chrm3, Chrm2/4 (*muscarinic acetylcholine receptor M3, M2/M4) KO mice	22% less REM sleep in M3 KO mice	30
Dat (dopamine transporter) KO mice	~18% more waking/24h, ~ 25% less NREM/24h No increase in waking after modafinil or amphetamines	31
Maoa (monoamine oxidase A) transgenic Tg8 mice (MAOA-deficient)	Normal sleep/waking amounts; increased sleep apneas	32
Dbh (dopamine beta hydroxylase) KO mice (norepinephrine and epinephrine deficient)	Increased total sleep (due to 30% more NREM); no increase in sleep time after deprivation reduced latency to sleep after mild stressors; increased arousal threshold after sleep deprivation	33 34 35
Sert (serotonin transporter) KO mice	~50% more REM sleep/24h	36 37
5-Htr1a (serotonin receptor 1A) KO mice	~40% more REM sleep/24h; no increase in REM sleep after sleep deprivation	38
5-Htr1b (serotonin receptor 1B) KO mice	~30% more REM sleep, and ~ 10% less NREM sleep in the light phase; no increase in REM sleep after sleep deprivation-	39

5-Htr2a (serotonin receptor 2A) KO mice	~25% less NREM sleep/24h; no increase in delta activity after sleep deprivation	40
5-Htr2c (serotonin receptor 2C) KO mice	~20% more waking/24h, ~ 20% less NREM sleep/24h; increase in NREM sleep duration after sleep deprivation (20-40% vs ns in controls); larger increase in delta activity after sleep deprivation relative to controls	41
5-Htr7 (serotonin receptor 7) KO mice	<20% less REM sleep/24h (decrease in the light period only)	42
Hdc (histidine decarboxilase) KO mice	>23% more REM sleep/24h; decreased waking around the light-to-dark transition; shorter sleep latency compared to wild type mice after behavioral stimuli	43
Hrh1 (histamine H1 receptor) KO mice	Normal sleep/waking amounts (but fewer brief awakenings); no increase in waking after infusion of orexin A in the lateral ventricle No increase in waking after infusion of H3 receptor antagonist	44 45 46
Hrh2 (histamine H2 receptor) KO mice *Hrh3* (histamine H3 receptor) KO mice *Hdc* (histidine-decarboxylase) KO mice	No increase in waking after infusion of H3 receptor antagonists in HDC or H3R KO mice; increased waking in H2R KO mice	46
Hcrt/Ox (Prepro-hypocretin/orexin) KO mice	"narcoleptic episodes" (behavioral arrest); sleep-onset REM episodes; decreased latency to REM sleep; more REM sleep in the dark period slightly more REM sleep in the dark period; fewer waking episodes of long duration; normal circadian and homeostatic sleep regulation	47 48 49
Hcrt/Ox -ataxin 3 transgenic mice (loss of orexin cells) *Hcrt/Ox -ataxin 3* transgenic rats (loss of orexin cells)	Effects on sleep very similar to those in the *Prepro-orexin* KO mice Narcoleptic phenotype similar to those in orexin-ataxin 3 mice	50 51
Hcrtr1 (Hypocretin receptor 1) KO mice *Hcrtr2* (Hypocretin receptor 2) KO mice *Hcrtr1,2* (Hypocretin receptor 1,2) double KO mice	Mild sleep fragmentation decrease in duration of waking and NREM sleep bouts (mostly in the dark phase); not as affected by "cataplexy-like" attacks of REM sleep as prepro-orexin KO mice effects on sleep very similar to those in the *Prepro-orexin* KO mice	52 53
Gabra1 (GABA-A receptor a1 subunit; point mutation H101R)	Normal 24h sleep/waking amounts; sleep effects of diazepam as in wild-type mice	54
Gabra2 (GABA-A receptor a2 subunit; point mutation H101R)	Smaller decrease in NREM delta activity after diazepam	55
Gabra3 (GABA-A receptor a3 subunit; point mutation H126R; diazepam-insensitive) *Gabra3* KO mice	Decrease in NREM delta activity after diazepam as in controls Normal 24h sleep/waking amounts; normal sleep homeostasis; reduced spindling activity (10-15Hz) at the NREM-REM transition	56 57
Gabrb3 (GABA-A receptor b3 subunit) KO mice	Normal 24h sleep/waking amounts; no increase in sleep after oleamide infusion ~ 25% less REM sleep during the light phase; ~50% increase in NREM EEG power (mainly <7Hz); blunted increase in spindling (sigma activity) at the transition NREM-REM	58 59
Gabrd (GABA-A receptor d subunit) KO mice	No abnormal EEG pattern after gaboxadol	60
Gria3 (glutamate AMPA receptor Glur3 subunit) KO mice	8h of recording in the light phase only; overall decrease in EEG power in waking and NREM sleep; no increase in low range (<7.5Hz) EEG power in NREM sleep relative to waking or REM sleep	61
Grin2a (glutamate NMDA receptor NR2A subunit) KO mice	Normal amount of NREM sleep	62
Other signaling pathways, hormones		
***Sleepless* (glycosyl-phosphatidylinositol-anchored protein) loss of function mutation (*P^1*)**	~85% decrease in daily sleep amounts, mainly due to decrease in sleep episode duration; no hyperactivity but motor incoordination; weak rest/activity rhythm, reduced response to sleep deprivation; reduced lifespan	63 Insertional mutagenesis

***Acads* (short-chain acyl-coenzyme A dehydrogenase)**	A deficiency in Acads is linked to a slower theta peak frequency during REM sleep (mouse chromosome 5)	[64] QTL analysis
***Rarb* (retinoid acid receptor beta)**	A deletion and polymorphisms affecting *Rarb* expression influence cortical EEG synchrony during NREM sleep as measured by the ratio between delta and theta activity (mouse chromosome 14)	[65] QTL analysis
Pgds (prostaglandin D synthase) transgenic mice *L-Pgds* (lipocalin-type PGDS) KO mice *H-Pgds* (hematopoietic-type PGDS) KO mice	Normal 24h sleep/waking amounts; increased NREM sleep after tail clipping Decreased sleep after infusion of PGDS inhibitor in *H-PGDS* KO mice but not in *L-PGDS* KO mice or *H-PGDS/L-PGDS* double KO mice	[66] [67]
Dp (prostaglandin receptor) KO mice	No increase in NREM sleep after prostaglandin D2 infusion No decrease in sleep after infusion of PGDS inhibitor	[68] [67]
Il1r1 (interleukin-1beta type 1 receptor) KO mice	Normal 24h sleep/waking amounts (<20% less NREM in the dark phase) No increase in sleep after IL-1 infusion	[69]
Il6 (interleukin 6) KO mice	~30% more REM sleep in baseline Smaller increase in NREM sleep after administration of lipopolysaccharide	[70] [71]
Il10 (interleukin 10) KO mice	Normal 24h sleep/waking amounts (<20% more NREM in the dark phase)	[72]
Tnfr1 (TNF receptor 1) KO mice	~20% less NREM sleep/24h (due to decrease in the light phase), and ~ 20% less REM sleep/24h (genetic background?) No change in 24h amounts of sleep	[73] [74]
Tnfr2 (TNF receptor 2) KO mice	No change in 24h amounts of sleep; ~15% less REM sleep in the light phase	[74]
Tnf-lt-alpha (TNF and lymphotoxin alpha) double KO mice	~15% less REM sleep/24h (due to a decrease in the light phase)	[74]
Ifnar1 (interferon type 1 receptor) KO mice	~30% less REM sleep/24h	[75]
Nfkb1 (nuclear factor-kappaB p50 subunit) KO mice	26% more sleep/24h (increase in both NREM and REM sleep); larger response after sleep deprivation (increase in NREM sleep and delta activity)	[76]
Nos (Nitric oxide synthase) KO mice	REM sleep reduced (33% less, light phase) in neuronal NOS KO, and increased (28% more, light phase) in inducible NOS KO mice	[77]
Prkg1 (cGMP-dep. Protein kinase type I) conditional KO mice (lacking *Prkg1* in the brain)	Normal total sleep/24h (but more awake in the light phase); ~25% decrease in REM sleep; reduced NREM delta activity during baseline, but normal delta rebound after sleep deprivation; increased sleep duration after sleep deprivation; increased fragmentation (shorter episodes) of both waking and NREM sleep	[78]
ArKO (aromatase cytochrome P450) deficient female mice (estrogen-deficient)	Normal total sleep/24h (but more sleep in the dark phase); normal response to sleep deprivation	[79]
Lep (ob/ob, leptin-deficient) mice	~10% increase in NREM sleep; sleep fragmentation; smaller increase in sleep time after sleep deprivation	[80]
Ghrl (ghrelin) KO mice	Slight decrease in NREM sleep, and slight increase in REM sleep; normal response to sleep deprivation	[81]
Prl (prolactin) KO mice	~30% less REM sleep (light phase only); smaller increase in REM sleep after sleep deprivation	[82]

Dwarf (*dw/dw*) rats (nonfunctional GHRH receptor)	~20% less NREM sleep (both light and dark phase); ~30% less REM sleep (light phase only); smaller increase in delta activity after sleep deprivation	83
Dwarf (*lit/lit*) mice (nonfunctional GHRH receptor)	~30% less NREM sleep and <20% less REM sleep in the light phase;	84
TH-hGH transgenic mice (somatotropic axis deficiency)	~ 30% less NREM sleep/24h	85
MT-rGH transgenic mice (growth hormone overexpression)	11% more NREM sleep and 40% more REM sleep during the light period only	86
Mchr1 (melanin-concentrating hormone receptor 1) KO mice	Normal total sleep/24h; 19% more REM sleep in the light phase; larger increase in NREM sleep after total sleep deprivation; no differences relative to controls after REM sleep deprivation	87
Faah (fatty acid amide hydrolase) KO mice (catabolism of endogenous cannabinoids)	<15% less waking and <10% more NREM sleep during the light period only; 6% more NREM delta activity during the light period; normal response to sleep deprivation	88
Plcb1 (phospholipase C, b1 isoform) KO mice	Irregular theta activity in REM sleep	89
CRH (corticotrophin-releasing hormone) conditional overexpressing mice (whole brain or forebrain only)	Increased REM sleep (dark period) and decreased NREM sleep (light period) after overexpression in the whole brain (similar trend after overexpression in forebrain only); increased REM rebound after sleep deprivation	90
Others: transcription factors, synaptic vesicle release, etc		
Prnp (prion) KO mice	Normal 24h sleep/waking amounts; increased sleep fragmentation (~ 2-fold increase in brief awakenings); larger increase in delta activity after sleep deprivation (40% increase vs 20% in controls)	91 92
Prnp transgenic mice (carrying the D178N/V129 mutation)	EEG abnormalities (bursts of polyphasic complexes), lack of sleep spindles, reduced REM sleep, presence of a mixed (sleep/wake) state	93
Beta-amyloid precursor protein overexpressing mice	~25% less REM sleep/24h	94
Stop (calmodulin-regulated microtubule-associated protein) KO mice	Videotape, 3h in the dark phase only: reduced “sleeping” time; less grooming before sleep	95
Rho-GDI gamma KO mice	Normal sleep/waking cycle and EEG	96
Ube3a (ubiquitin-protein ligase) KO mice (animal model for Angelman syndrome)	44% less REM sleep/24h; no increase in NREM sleep and delta activity after sleep deprivation; paroxysmal EEG discharges in waking and NREM sleep	97
Rab3 (earlybird), Asp77Gly point mutation *Rab3* KO mice	~ 25% increase NREM sleep/24h in *Rab3a-/-* (but not in *Rab3 Ebd/Ebd*); reduced increase in sleep time after sleep deprivation in both (EEG power not studied)	98
Rim1alpha (Rab3 interacting molecule 1 alpha) KO mice	~ 50% less REM sleep /24h; ~ 35% less NREM sleep in the dark phase only	99
Fos KO mice	~27% more waking/24h, ~ 25% less NREM/24h	100
Fosb KO mice	~35% less REM/24h	100

CREB alpha/delta (cyclic AMP-response element binding protein, alpha and delta isoforms) deficient mice	<20% more NREM sleep/24h; normal response to sleep deprivation	[101]
Ion Channels		
***Shaker* (voltage-dependent potassium channel, alpha subunit) loss of function mutations (*Sh^{msn}*, *Sh^{102}*, *Sh^{133}*, *Sh^{M}*)**	~60-85% decrease in daily sleep amount (depending on allele and genetic background), mainly due to decrease in sleep episode duration; hyperactivity; normal circadian and homeostatic regulation of sleep; memory impairment, reduced lifespan	[102] EMS mutagenesis
Cav2.2 (N-type Ca++ channel, alpha1B subunit) KO mice	Normal 24h sleep/waking amounts; longer, fewer REM sleep episodes; overall EEG spectral power increased in waking and REM sleep and decreased in NREM sleep	[103]
Cav3.1 (T-type calcium channel, alpha1G subunit) global KO mice *Cav3.1* (T-type calcium channel, alpha1G subunit) global, thalamic, or cortical KO mice	~10% less NREM sleep/24h; more brief awakenings; decreased NREM EEG power in the 2-6.5Hz range and at 9.5-10Hz (2.5min recordings only) <20% less NREM sleep and more brief awakenings in mice with global or thalamic deletion; normal sleep mice with cortical deletion; increase in NREM delta activity in global and thalamic KO mice is mentioned	[104] [105]
Kv1.2 (voltage-dependent potassium channel) KO mice	23% less NREM sleep/24h (at P17; early death due to seizures)	[106]
*Kcnc1, Kcnc3, Kcnc1/3 (*Kv3.1, Kv3.3 voltage-dependent potassium channel) KO mice	Double KO (Kv3.1/Kv3.3): ~30% less total sleep/24h (37% less in the light phase, 23% less in the dark phase), shorter NREM sleep episodes; similar effects in Kv3.1 KO mice; no sleep loss in Kv3.3 KO mice overall decrease in EEG spectral power, but mainly in NREM sleep (<15Hz); no increase in sleep time or delta activity after sleep deprivation	[107] [108]
Kcnc2 (Kv3.2 voltage-dependent potassium channel) KO mice	Normal 24h sleep/waking amounts; normal response to sleep deprivation; subtle change in EEG power spectrum (3-6Hz) in sleep	[109]
Kcnn2 (Sk2 calcium-dep. small conductance potassium channel*)* KO mice	Overall decrease in EEG power in all states, but more pronounced in NREM sleep; increased brief awakenings	[110]

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