Review

Genetic Mechanisms of Natural Short Sleep: A Review of DEC2, ADRB1, NPSR1, GRM1 Mutations and Recommended Testing for Chronic Health Implications

Helene Gu *

Posted Date: 15 October 2024

doi: 10.20944/preprints202410.0974.v1

Keywords: Familial Natural Short Sleep; Sleep Genetics; Sleep Medicine; Chronic Sleep Deprivation; ADRB1; DEC2; GRM1; NPSR1

Review

Genetic Mechanisms of Natural Short Sleep: A Review of DEC2, ADRB1, NPSR1, GRM1 Mutations and Recommended Testing for Chronic Health Implications

Helene Gu

Duke Kunshan University, Division of Natural and Applied Sciences, Kunshan, China;
helene.gu@dukekunshan.edu.cn

Abstract: Sleep deprivation is an increasing problem in the modern age. While molecular theories on the mechanism of sleep are still developing, sleep's importance for cognitive function and physical health has been well reported. In the past 2 decades, major advances in the genetics of sleep have been made. Among families of natural short sleepers averaging around 4-6 hours nightly, mutations on 4 genes (DEC2, ADRB1, NPSR1, and GRM1) have been associated with significantly shorter sleep without observed cognitive or health detriments. Studies in mice have further established causality of these mutations as well as finding increased resistance to neurodegeneration. Yet, despite these promising results, there is a current lack of studies investigating potential chronic risks of sleep deprivation, particularly physical and physiological effects that may not be apparent. For circadian repressor element DEC2, circadian dysregulation risks should be evaluated further. For adrenergic receptor ADRB1, cardiovascular and heart failure risks would be of interest. For NPSR1, asthma and other immune responses, as well as mood disorders are relevant. For the currently least studied G-protein receptor GRM1, its altered regulation of the extracellular signal-regulated kinase (ERK) pathway could result in developmental and proliferation effects. While these familial natural short sleep genes hold potential for our understanding of sleep and therapeutic development, it is critical not to overdraw conclusions. By investigating the possible downstream effects, one can be aware of the potential risks of natural short-sleep genetics, better understand the mechanisms of sleep, and advance research in reducing the harms of sleep deprivation.

Keywords: familial natural short sleep; sleep genetics; sleep medicine; chronic sleep deprivation; ADRB1; DEC2; GRM1; NPSR1

1. Introduction

Sleep is a pressing theoretical and practical enigma. The regulation of blood pressure, heart rate, hormone release, cellular repair, memory consolidation, and metabolic waste clearance in the brain all happen during sleep (Liew and Aung, 2020), but an integrated theory of what sleep is has yet to be achieved.

The Two-Process model of sleep regulation has been a major framework for sleep research. Sleep regulation is represented as an interaction between a fluctuating drive controlled by the body's circadian rhythm (Process C), and a sleep debt that increases with wake and decreases during sleep (Process S) (Pellegrino et al., 2014). With this, artificial light-altered circadian rhythms, online activities, shift work, "around the clock" studying hours, and other changes in lifestyles can all affect the sleep of adolescents and adults today (Morrison et al., 2022; Walker et al., 2020).

Among certain populations, sleep deprivation (SD) is known to be an increasing problem in the modern age (Hoyos, Glozier and Marshall, 2015). A 2010 Centers for Diseases Control and Prevention (CDC) report on health behavior of adults in the US indicates that sleep decreased from 9 h to 7h on average throughout the 20th century (Liew and Aung, 2020). Similarly, the average sleep duration for the Chinese decreased from 8.56 h in 2012 to 7.06 h per night in 2021 (Li et al., 2024). Reports range

 doi:10.20944/preprints202410.0974.v1

from most university students acquiring less sleep than recommended by guidelines (Liew and Aung, 2020) to about 1/3 of adults suffering from sleep deprivation (Han,Yang and Huang, 2024; Liu et al., 2017). Although the exact amount of sleep required differs between individuals, many report getting less than the amount of sleep they feel their bodies need (Ford et al., 2014).

Because sleep functions in nearly every system of the body, SD is associated with many health and cognitive outcomes. These harms differ based on the nature of the sleep deprivation, which can be characterized as acute or chronic. In humans, acute sleep deprivation is defined as reducing normal total sleep time during 1-2 days, and being awake longer than 16-18 hours in a 24 hour cycle (Li et al., 2024). Acute sleep deprivation can lead to cognitive impairments of attention, memory, and learning, as well as physical and physiological symptoms of higher heart recovery rate, higher cortisol levels, changes in gut microbiota, or decreased muscle protein synthesis (Han,Yang and Huang, 2024; Liew and Aung, 2020; Morrison et al., 2022). Chronic sleep deprivation refers to getting less than optimal sleep for an extended period of time, such as at least 3 months (Li et al., 2024). It is both more typical to human lifestyles and often has more severe consequences (Alhola and Polo-Kantola, 2007). Numerous studies have found lasting effects on cognition and systems of the body. Cognitively, SD is strongly implicated in diminished learning and memory (Han,Yang and Huang, 2024), mood disorders (Liu et al., 2017), changes in adenosine/noradenosine receptors that contribute to cognitive impairment(Liew and Aung, 2020), Aβ amyloid precursor formation in interstitial fluid (ISF) in the brain (Han,Yang and Huang, 2024), neuroinflammation (Liew and Aung, 2020), and microglial phagocytosis by astrocytes(Liew and Aung, 2020). With regards to endocrine metabolic and circadian effects, this includes disruption of circadian genes such as BMAL1, CLOCK, and CRY1 (Han,Yang and Huang, 2024), glucose metabolism changes of leptin decreases and ghrelin increases promoting overeating (Liew and Aung, 2020), insulin resistance (Liew and Aung, 2020), prolactin, growth hormone, and insulin-like growth factor 1 (IGE-1) decreases(Morrison et al., 2022). Physical and immune system changes include muscle protein synthesis decrease (Morrison et al., 2022), increased blood pressure (Han,Yang and Huang, 2024), lipid abnormalities (Liew and Aung, 2020), atherosclerosis (Liew and Aung, 2020), stroke (Han,Yang and Huang, 2024), reduction in anti-tumor and natural killer (NK) immune cells (Li et al., 2024), increased immunosuppressors and pro-inflammatory cytokines (Liew and Aung, 2020), increased DNA damage triggered by oxidative stress (Liew and Aung, 2020), neutrophilic inflammation/asthma (Liew and Aung, 2020) and breast cancer (Liew and Aung, 2020).

In 2009, the first short sleep gene mutation was discovered in the DEC2 gene (He et al., 2009). This dominant P384R mutation in a circadian clock transcription element led heterozygous carriers to sleep for 6.25 hours on average without any apparent physical or psychological harm (He et al., 2009). These effects were replicated when the mutation was introduced to mice, indicating causality (He et al., 2009).

Since these findings, more work in the genetics of sleep has been done, particularly in looking for familial natural short sleepers (FNSS). While many genes —neuropeptides, ion channels, transcription factors, synaptic proteins, kinases, and intracellular signaling cascade proteins— have been found to be involved in sleep regulation, most mutations lead to unintended effects or behavioral changes in mice (Webb and Fu, 2021).

This review follows Zheng and Zhang in covering genes with mutations that have shown no detrimental effects thus far besides shortened sleep as promising directions for future research and therapeutics (Zheng and Zhang, 2022).This review will focus on four FNSS genes—DEC2, ADRB1, NPSR1, and GRM1—covering the experimental work surrounding each of them and proposing next steps for experimentation.

 doi:10.20944/preprints202410.0974.v1

Table 1. Summary of Familial Natural Short Sleep (FNSS) Genes.

Time of Report	Gene	Normal Function	Locations expressed	Mutation	Effect on human sleep	Effect on mouse sleep	Mechanism driving short sleep
2009 (He et al., 2009)	DEC2/BHLHE41	Transcription factor, represses CLOCK/BMAL1	Brain, skeletal tissues	P384R	6.25h	Transgenic mice had reduced sleep (72 min), both REM and NREM but no significant change in NREM delta or REM theta power. Less recovery sleep duration after SD.	Decreased repression of CLOCK/BMAL1 transcription, increased (target gene product) orexin levels, particularly in the hypothalamus.
2014 (Pellegrino et al., 2014)				Y362H	4.99h		
2019 (Shi et al., 2019)	ADRB1	B1 adrenergic receptor	Brain, heart, kidney, adipose	A187V	5.7h	Global ADRB1-A187V knock-in mice supported a causal effect on shorter sleep (60 min). REM and NREM decreased. An increase in delta power was observed at the beginning of sleep.	Enhanced wake promoting neuron activity due to reduced inhibition by agonists.
2019 (Xing et al., 2019)	NPSR1	G-protein receptor reactive to NPS	Various tissues (Brain, lungs, gastrointestinal)	Y206H	5.5h and 4.3h	Global NPSR1-Y206H knock-in mice supported a causal effect on shorter sleep (71 min). REM and NREM decreased. An increase in delta power was observed at the beginning of sleep. Normal recovery sleep duration after SD.	Enhanced reaction to NPS, promoting wakefulness.
2021 (Shi et al., 2020)	GRM1/mGluR1	Glutamate metabotropic receptor	Primarily brain and nervous system	R889W	6.05h, 5.15h, and 5.1h	Global mGluR1-S458A and mGluR1b-R889W knock-in mice supported a causal effect on shorter sleep	Reduced ERK phosphorylation.

 doi:10.20944/preprints202410.0974.v1

	S458A	6h	(25 min). NREM sleep decreased but REM didn't. There was no significant change in delta power. Normal recovery sleep duration after SD.

This table summarizes the 4 reported genetic mutations and the average sleep duration in human carriers, as well as the effects on sleep when the mutation is induced in mice.

2. DEC2 Mutations

In 2009, the first short sleep mutation was discovered in DEC2 (He et al., 2009). DEC2, also known as Basic Helix-Loop-Helix Family Member E41 (BHLHE41), is a protein-coding gene on the short arm of chromosome 12 12p11.23-p12.1 that codes for a transcription repressor found primarily in the brain and skeletal muscle, involved in circadian regulation (Fujimoto et al., 2001). The core circadian clock is composed of two main components, the transcription factor complex CLOCK/BMAL1 and its inhibitors PER/CRY. CLOCK/BMAL1 promote the transcription of PER and CRY, which in turn form a dimer to repress CLOCK/BMAL1 activities (Yook et al., 2021). As PER/CRY naturally degrades, it allows for a cyclic transcription of CLOCK/BMAL1 target genes (Yook et al., 2021). As another element of the circadian clock, DEC2 also inhibits CLOCK/BMAL1 and represses transcription of its target genes (Hirano et al., 2018; Yook et al., 2021). One of these target genes is the hypocretin (Hcrt) gene, which encodes protein product orexin (Zheng and Zhang, 2022). Orexin is a neuropeptide with known functions in promoting wakefulness, along with cognition, anxiety, neuroprotection, eating, and reward (Han,Yang and Huang, 2024) and it is enriched in the hypothalamus (Hirano et al., 2018). It was found that both the P384R (He et al., 2009) and Y362H (Pellegrino et al., 2014) DEC2 mutations in mice led to impaired repressive activity compared to the wild type DEC2 and increased Hcrt gene expression and orexin protein levels measured in the hypothalamus (Hirano et al., 2018). This mechanism was supported when administration of an orexin receptor antagonist partially reduced the short sleep effect of the DEC2-P384R mutation in mice (Hirano et al., 2018).

2.1. DEC2 observations in humans

In humans, these mutations have resulted in daily sleep of 6.25h for P384R (He et al., 2009) and 4.99h for Y362H (Ashbrook et al., 2019). A dizygotic twin with the Y362H mutation had comparatively less recovery sleep and fewer performance lapses after sleep deprivation (Ashbrook et al., 2019).

2.2. DEC2 observations in mice

In mice studies, the P384R mutation led to reduced non rapid eye movement (NREM) and rapid eye movement (REM) sleep by around 60 mins combined (He et al., 2009; Zheng and Zhang, 2022). This was without significant difference in NREM delta power or REM theta power, which have been used as measures of how deep or efficient sleep is (Zheng and Zhang, 2022). Notably though, high delta power is also regularly seen in some psychiatric disorders (Long et al., 2021). When wild type mice and mutant P384R mice were sleep deprived for 6h, P384R mice also showed less recovery sleep, implying that this mutation alters sleep homeostasis regulation and leads to tolerance of higher sleep pressure (He et al., 2009).

A point of interest is that orexin upregulation in cerebrospinal fluid (CSF) can contribute to the progression of Alzheimer's disease (Han,Yang and Huang, 2024). In vivo, it can inhibit brain

 doi:10.20944/preprints202410.0974.v1

autophagy and in vitro, it has also been found to impair breakdown of Aβ (Han,Yang and Huang, 2024). However, an experiment investigating the effect of the DEC2-P384R mutation on tau and Aβ found that while there were higher Aβ and phosphorylated tau levels in mutant mice at 3 months, this difference decreased by 6 months, indicating a compensatory mechanism before the age of severe Alzheimer's risk in the mouse strain (Dong et al., 2022).

3. ADRB1 Mutation

In 2019, another family with a short sleep mutation in the ADRB1 gene was reported (Zheng and Zhang, 2022). ADRB1 on the long arm of chromosome 10 (10q24-q26) encodes for the B1 adrenergic receptor, which is activated by noradrenaline and adrenaline (Pacanowski and Johnson, 2007). It is found in the heart, but also the brain, kidney, and adipose, regulating activities of the sympathetic nervous system (Pacanowski and Johnson, 2007). ADRB1 expressing neurons are active during wakefulness and REM sleep, but not NREM, and optogenetic activation of these neurons in mice can lead to wake (Shi et al., 2019; Zheng and Zhang, 2022). This mutation resulted in decreased stability of the ADRB1 protein in vitro and in vivo, with decreased protein levels despite no change in mRNA level (Shi et al., 2019). The mechanism of this is likely to be linked with a change in the behavior of ADRB1 in presence of agonists, which can excite, inhibit, or cause no change when binding to the receptor (Shi et al., 2019). While the portion of mutant ADRB1+ neurons excited by the agonist was comparable to wild type ADRB1, the portion inhibited was significantly lower, indicating increased activation of the mutant ADRB1+ neurons and increased wakefulness (Shi et al., 2019).

3.1. ADRB1 observations in humans

In humans, carriers of the A187V mutation resulted in sleep of 5.7h per day on average (Shi et al., 2019).

3.2. ADRB1 observations in mice

Knock-in mice had the same effect of significantly reduced sleep, with NREM decreases of 53 minutes and REM decreases of around 7 minutes compared to wild type mice (Shi et al., 2019). Furthermore, an increase in delta power was observed at the beginning of rest (Yook et al., 2021). Notably, recovery sleep after sleep deprivation has not yet been investigated or reported as of 2022 (Zheng and Zhang, 2022).

Like the DEC2 mutation, the A187V mutation showed beneficial effects in a mouse model of Alzheimer's disease. In the PS19 strain, the mutation restored REM sleep and decreased the spread and accumulation of tau (Dong, Ptáček and Fu, 2023).

4. NPSR1 Mutation

In 2019, another mutation in the Neuropeptide S Receptor 1 (NPSR1) or G-protein-coupled receptor for asthma susceptibility (GPRA/ GPRA154) gene was discovered in a short sleeping family (Vercelli, 2008; Zheng and Zhang, 2022). NPSR1, located at chromosome position 7p14.3 (Henström et al., 2014), is a G-protein coupled receptor activated by the ligand neuropeptide S (NPS) and is the only known receptor for NPS, a neurotransmitter involved in wakefulness, arousal, mood, food intake, and memory (Xing et al., 2024; Zheng and Zhang, 2022). NPS activation of NPSR1 in different regions of the brain can promote wake, sleep, or be irrelevant to sleep/wake (Xing et al., 2024). This Y206H mutation is proposed to increase NPSR1 signaling to hyperactivate centromedial thalamus (CMT) neurons that lead to shortened sleep (Zheng and Zhang, 2022).

4.1. NPSR1 observations in humans

In a small family, a father and son who carried the mutation slept 5.5 and 4.3 h on average (Zheng and Zhang, 2022).

4.2. NPSR1 observations in mice

 doi:10.20944/preprints202410.0974.v1

Knock-in mice supported the effect of significantly reduced NREM and REM sleep for a total reduction of 71 minutes (Yook et al., 2021). The mobile time increased, but mobile periods decreased (Xing et al., 2019)

Tests were done for cognitive performance, specifically a contextual fear conditioning test typically sensitive to sleep deprivation in wild type mice (Xing et al., 2019). Learning and memory for the Y206H mutant mice were found to be intact. When acutely sleep deprived for 6h, Y206H mutant mice were also more resistant, as they did not suffer impaired memory while WT mice did (Xing et al., 2019). Similar to ADRB1, higher delta power was observed at the beginning of sleep but fell quickly to WT levels during sleep, suggesting the mutation increased sleep efficiency (Webb and Fu, 2021). Unlike with DEC2, recovery sleep was normal, suggesting that despite a similar sustaining of wakefulness with higher sleep pressure (Xing et al., 2019), this sleep pressure dissipated more upon sleep.

As with DEC2 and ADRB1, the NSPR1 Y206H mutation had an effect decreasing tau proteins and amyloid plaque formation that can contribute to Alzheimer's disease (Dong et al., 2022). Sleep typically removes harmful metabolites by transferring them into CSF and clearing it through the glymphatic system (Han,Yang and Huang, 2024). In Y206H mutant PS19 mice, there is less tau found in CSF, however, this did not result in changes to extracellular tau levels (Dong et al., 2022). This implies another clearance mechanism of tau in mutant mice compared to wild type mice(Dong et al., 2022). Given less synaptic loss and astrogliosis observed in NPSR1-Y206H, alternative pathways, such as degradation within glia may participate in the clearance of extracellular tau, leading to sleep resistance (Dong et al., 2022).

5. GRM1 Mutations

Most recently, two mutations in the Glutamate Metabotropic receptor 1 (GRM1) were found to result in shortened sleep in 2021 (Zheng and Zhang, 2022). GRMs are G-protein coupled receptors involved in the modulation of synaptic transmission and neuronal excitability (Zheng and Zhang, 2022) and GRM1 is a member of the family coded for on chromosome 6, likely around 6q24.2–24.3 (Davarniya et al., 2015). These mutations were R889W and S458A (Zheng and Zhang, 2022). Although the mutations were found on different domains of the protein, with the R889W on the C-terminal intracellular domain and S458A on the N-terminal extracellular domain, both are believed to reduce extracellular signal-regulated kinase (ERK) phosphorylation and activity to decrease sleep (Zheng and Zhang, 2022).

5.1. GRM1 observations in humans

In one family, the R889W mutation resulted in average sleep durations of 6.05, 5.15, and 5.10h in 3 members while the S458A mutation resulted in a carrier sleeping 6.00h on average, compared to around 6.93 hours in a noncarrier sibling (Zheng and Zhang, 2022).

5.2. GRM1 observations in mice

Knock-in mice supported the effect of decreased sleep but only by around 25 minutes (Shi et al., 2020). Notably, only NREM sleep decreased without changes in delta power compared to WT mice (Shi et al., 2020). Sleep pressure and the sleep recovery process as well as other sleep parameters showed no significant changes, making these GRM1 mutations comparatively the most mild (Shi et al., 2020).

6. Recommended Testing for Chronic Health Implications

Aside from neurodegeneration (Dong et al., 2022), chronic effects common to SD haven't been looked into in depth. Because chronic SD is more likely to accurately reflect the sleep pattern in mutation carrier lifestyles, and most significant effects of SD occur over a longer timeframe, chronic short sleep and its effects should be tested in these relatively newly discovered mutations. These effects may be less apparent without closer monitoring. Furthermore, it has reported that among

 doi:10.20944/preprints202410.0974.v1

students, SD has mostly had physical effects as opposed to cognitive ones (Liew and Aung, 2020). In researching these genes, mice should be physically tested as well. While all previously mentioned sleep deprivation effects would ideally be monitored, more practically, there are specific effects that may be more significant or likely in specific mutations.

For DEC2 in particular, the potential for Alzheimer's Disorder is a logical concern given the known impact of increased orexin found to reduce Aβ clearance in sleep deprivation (Dong et al., 2022; Han,Yang and Huang, 2024). Upregulation of orexin can prevent expansion of interstitial spaces for glymphatic clearance to contribute to the acceleration of AD (Han,Yang and Huang, 2024). However, in experimentation, it has been found that there may be another mechanism of this mutation that decreases tau aggregates, at least for the P384R mutation (Dong et al., 2022). Further directions with DEC2 mutations could be in the circadian rhythm in general, as DEC2 is central to its core regulation (Zheng and Zhang, 2022), and sleep and the circadian rhythm are closely linked processes (Franken and Dijk, 2009). While circadian rhythm dysregulation is not a direct health issue, circadian control of the endocrine system and metabolism can be and should also be studied (Li et al., 2024). Finally, DEC2's potential role as a tumor suppressor in breast cancer may be of attention as well, as the mutation decreases the activity of DEC2 (Fang et al., 2020).

For ADRB1, this receptor is also seen in the heart, with the B1 adrenergic receptor being the most expressed B adrenergic receptor (60-80%) and polymorphisms having led to heart failure (Muthumala et al., 2008). Increased activity in B1AR could lead to heart failure (Muthumala et al., 2008), and as activity was increased by the mutation (Shi et al., 2019), this should be looked into.

For NPSR1, the main significance could be in its role in asthma and immune response (Vercelli, 2008). Although causation has yet to be identified, NPSR1 polymorphisms have been associated with asthma, inflammatory bowel disease, and panic disorders (Aneddaet al., 2011). Upregulation was present in mice susceptible to inflammation (Vercelli, 2008). Therefore, it is plausible that overactivation could increase anxiety, fear responses, nociception or inflammation (Aneddaet al., 2011).

For GRM1, the downstream targets and effects of the ERK pathway are critical for many processes. ERK is important for proliferation, differentiation, and apoptosis, along with brain memory formation and learning (Guo et al., 2020). Downregulation of the ERK pathway may be hypothesized to have inhibitory effects on development or make cells more likely to apoptose under stress, as ERK activation and entry in the nucleus has an anti-apoptotic effect (Guo et al., 2020). However, given the lack of apparent effects and the milder change in sleep duration, it is possible that there are control mechanisms in place in vivo (Shi et al., 2020). So far, small hippocampus transcriptome differences were observed between S458A mutant mice and WT mice (Shi et al., 2020). Notably, the GRM1 FNSS mutations differ from the other 3 gene mutations in that only NREM sleep decreased (Shi et al., 2020). There also have not been studies on its impact on Aβ or tau concentrations/clearance as there have with the other mutations, showing neurodegeneration resistance mechanisms, and these experiments could be conducted.

In experiments with mice, acute SD is often 6-8 hours of gentle prodding (Bellesi et al., 2018). Chronic SD typically refers to at least 4 days, up to months and can also be achieved by daytime gentle stimuli, the modified multi-platform (MMP) method, or nighttime forced locomotion on a slow treadmill (Bellesi et al., 2018; Niu et al., 2021).

 doi:10.20944/preprints202410.0974.v1

Table 2. Summary of Critical Health Effects to Test for in Mice.

Relevant gene(s)	System affected	Effects to test for	Estimated duration of study	Relevant paper(s)
DEC2, NPSR1	Immune response	Neuroinflammation Inflammation Asthma Immune Function	21 days (De Lorenzo et al., 2018)	Chronic Sleep Restriction Impairs the Antitumor Immune Response in Mice (De Lorenzo et al., 2018)
DEC2	Metabolism and hormones	Leptin,Ghrelin,Obesity Insulin resistance Prolactin/Growth hormone/Insulin-like growth factor 1 Corticosterone	24 weeks (Van Dycke et al., 2015)	Chronically Alternating Light Cycles Increase Breast Cancer Risk in Mice (Van Dycke et al., 2015)
			5 days (Shigiyama et al., 2018)	Mechanisms of sleep deprivation-induced hepatic steatosis and insulin resistance in mice(Shigiyama et al., 2018)
DEC2	Alzheimer's Disease	Extracellular and CSF Aβ and Tau protein levels	6 months (Dong et al., 2022)	Familial natural short sleep mutations reduce Alzheimer pathology in mice (Dong et al., 2022)
DEC2	Breast Cancer	Tumor presence Tumor characterization	51 weeks (Van Dycke et al., 2015)	Chronically Alternating Light Cycles Increase Breast Cancer Risk in Mice (Van Dycke et al., 2015)
ADRB1	Cardiovascular System	Blood pressure Heart Failure	4 months (Song et al., 2023)	Long-Term Sleep Deprivation-Induced Myocardial Remodeling and Mitochondrial Dysfunction in Mice Were Attenuated by Lipoic Acid and N-Acetylcysteine (Song et al., 2023)
NPSR1	Mood disorders	Anxiety Depressive Symptoms	9 weeks (Arora et al., 2021)	Neurobehavioral alterations in a mouse model of chronic partial sleep deprivation (Arora et al., 2021)
GRM1	ERK pathway	ERK phosphorylation Development	5 weeks (Li et al., 2022)	Role of Sleep Restriction in Daily Rhythms of Expression of Hypothalamic Core Clock Genes in Mice (Li et al., 2022)
			20 days (Wen-jing, 2018)	The Effect of Sleep Deprivation on Growth and Development in Mice (Wen-jing, 2018)
General	Muscle	Muscle synthesis and breakdown	8 weeks (Yang et al., 2019)	Sleep deprivation reduces the recovery of muscle injury induced by high-intensity exercise in a mouse model (Yang et al., 2019)

 doi:10.20944/preprints202410.0974.v1

This table introduces effects observed in typical SD to be tested for in FNSS gene mutated mice. It also includes a relevant paper to provide sample methods, with an estimated duration of study based on how long it took for the results reported in the paper. A comprehensive summary of all experiments conducted in mice SD is beyond the scope of this current review.

7. Discussion

In recent decades, research into the genetics of sleep has been promising. With the prevalence of genetic study tools applied and general growing attention towards the field of sleep, it is likely that more sleep genes will be discovered (Pandi-Perumal et al., 2024).

As the previous review article by Zheng and Zhang summarized, the 4 FNSS genes have different functions and differential impacts on sleep when mutated, indicating different mechanisms (Zheng and Zhang, 2022). Of the four mutations, DEC2, ADRB1, and NPSR1 all lead to enhanced wake promoting signals, suggesting they don't directly alter Process S and sleep homeostasis. Increased wake signals can increase sleep debt tolerance (DEC2) or sleep power (ADRB1, NPSR1), so it is possible natural short sleep does not lead to accumulation of sleep debt (Zheng and Zhang, 2022). With the more recently discovered GRM1, more sleep-specific investigations have yet to be conducted so far.

Comparing chronic SD mice with mutant mice could reveal differences in physiology, paying attention to the developmental age in mice compared to humans (Dutta and Sengupta, 2016). Finally, studies in mortality have not been reported, taking up to 4 years to conduct across a mouse's lifespan (Dutta and Sengupta, 2016).

Given the lack of cognitive deficit observed in these short sleepers, one may rethink the role of sleep duration in memory consolidation. Shorter sleep duration in itself may not impair memory or cognitive function. Interestingly, 3 of 4 genes (DEC2, ADRB1, and NPSR1) have shown mechanisms for preventing amyloid and tau accumulation, in line with no negative effects compensating SD's role in Alzheimer's progression (Han,Yang and Huang, 2024). This has yet to be investigated in GRM1, but would be unsurprising to find as also the case. FNSS mutations could advance research in neuroprotection and neurodegeneration. Additionally, as ADRB1, GRM1, and NPSR1 are receptors studied as therapeutic targets, drugs that manipulate these activities could be researched for sleep associated disorders (Bender, 2019; Soriano-Ursúa et al., 2013). While FNSS genes hold great potential for scientific understanding and therapeutics, it is important not to overdraw conclusions and conduct rigorous experiments for a fuller understanding. By investigating the mechanisms of each genetic mutation and possibilities of unintended consequences, research in sleep and reducing the harms of its deprivation can be advanced.

Conflict of Interest: The author declares that all research was conducted in the absence of any commercial or financial relationships that could be a potential conflict of interest.

Author contributions: HG conceived of, drafted, and edited the manuscript.

Funding: Not applicable.

Acknowledgements: The author would like to thank Aleksandra Stryjska at Duke Kunshan University and Kehan (Wendy) Wang at Duke University for thorough feedback on improving the clarity and organization of previous versions of the manuscript.

Supplementary Materials: Primer Design for Short Sleep Gene Mutation Screening; Laboratory Methods to Test for Health Effects In Mice

References

1. Alhola, P. and Polo-Kantola, P. (2007). Sleep deprivation: Impact on cognitive performance, Neuropsychiatric Disease and Treatment, 3(5), pp. 553–567. doi: https://doi.org/10.2147/ndt.s12160203.
2. Anedda, F., Zucchelli, M., Schepis, D., Hellquist, A., Corrado, L., D'Alfonso, S., Achour, A., McInerney, G., Bertorello, A., Lördal, M., Befrits, R., Björk, J., Bresso, F., Törkvist, L., Halfvarson, J., Kere, J. and D'Amato,

M. (2011). Multiple Polymorphisms Affect Expression and Function of the Neuropeptide S Receptor (NPSR1). PLoS ONE, 6(12), p.e29523. doi:https://doi.org/10.1371/journal.pone.0029523.

3. Arora, S., Dharavath, R.N., Bansal, Y., Bishnoi, M., Kondepudi, K.K. and Chopra, K. (2021). Neurobehavioral alterations in a mouse model of chronic partial sleep deprivation. Metabolic Brain Disease, 36(6), pp.1315–1330. doi:https://doi.org/10.1007/s11011-021-00693-9.
4. Ashbrook, L.H., Krystal, A.D., Fu, Y.-H. and Ptáček, L.J. (2019). Genetics of the human circadian clock and sleep homeostat. Neuropsychopharmacology, 45(1), pp.45–54. doi:https://doi.org/10.1038/s41386-019-0476-7.
5. Bellesi, M., Haswell, J.D., de Vivo, L., Marshall, W., Roseboom, P.H., Tononi, G. and Cirelli, C. (2018). Myelin modifications after chronic sleep loss in adolescent mice. Sleep, [online] 41(5). doi:https://doi.org/10.1093/sleep/zsy034.
6. Bender, E. (2019). A Genetic Mutation for Short Sleep Prevents Memory Deficits in a Mouse Model. Neurology Today, 19(23), pp.19–23. doi:https://doi.org/10.1097/01.nt.0000617160.87834.82.
7. Davarniya, B., Hu, H., Kahrizi, K., Musante, L., Fattahi, Z., Hosseini, M., Maqsoud, F., Farajollahi, R., Wienker, T.F., Ropers, H.H. and Najmabadi, H. (2015). The Role of a Novel TRMT1 Gene Mutation and Rare GRM1 Gene Defect in Intellectual Disability in Two Azeri Families. PLOS ONE, 10(8), p.e0129631. doi:https://doi.org/10.1371/journal.pone.0129631.
8. De Lorenzo, B., Novaes e Brito, R., Paslar Leal, T., Piqueira Garcia, N., Martins dos Santos, R., Alvares-Saraiva, A., Perez Hurtado, E., Braga dos Reis, T. and Duarte Palma, B. (2018). Chronic Sleep Restriction Impairs the Antitumor Immune Response in Mice. Neuroimmunomodulation, 25(2), pp.59–67. doi:https://doi.org/10.1159/000490352.
9. Dong, Q., Gentry, N.W., McMahon, T., Yamazaki, M., Benitez-Rivera, L., Wang, T., Gan, L., Ptáček, L. and Fu, Y.-H. (2022). Familial natural short sleep mutations reduce Alzheimer pathology in mice. iScience, [online] 25(4), p.103964. doi:https://doi.org/10.1016/j.isci.2022.103964.
10. Dong, Q., Ptáček, L.J. and Fu, Y. (2023). Mutant β 1 -adrenergic receptor improves REM sleep and ameliorates tau accumulation in a mouse model of tauopathy. Proceedings of the National Academy of Sciences of the United States of America, 120(15). doi:https://doi.org/10.1073/pnas.2221686120.
11. Dutta, S. and Sengupta, P. (2016). Men and mice: Relating their ages. Life Sciences, 152, pp.244–248. doi:https://doi.org/10.1016/j.lfs.2015.10.025.
12. Fang, W., Li, Q., Wang, M., Zheng, M. and Xu, H. (2020). DEC2 Serves as Potential Tumor Suppressor in Breast Carcinoma. Disease Markers, [online] 2020, pp.1–10. doi:https://doi.org/10.1155/2020/6053154.
13. Ford, E.S., Wheaton, A.G., Cunningham, T.J., Giles, W.H., Chapman, D.P. and Croft, J.B. (2014). Trends in Outpatient Visits for Insomnia, Sleep Apnea, and Prescriptions for Sleep Medications among US Adults: Findings from the National Ambulatory Medical Care Survey 1999-2010. Sleep, 37(8), pp.1283–1293. doi:https://doi.org/10.5665/sleep.3914.
14. Franken, P. and Dijk, D.-J. . (2009). Circadian clock genes and sleep homeostasis. European Journal of Neuroscience, 29(9), pp.1820–1829. doi:https://doi.org/10.1111/j.1460-9568.2009.06723.x.
15. Fujimoto, K., Shen, M., Noshiro, M., Matsubara, K., Shingu, S., Honda, K., Yoshida, E., Suardita, K., Matsuda, Y. and Kato, Y. (2001). Molecular Cloning and Characterization of DEC2, a New Member of Basic Helix-Loop-Helix Proteins. Biochemical and Biophysical Research Communications, [online] 280(1), pp.164–171. doi:https://doi.org/10.1006/bbrc.2000.4133.
16. Guo, Y., Pan, W., Liu, S., Shen, Z., Xu, Y. and Hu, L. (2020). ERK/MAPK signalling pathway and tumorigenesis (Review). Experimental and Therapeutic Medicine, [online] 19(3). doi:https://doi.org/10.3892/etm.2020.8454.
17. Han, Z., Yang, X. and Huang, S. (2024). Sleep deprivation: A risk factor for the pathogenesis and progression of Alzheimer's disease. Heliyon, [online] 10(7), pp.e28819–e28819. doi:https://doi.org/10.1016/j.heliyon.2024.e28819.
18. He, Y., Jones, C.R., Fujiki, N., Xu, Y., Guo, B., Holder, J.L., Rossner, M.J., Nishino, S. and Fu, Y.-H. . (2009). The Transcriptional Repressor DEC2 Regulates Sleep Length in Mammals. Science, 325(5942), pp.866–870.
19. doi:https://doi.org/10.1126/science.1174443.
20. Henström, M., Zucchelli, M., Söderhäll, C., Bergström, A., Kere, J., Melén, E., Olén, O. and D'Amato, M. (2014). NPSR1polymorphisms influence recurrent abdominal pain in children: a population-based study. Neurogastroenterology & Motility, 26(10), pp.1417–1425. doi:https://doi.org/10.1111/nmo.12401.
21. Hirano, A., Hsu, P.-K., Zhang, L., Xing, L., McMahon, T., Yamazaki, M., Ptáček, L.J. and Fu, Y.-H. (2018). DEC2 modulates orexin expression and regulates sleep. Proceedings of the National Academy of Sciences, [online] 115(13), pp.3434–3439. doi:https://doi.org/10.1073/pnas.1801693115.
22. Hoyos, C., Glozier, N. and Marshall, N.S. (2015). Recent Evidence on Worldwide Trends on Sleep Duration. Current Sleep Medicine Reports, 1(4), pp.195–204. doi:https://doi.org/10.1007/s40675-015-0024-x.
23. Li, W., Wang, Z., Cao, J., Dong, Y. and Chen, Y. (2022). Role of Sleep Restriction in Daily Rhythms of Expression of Hypothalamic Core Clock Genes in Mice. Current Issues in Molecular Biology, [online] 44(2), pp.609–625. doi:https://doi.org/10.3390/cimb44020042.

24. Li, Y.-F., Niu, L.-Y., Fan, J.-F., Yao, Z.-C., Shen, L.-Y., Wang, Y.-K. and He, Y. (2024). The Effect and Underlying Mechanism of Sleep Deprivation on Several Gastrointestinal Physiology and Diseases. Medicine Research, [online] 8(Li et al., 2024), pp.230006–230006. doi:https://doi.org/10.21127/yaoyimr20230006.
25. Liew, S.C. and Aung, T. (2020). Sleep deprivation and its association with diseases- a review. Sleep Medicine, [online] 77. doi:https://doi.org/10.1016/j.sleep.2020.07.048.
26. Liu, D.-X., He, X., Wu, D., Zhang, Q., Yang, C., Liang, F.-Y., He, X.-F., Dai, G.-Y., Pei, Z., Lan, Y. and Xu, G.-Q. (2017). Continuous theta burst stimulation facilitates the clearance efficiency of the glymphatic pathway in a mouse model of sleep deprivation. Neuroscience Letters, [online] 653, pp.189–194. doi:https://doi.org/10.1016/j.neulet.2017.05.064.
27. Long, S., Ding, R., Wang, J., Yu, Y., Lu, J. and Yao, D. (2021). Sleep Quality and Electroencephalogram Delta Power. Frontiers in Neuroscience, 15. doi:https://doi.org/10.3389/fnins.2021.803507.
28. Morrison, M., Halson, S.L., Weakley, J. and Hawley, J.A. (2022). Sleep, circadian biology and skeletal muscle interactions: Implications for metabolic health. Sleep Medicine Reviews, [online] 66, p.101700. doi:https://doi.org/10.1016/j.smrv.2022.101700.
29. Muthumala, A., Drenos, F., Elliott, P.M. and Humphries, S.E. (2008). Role of β adrenergic receptor polymorphisms in heart failure: Systematic review and meta-analysis. European Journal of Heart Failure, 10(1), pp.3–13. doi:https://doi.org/10.1016/j.ejheart.2007.11.008.
30. Niu, L., Zhang, F., Xu, X., Yang, Y., Li, S., Liu, H. and Le, W. (2021). Chronic sleep deprivation altered the expression of circadian clock genes and aggravated Alzheimer's disease neuropathology. Brain Pathology. doi:https://doi.org/10.1111/bpa.13028.
31. Pacanowski, M.A. and Johnson, J.A. (2007). PharmGKB Submission Update: IX. ADRB1 Gene Summary. Pharmacological Reviews, 59(1), pp.2–4. doi:https://doi.org/10.1124/pr.59.1.6.
32. Pandi-Perumal, S.R., Saravanan Konda Mani, Paul, S., Pandian, G.N. and Saravana Babu Chidambaram (2024). Waking Up the Sleep Field: An Overview on the Implications of Genetics and Bioinformatics of Sleep. Molecular Biotechnology. doi:https://doi.org/10.1007/s12033-023-01009-1.
33. Pellegrino, R., Kavakli, I.H., Goel, N., Cardinale, C.J., Dinges, D.F., Kuna, S.T., Maislin, G., Van Dongen, H.P.A., Tufik, S., Hogenesch, J.B., Hakonarson, H. and Pack, A.I. (2014). A Novel BHLHE41 Variant is Associated with Short Sleep and Resistance to Sleep Deprivation in Humans. Sleep, [online] 37(8), pp.1327–1336. doi:https://doi.org/10.5665/sleep.3924.
34. Shi, G., Xing, L., Wu, D., Bhattacharyya, B.J., Jones, C.R., McMahon, T., Chong, S.Y.C., Chen, J.A., Coppola, G., Geschwind, D., Krystal, A., Ptáček, L.J. and Fu, Y.-H. (2019). A Rare Mutation of β1-Adrenergic Receptor Affects Sleep/Wake Behaviors. Neuron, 103(6), pp.1044-1055.e7. doi:https://doi.org/10.1016/j.neuron.2019.07.026.
35. Shi, G., Yin, C., Fan, Z., Xing, L., Mostovoy, Y., Kwok, P.-Y., Ashbrook, L.H., Krystal, A.D., Ptáček, L.J. and Fu, Y.-H. (2020). Mutations in Metabotropic Glutamate Receptor 1 Contribute to Natural Short Sleep Trait. Current Biology. doi:https://doi.org/10.1016/j.cub.2020.09.071.
36. Shigiyama, F., Kumashiro, N., Tsuneoka, Y., Igarashi, H., Yoshikawa, F., Kakehi, S., Funato, H. and Hirose, T. (2018). Mechanisms of sleep deprivation-induced hepatic steatosis and insulin resistance in mice. American Journal of Physiology-Endocrinology and Metabolism, 315(5), pp.E848–E858. doi:https://doi.org/10.1152/ajpendo.00072.2018.
37. Song, F., Lin, J., Zhang, H., Guo, Y., Mao, Y., Liu, Z., Li, G. and Wang, Y. (2023). Long-Term Sleep Deprivation-Induced Myocardial Remodeling and Mitochondrial Dysfunction in Mice Were Attenuated by Lipoic Acid and N-Acetylcysteine. Pharmaceuticals, [online] 16(1), p.51. doi:https://doi.org/10.3390/ph16010051.
38. Soriano-Ursúa, M.A., Trujillo-Ferrara, J.G., José Correa-Basurto and Vilar, S. (2013). Recent Structural Advances of β1 and β2 Adrenoceptors Yield Keys for Ligand Recognition and Drug Design. Journal of Medicinal Chemistry, 56(21), pp.8207–8223. doi:https://doi.org/10.1021/jm400471z.
39. Van Dycke, Kirsten C.G., Rodenburg, W., van Oostrom, Conny T.M., van Kerkhof, Linda W.M., Pennings, Jeroen L.A., Roenneberg, T., van Steeg, H. and van der Horst, Gijsbertus T.J. (2015). Chronically Alternating Light Cycles Increase Breast Cancer Risk in Mice. Current Biology, 25(14), pp.1932–1937. doi:https://doi.org/10.1016/j.cub.2015.06.012.
40. Vercelli, D. (2008). Discovering susceptibility genes for asthma and allergy. Nature Reviews Immunology, 8(3), pp.169–182. doi:https://doi.org/10.1038/nri2257.
41. Walker, W.H., Walton, J.C., DeVries, A.C. and Nelson, R.J. (2020). Circadian rhythm disruption and mental health. Translational Psychiatry, [online] 10(1). doi:https://doi.org/10.1038/s41398-020-0694-0.
42. Webb, J.M. and Fu, Y.-H. (2021). Recent advances in sleep genetics. Current Opinion in Neurobiology, [online] 69, pp.19–24. doi:https://doi.org/10.1016/j.conb.2020.11.012.
43. Wen-jing, Y. (2018). The Effect of Sleep Deprivation on Growth and Development in Mice. Laboratory Animal and Comparative Medicine, [online] 38(3), p.212. doi:https://doi.org/10.3969/j.issn.1674-5817.2018.03.009.

 doi:10.20944/preprints202410.0974.v1

44. Xing, L., Shi, G., Mostovoy, Y., Gentry, N.W., Fan, Z., McMahon, T.B., Kwok, P.-Y., Jones, C.R., Ptáček, L.J. and Fu, Y.-H. (2019). Mutant neuropeptide S receptor reduces sleep duration with preserved memory consolidation. Science Translational Medicine, 11(514). doi:https://doi.org/10.1126/scitranslmed.aax2014.
45. Xing, L., Zou, X., Yin, C., Webb, J.M., Shi, G., Ptáček, L.J. and Fu, Y.-H. (2024). Diverse roles of pontine NPS-expressing neurons in sleep regulation. Proceedings of the National Academy of Sciences, 121(9). doi:https://doi.org/10.1073/pnas.2320276121.
46. Yang, D.-F., Shen, Y.-L., Wu, C., Huang, Y.-S., Lee, P.-Y., Er, N.X., Huang, W.-C. and Tung, Y.-T. (2019). Sleep deprivation reduces the recovery of muscle injury induced by high-intensity exercise in a mouse model. Life Sciences, 235, p.116835. doi:https://doi.org/10.1016/j.lfs.2019.116835.
47. Yook, J.H., Rizwan, M., Shahid, N. ul ain, Naguit, N., Jakkoju, R., Laeeq, S., Reghefaoui, T., Zahoor, H. and Mohammed, L. (2021). Some Twist of Molecular Circuitry Fast Forwards Overnight Sleep Hours: A Systematic Review of Natural Short Sleepers' Genes. Cureus. [online] doi:https://doi.org/10.7759/cureus.19045.
48. Zheng, L. and Zhang, L. (2022). The molecular mechanism of natural short sleep: A path towards understanding why we need to sleep. Brain Science Advances. doi:https://doi.org/10.26599/bsa.2022.9050003.