SLEEPSUMMIT
Prader-Willi Syndrome Association | USA

Genetics of Sleep & Sleep Disorders in Children with PWS

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Althea Robinson Shelton, M.D.
Associate Professor
Department of Neurology
Vanderbilt University Medical Center

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Session overview

I. Research updates (Olivia J. Veatch, Ph.D.)
   a. Background on biology of circadian rhythms and sleep
   b. Overview of how genetics of PWS and sleep are connected
   c. Current knowledge of how sleep disorders relate to molecular subtype

II. Clinical knowledge (Althea Robinson Shelton, M.D.)
   a. Prevalent sleep disorders in individuals with PWS
   b. How to recognize symptoms and how to diagnose sleep disorders
   c. Treatment approaches for sleep disorders in PWS

III. Questions and discussion

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Genetics of Sleep & Sleep Disorders in Children with PWS: Current knowledge & research

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University of Kansas Medical Center

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Sleep is important for health

- **Brains build connections during sleep (aka plasticity)**
  - **Restricting sleep during adolescence impacts adult behavior in animal models** Kayser et al., Science 2014, PMC4479292

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- **Sleeping helps stimulate metabolism**
  - **Sleeping less relates to BMI increases in typically-developing children**
    Grandner et al., Obesity 2015, PMC4700549

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- Brain plasticity and metabolism are disrupted in PWS making healthy sleep especially important

- Finding genetic changes in PWS that alter sleep may help improve treatment for sleep problems

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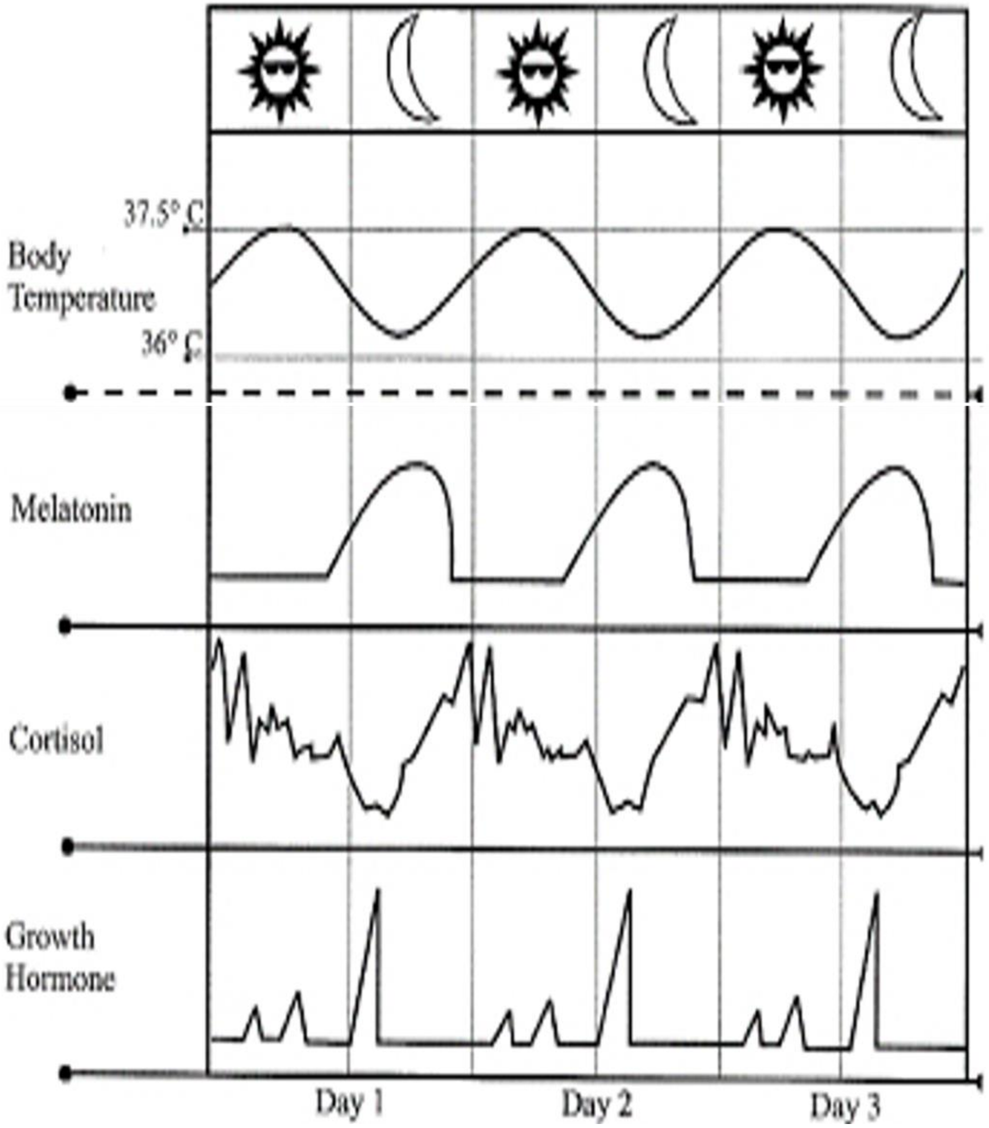
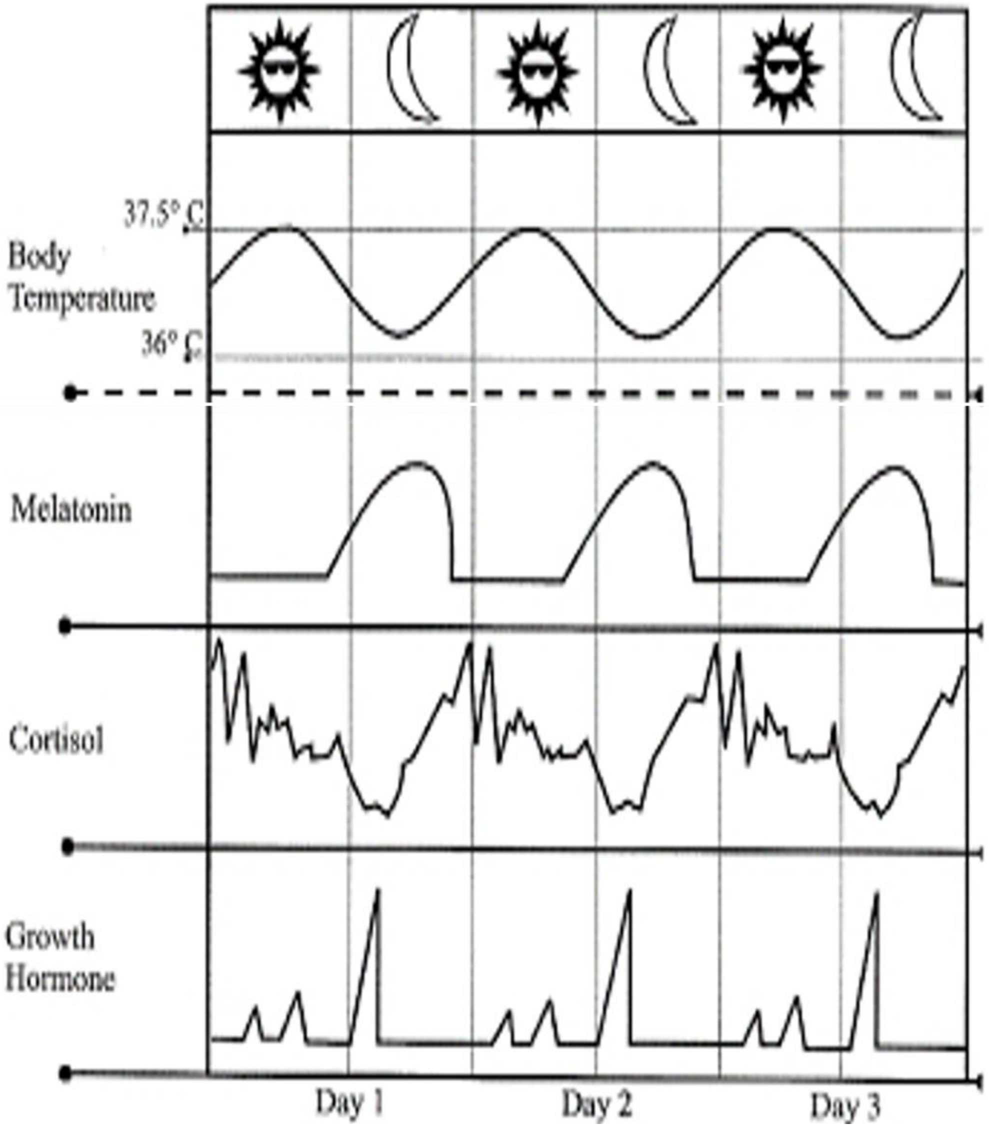
Circadian rhythms and how they regulate sleep



- Physical, mental, and behavioral changes follow a daily cycle

Circadian rhythms and how they regulate sleep



- Physical, mental, and behavioral changes follow a daily cycle
- Production of several hormones peaks at night

GH-promotes metabolism & growth

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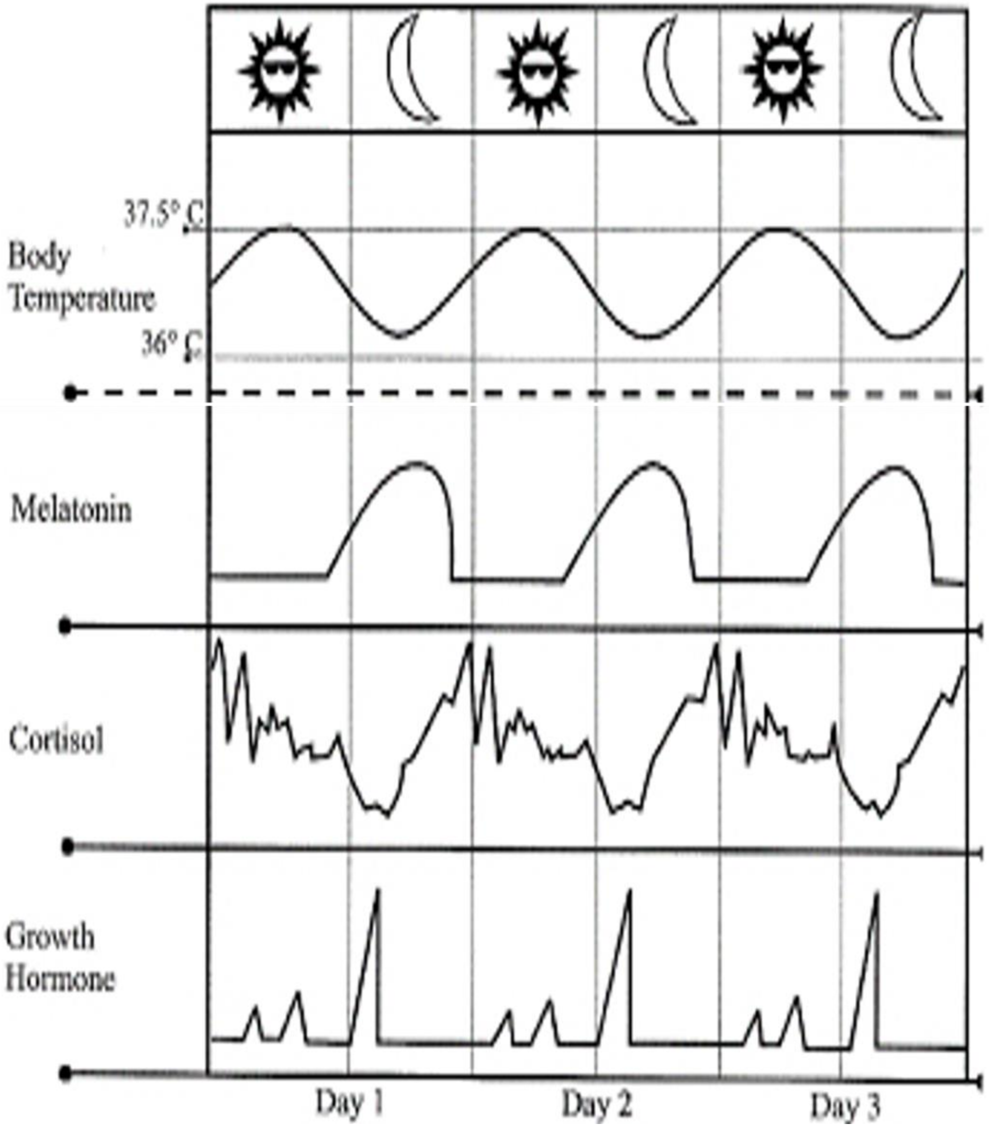

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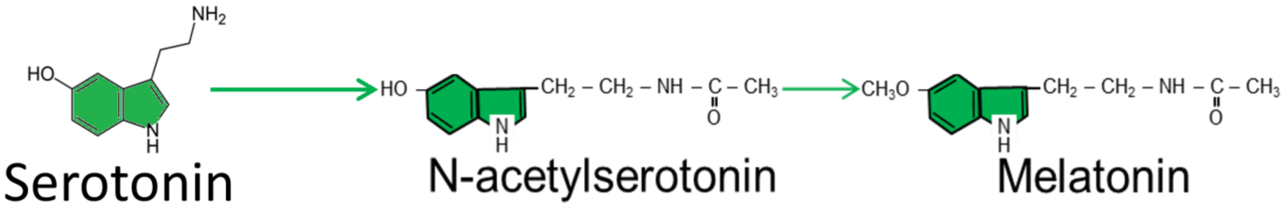
<u>Melatonin</u>-promotes sleep



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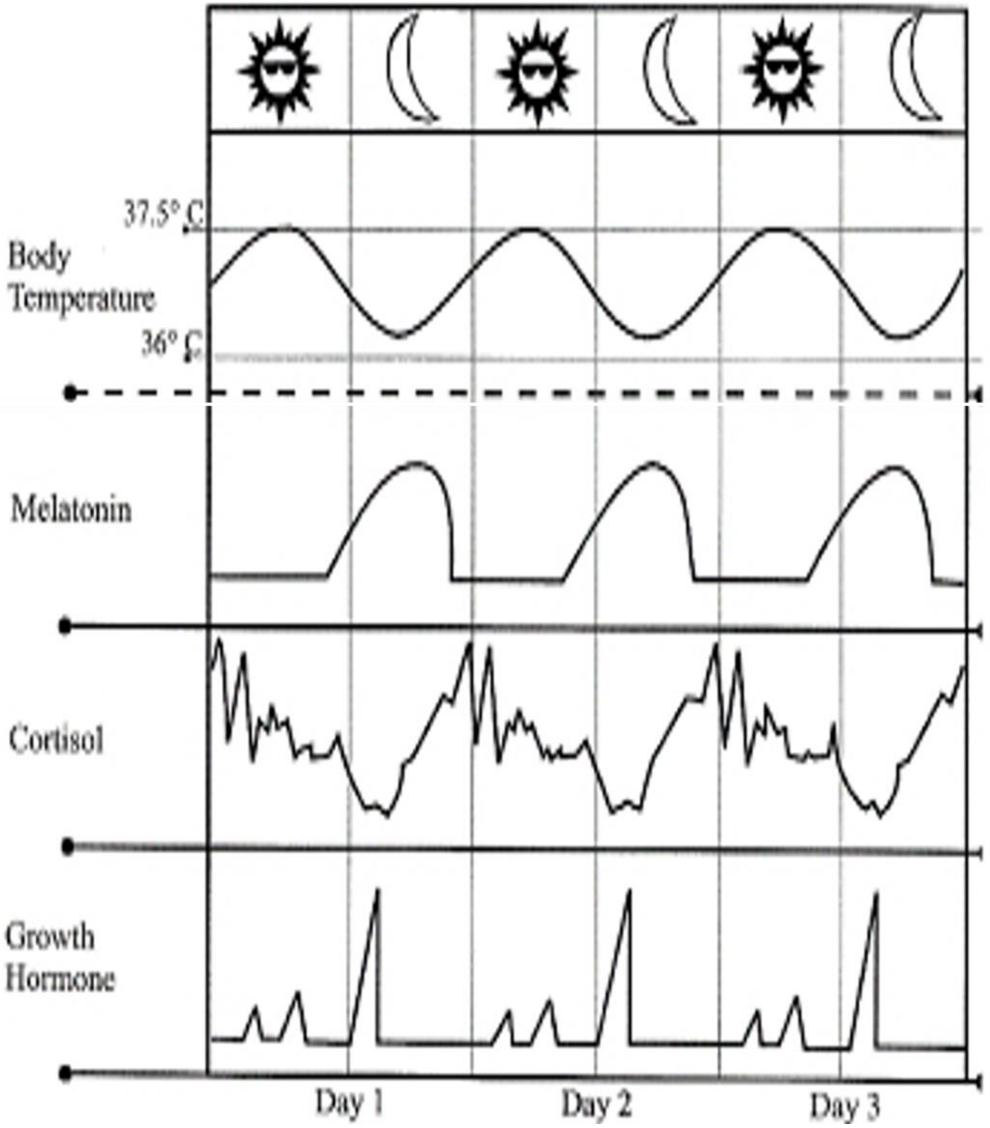

- Physical, mental, and behavioral changes follow a daily cycle
- Production of several hormones peaks at night
- Other hormones and physical changes peak during the day

Cortisol-slows metabolism & reduces inflammation

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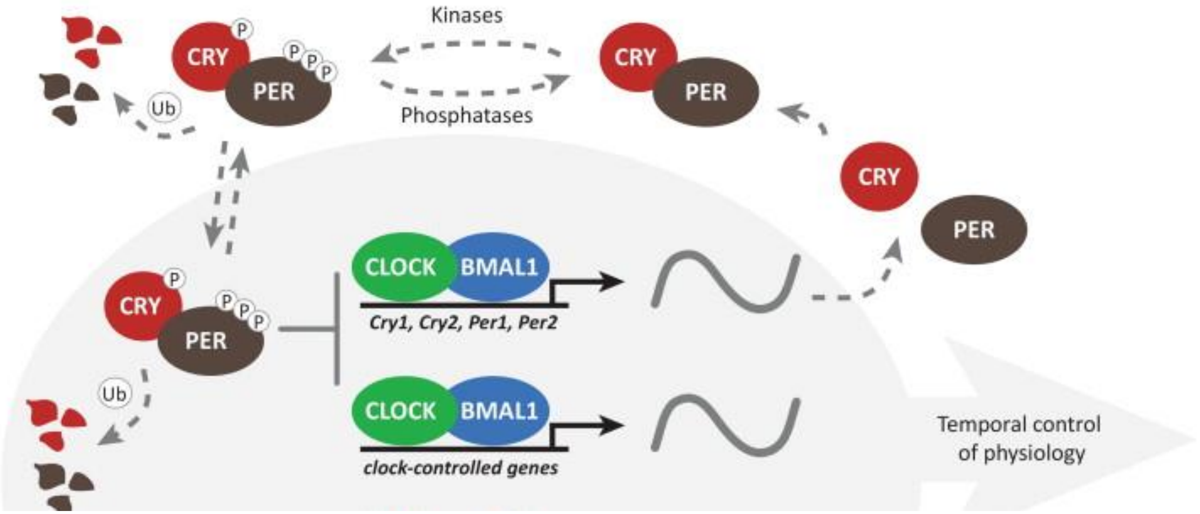
Circadian rhythms and how they regulate sleep

- Sleep/wake cycle in humans controlled by genes



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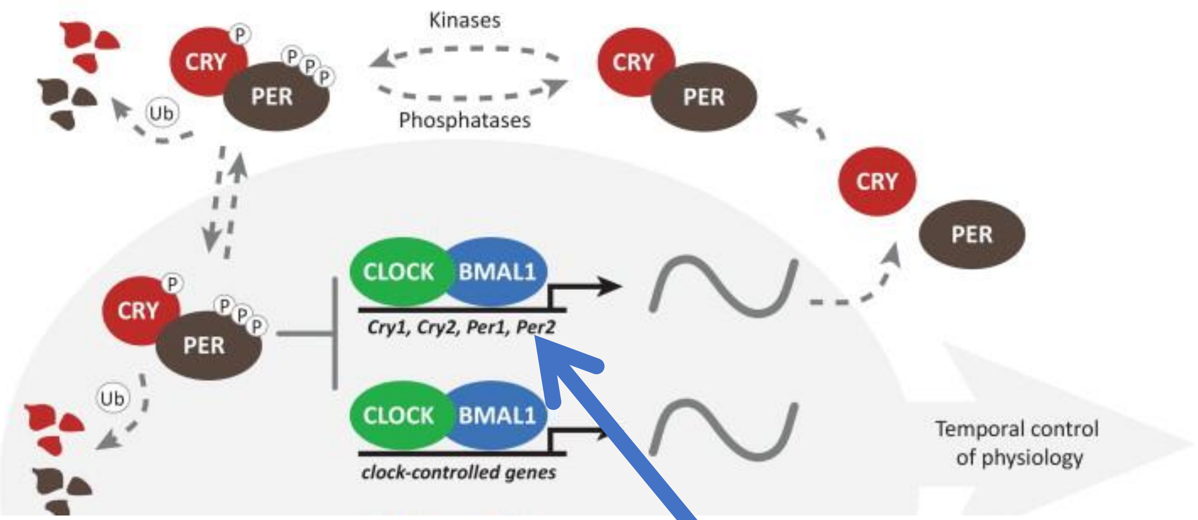

Positive:
Promotes sleep
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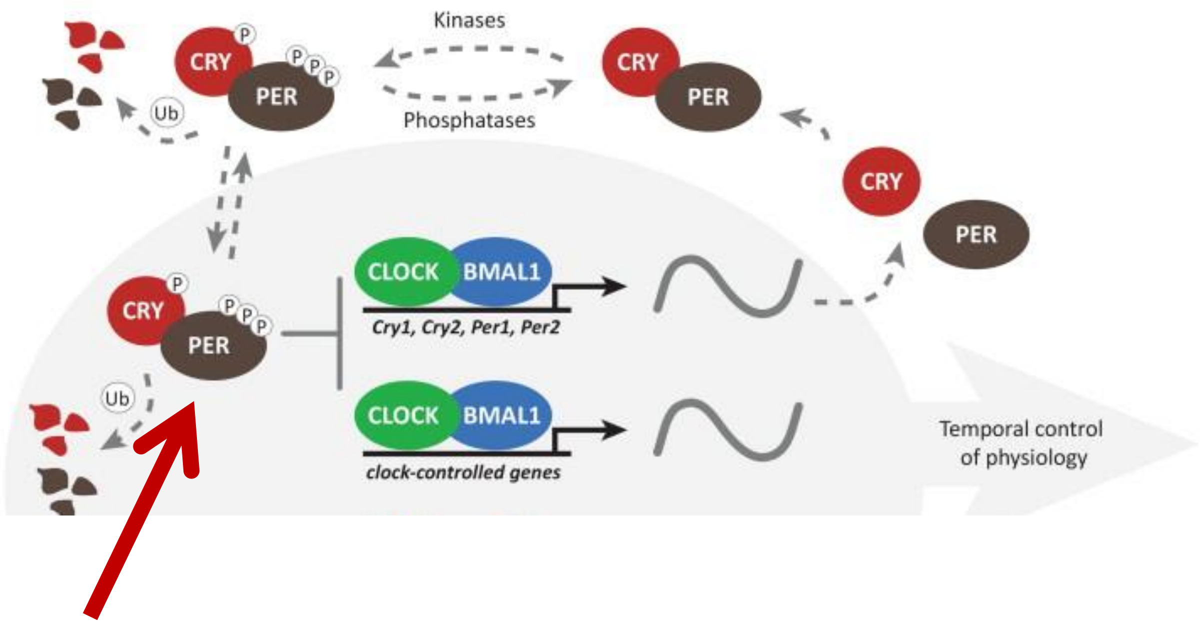

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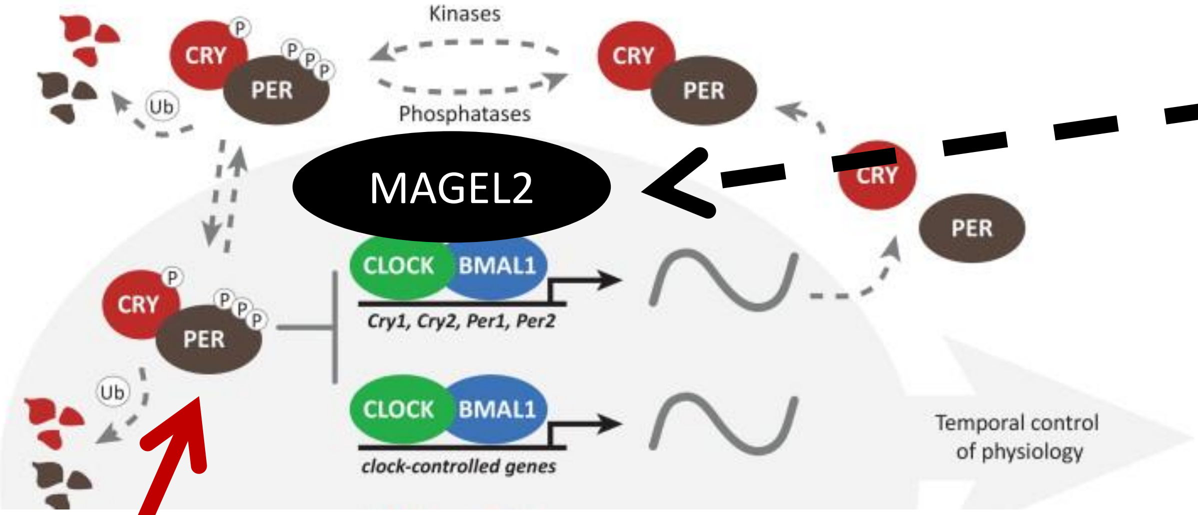
PWS genes in Master Clock



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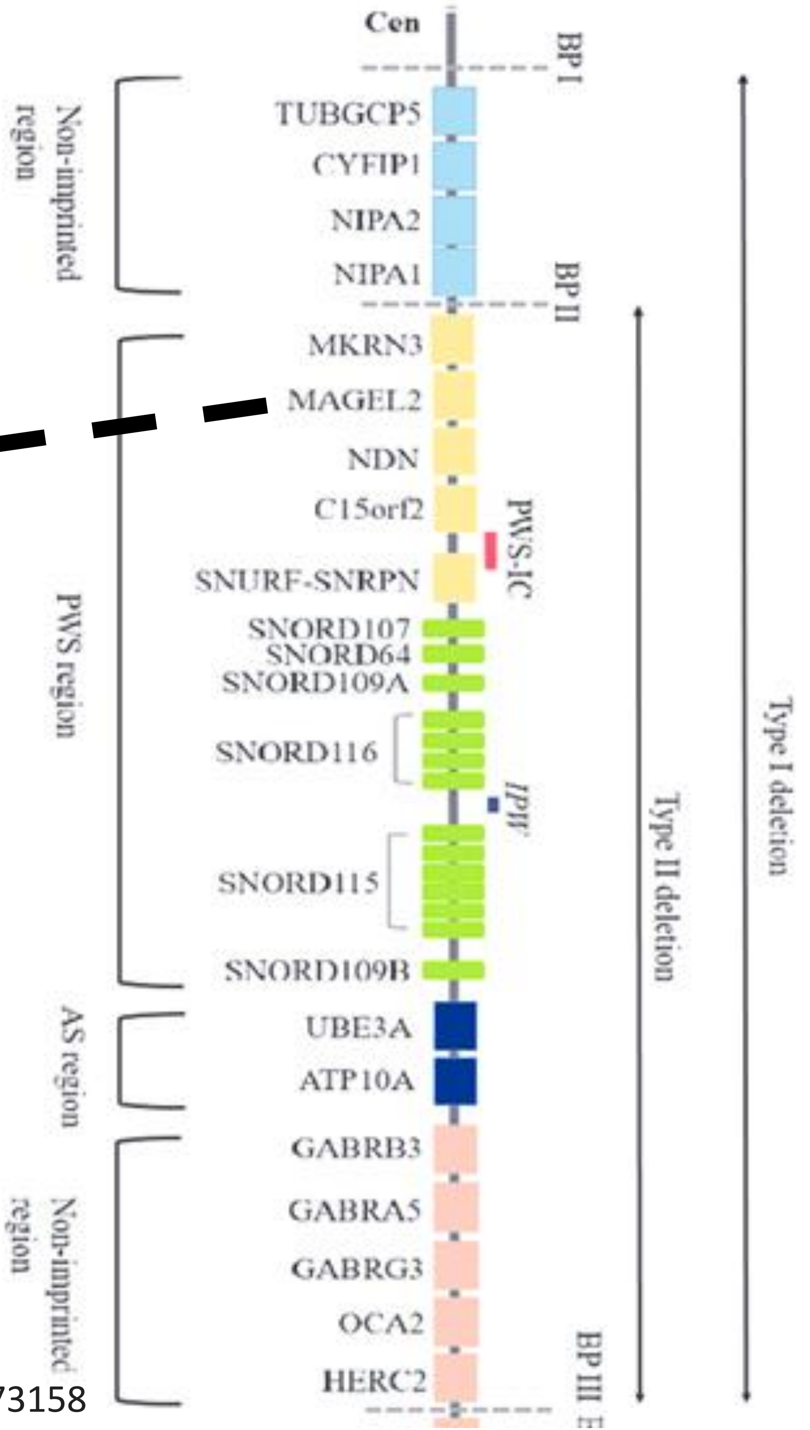

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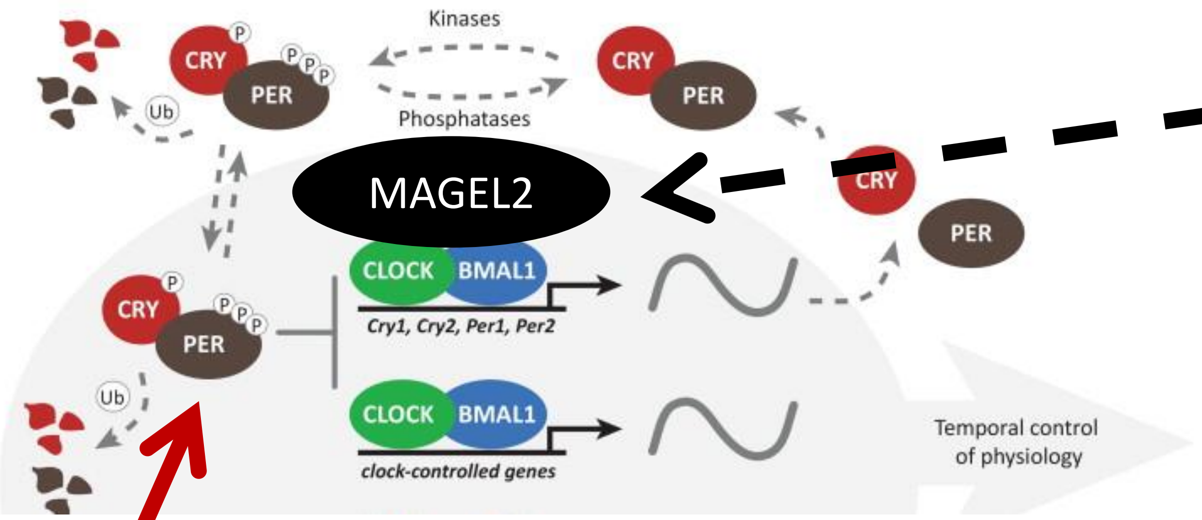

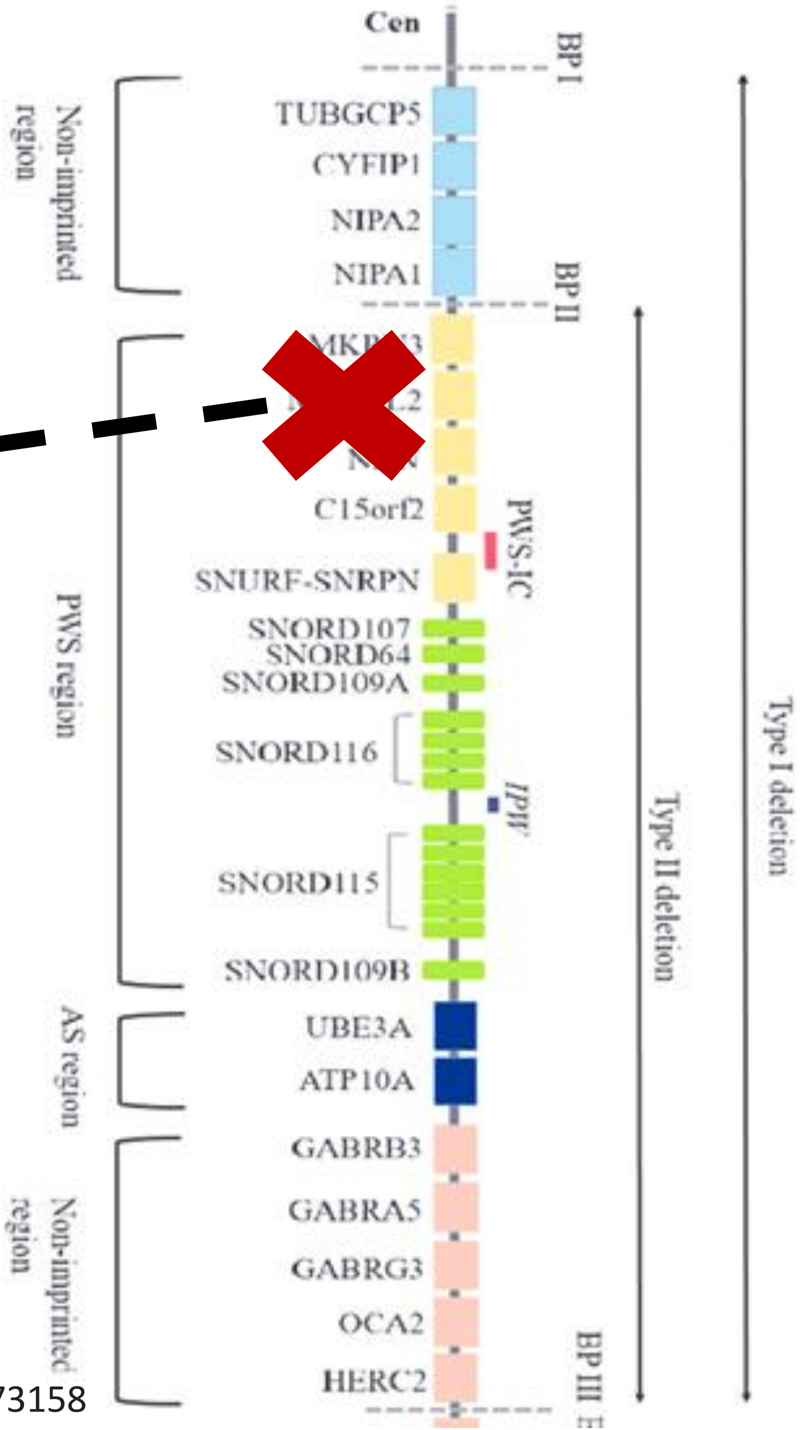

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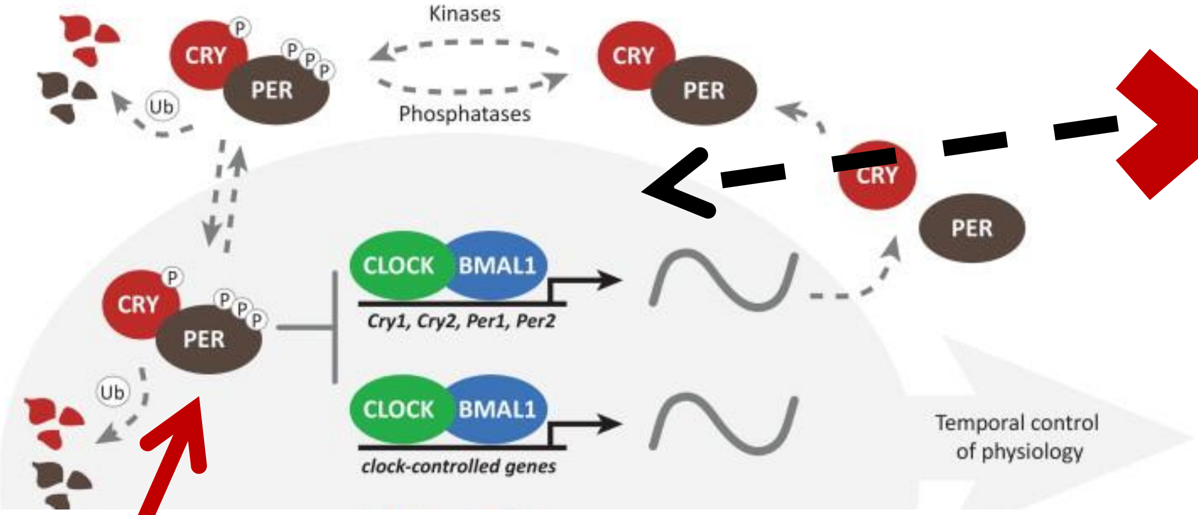

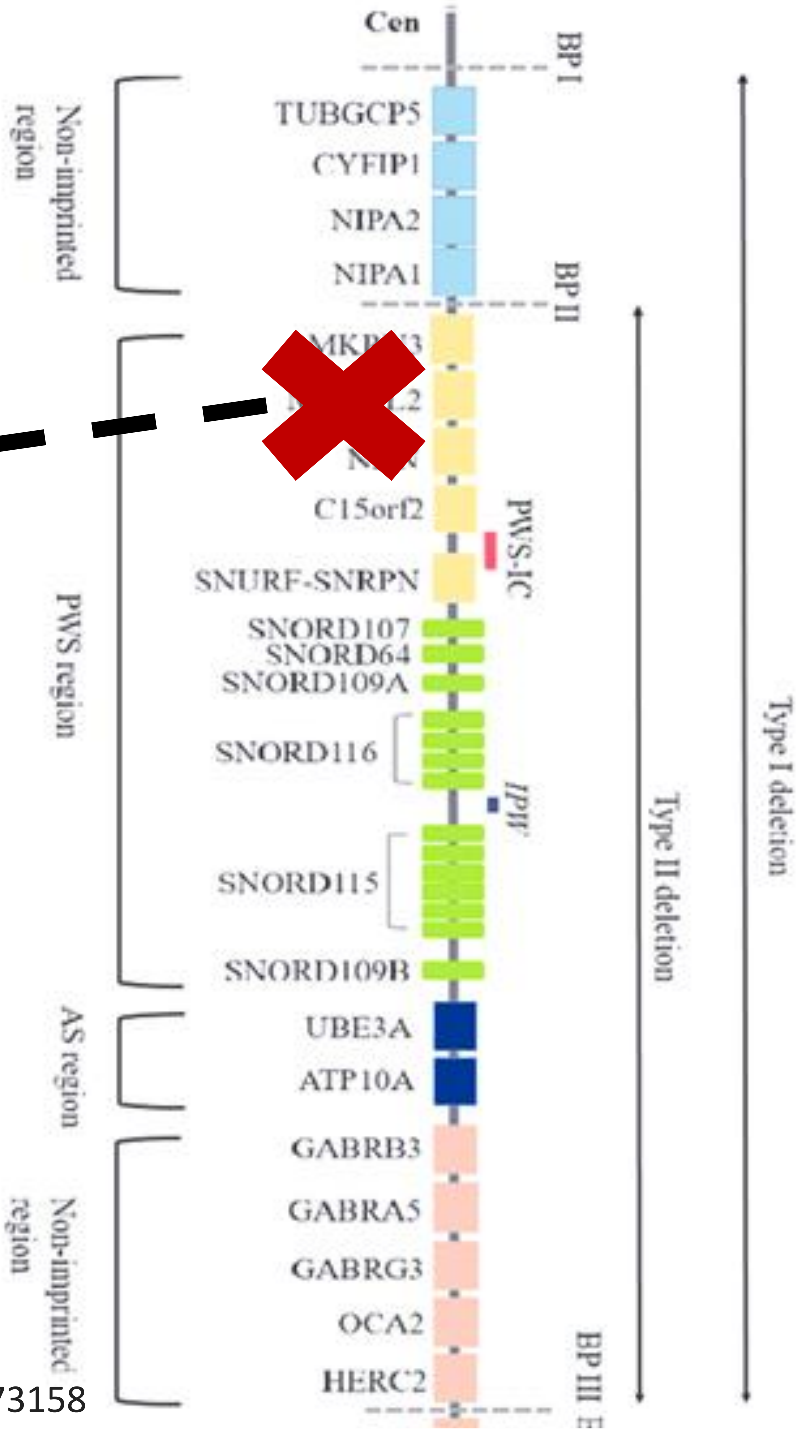

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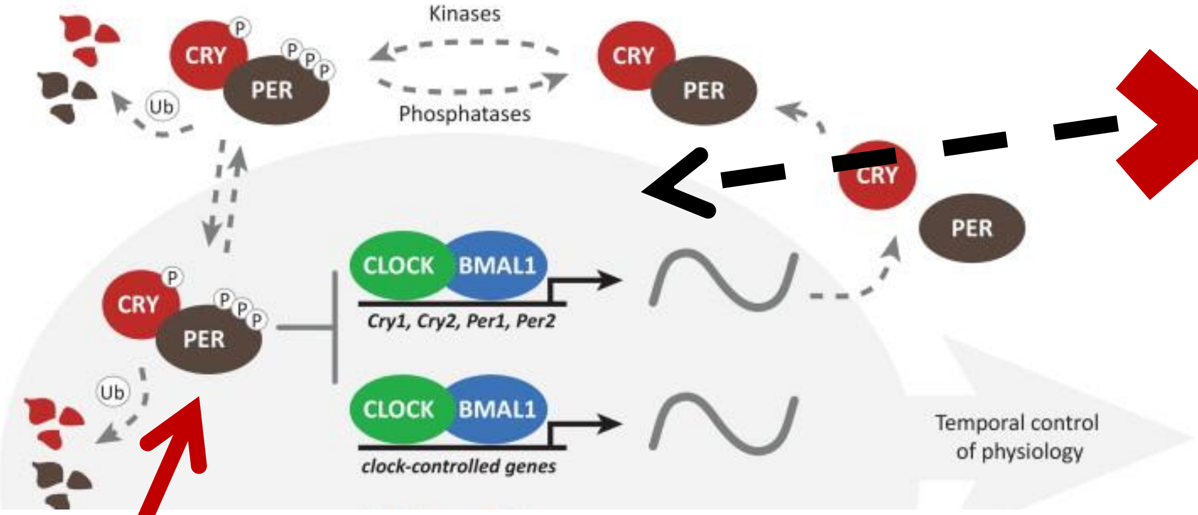
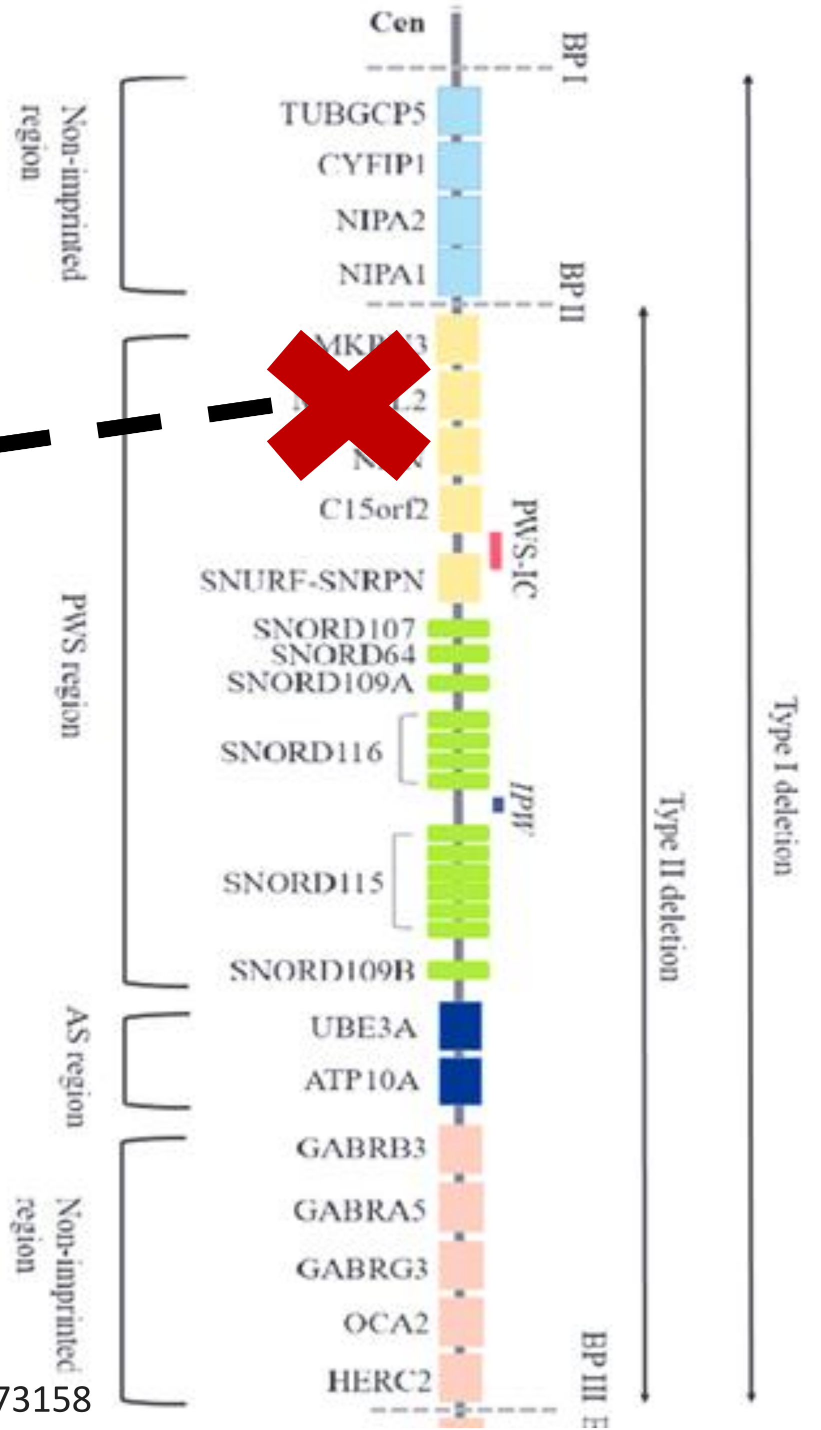
PWS genes in Master Clock

- May result in lots of daytime sleepiness and mistimed sleep





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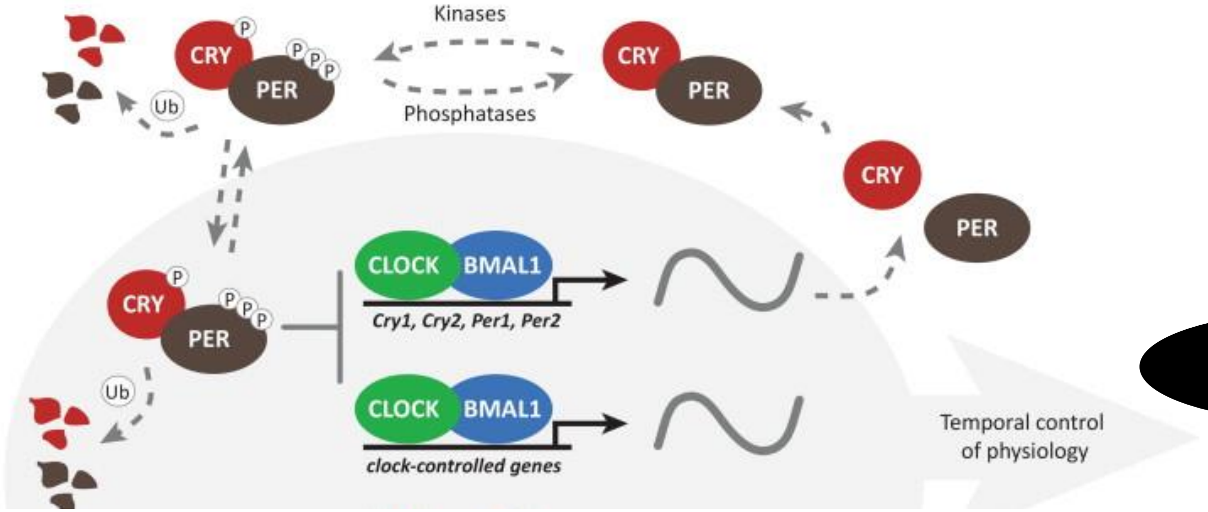
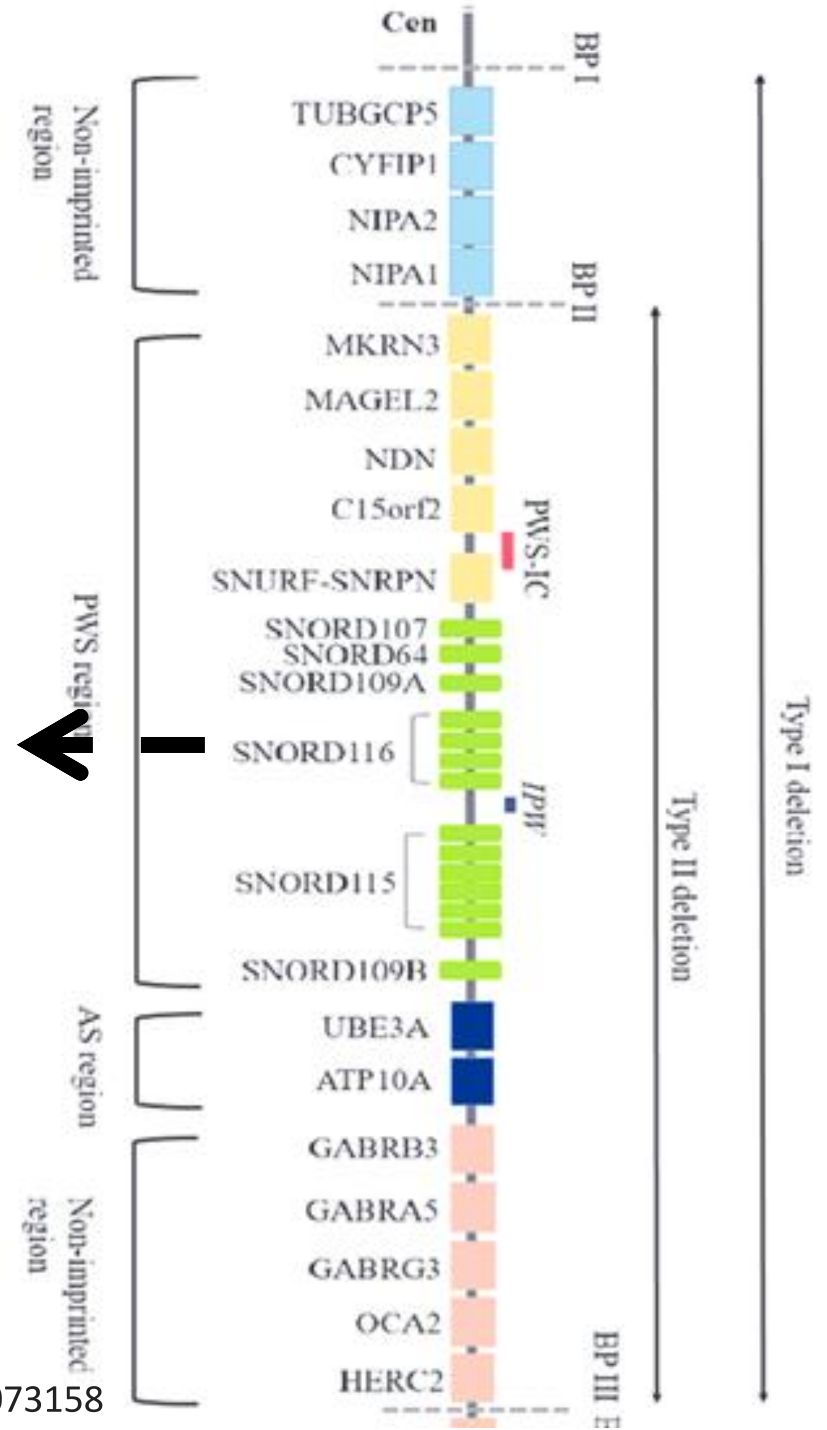


SNORD116



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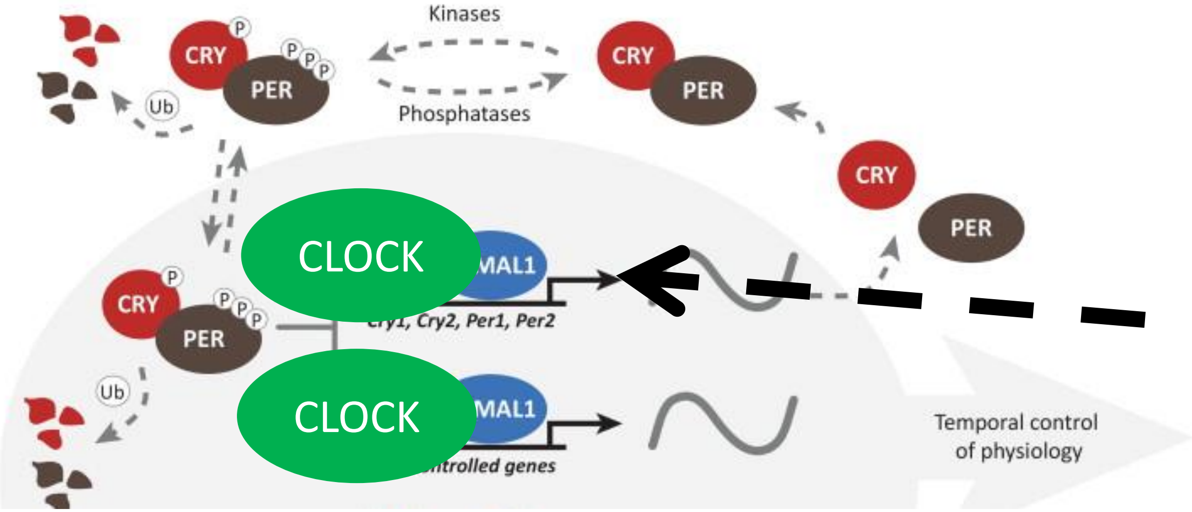

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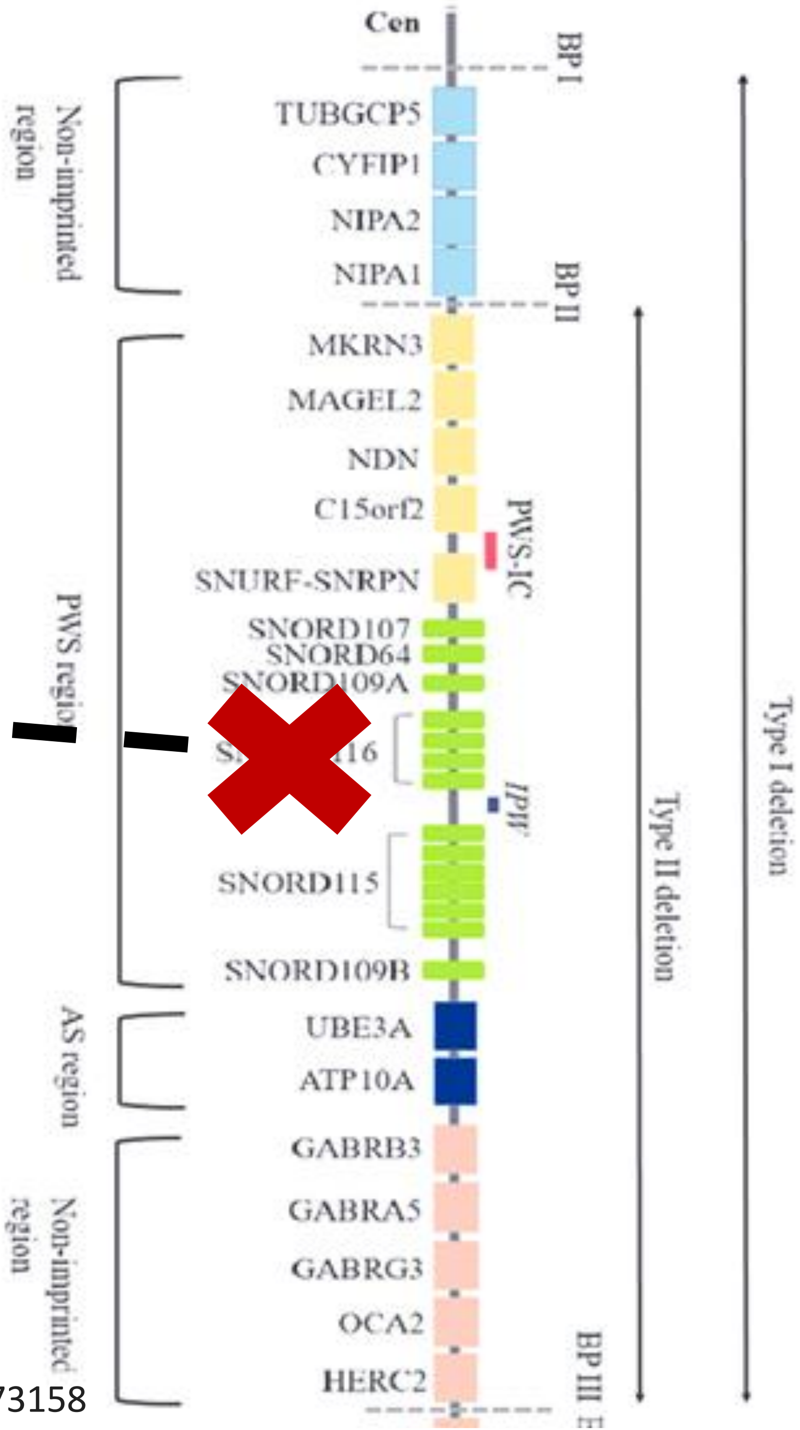

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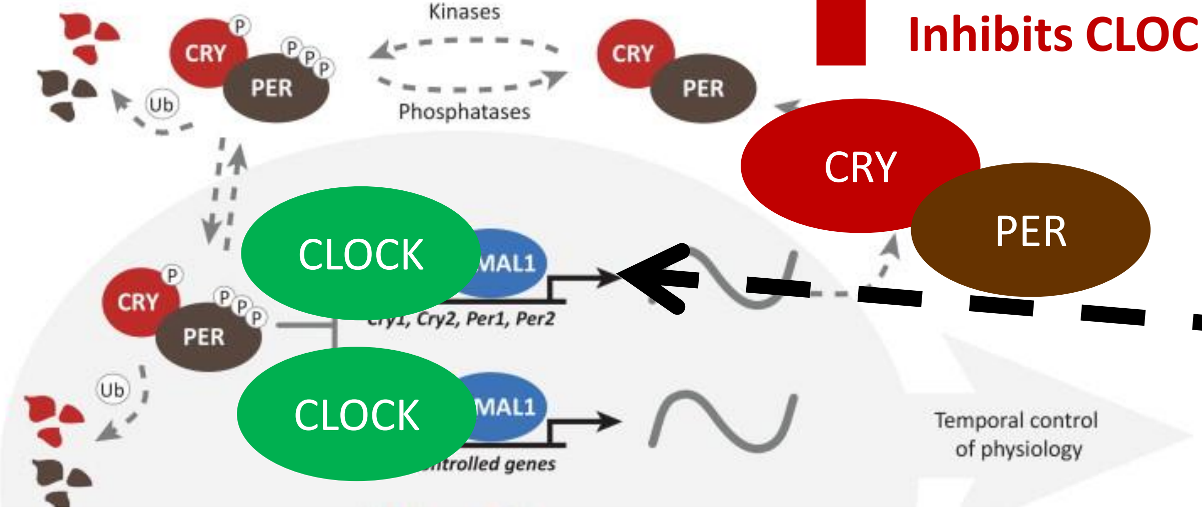

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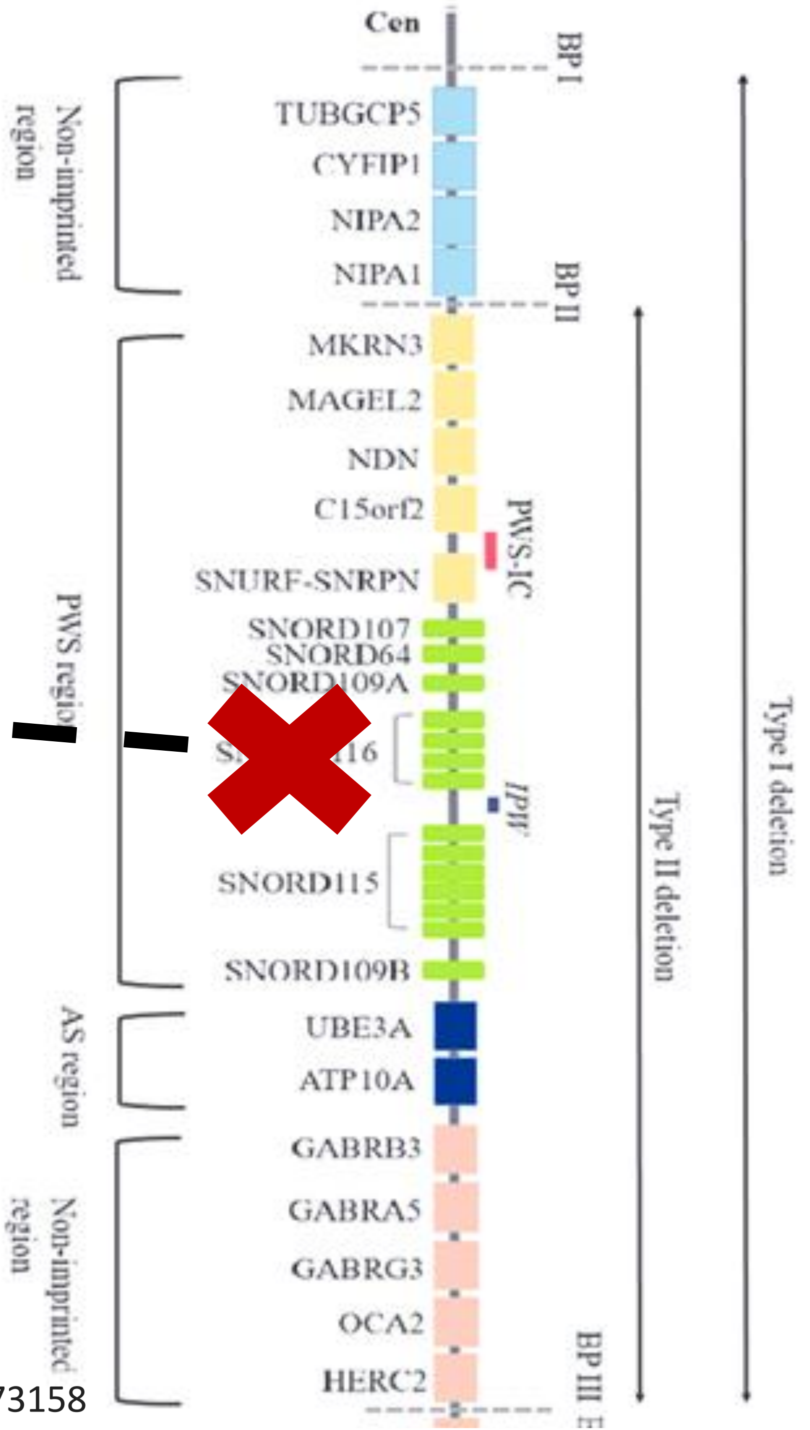

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What are other common sleep problems parents & caregivers observe?

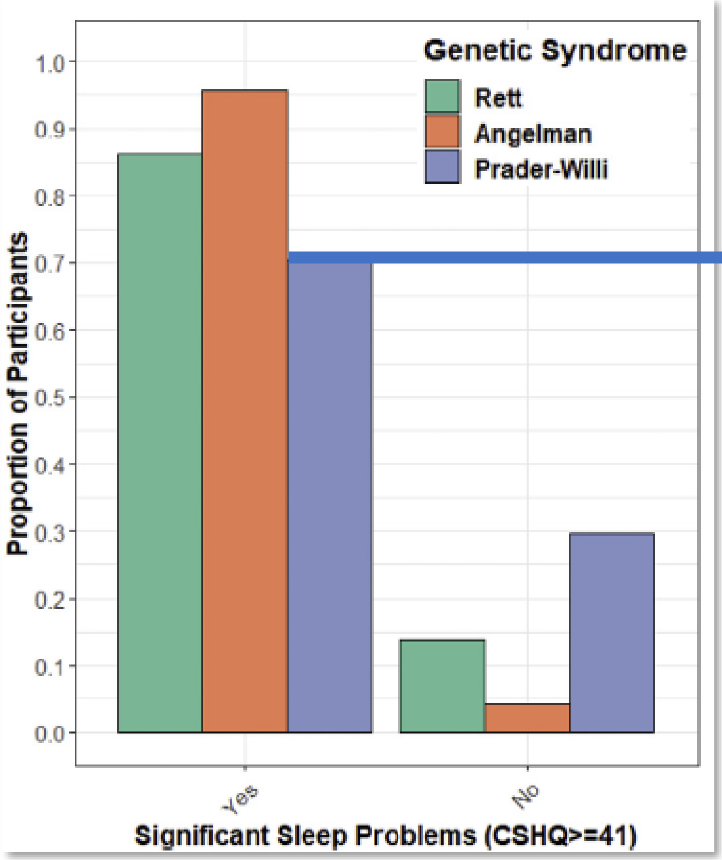
Sleep disordered breathing is common in PWS

- Parent-reported sleep data were analyzed from 95 individuals with PWS and 40 of their unaffected siblings (2-18 years old)

Veatch et al., Pediatric Neurol. 2021, PMC8429141

Sleep disordered breathing is common in PWS

- Parent-reported sleep data were analyzed from 95 individuals with PWS and 40 of their unaffected siblings (2-18 years old)
- Many children with PWS had lots of sleep problems (2-10 years old)



~70% had parents notice problems with:

- Falling asleep
- Staying asleep
- Feeling sleepy during the day
- Having trouble breathing during sleep

Veatch et al., Pediatric Neurol. 2021, PMC8429141

Sleep disordered breathing is common in PWS

- Parent-reported sleep data were analyzed from 95 individuals with PWS and 40 of their unaffected siblings (2-18 years old)
- Many children with PWS had lots of sleep problems (2-10 years old)
- Sleep problems were also prevalent in typically developing, similar age siblings

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- Parent-reported sleep data were analyzed from 95 individuals with PWS and 40 of their unaffected siblings (2-18 years old)
- Many children with PWS had lots of sleep problems (2-10 years old)
- Sleep problems were also prevalent in typically developing, similar age siblings
- Sleep disordered breathing was worse in individuals with PWS compared to their typically developing siblings

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Veatch et al., Pediatric Neurol. 2021, PMC8429141

Sleep problems in PWS may differ depending on genetic cause

	Whole group (n:31)	Deletion type (n:24)	UPD type (n:7)	p
Total sleep time (SD)	364.5 (61.2)	359.8 (74.1)	373.6 (30.3)	0.1
Sleep efficiency (SD)	78.3 (11.6)	77.6 (13.8)	79.2 (7.9)	0.3
REM% (SD)	14.1 (5.9)	13.2 (5.8)	12.9 (7.3)	0.04[b]
N1% (SD)	9.4 (8)	10.1 (8.6)	11.3 (8.9)	0.7
N2% (SD)	56 (9.8)	53.8 (10)	62.3 (10)	0.07
N3% (SD)	20.9 (7.6)	23.8 (6.6)	13.4 (7.6)	0.003[b]
Sleep latency (IQR)	10.2 (5–23)	9 (4.5–30.5)	8.5 (5–15.5)	0.7
REM latency (IQR)	115.5 (62.5–175.5)	70 (50.5–167)	167.5 (93.5–385)	0.1
Initial SaO_2 (IQR)	95 (93–96)	94 (92–95)	96 (96–97)	0.01[b]
Mean SaO_2 (IQR)	94.5 (93–96)	93.5 (92–95)	96 (95–96)	<0.05[b]
Minimum SaO_2 (IQR)	78.5 (74–80)	77.7 (74.5–80)	79.7 (73–89)	0.7
Sleep time with SaO_2 below 90% (IQR), minute	7.7 (27–273)	15.2 (7.6–48)	1.8 (0.8–6.4)	0.01[b]
Oxygen desaturation % (IQR)	1.4 (0.3–6.4)	3 (0.9–12.6)	0.3 (0.1–1.3)	0.02[b]
AHI-total (IQR)	11.7 (6.3–16)	14.6 (9.5–16.6)	6.7 (1.6–12.2)	0.04[b]
Obstructive apnea index (IQR)	0 (0–0.1)	0 (0–0.05)	0 (0–0.02)	0.9
Central apnea index (IQR)	2.6 (0.5–3.9)	3.4 (1.2–6.6)	0.5 (0.3–3)	0.06
Hypopnea index (IQR)	7.4 (3.6–11.6)	8.1 (6.3–12.8)	7 (1–9)	0.2
Arousal index (IQR)	7.8 (4.4–12.1)	7.9 (4.5–12.1)	4.7 (4–9.9)	0.2

Deletion

↓Oxygen

Ozsezen et al., Resp. Med. 2021, PMID: 34411906

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Deletion

- ↓ Oxygen
- ↑ Central apneas (?) – small numbers need replicating to confirm
- ↑ Apnea hypopnea index
- ↓ N3 %
- ↑ Rapid Eye Movement %

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Ozsezen et al., Resp. Med. 2021, PMID: 34411906

Co-occurring conditions also impact sleep

- **People with uniparental disomy may be more likely to have autism** Butler MG et al., J Med Genet. 2019, PMC7387113

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Reviewed in Veatch et al., J Nat Sci. 2015

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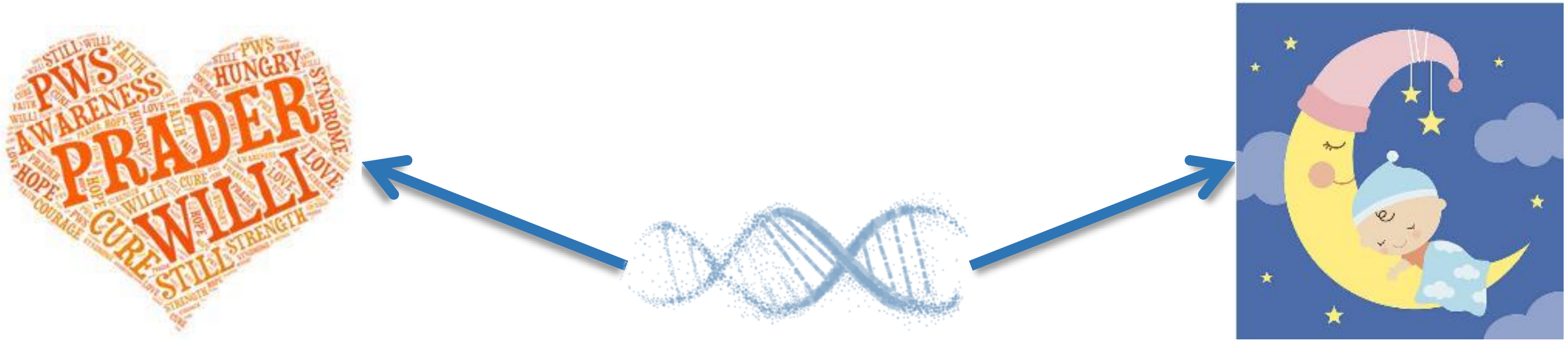
- Finding connections between PWS and sleep may help us find better treatments for sleep problems



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