Genetics of Sleep & Sleep Disorders in Children with PWS

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Department of Psychiatry & Behavioral Sciences
University of Kansas Medical Center

Althea Robinson Shelton, M.D.
Associate Professor
Department of Neurology
Vanderbilt University Medical Center
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
Genetics of Sleep & Sleep Disorders in Children with PWS: Current knowledge & research

Olivia J. Veatch, M.S., Ph.D.
Assistant Professor
Department of Psychiatry & Behavioral Sciences
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University of Kansas Medical Center
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
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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
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
Circadian rhythms and how they regulate sleep

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

- Melatonin promotes sleep
- Serotonin
- N-acetylserotonin
- Melatonin
Circadian rhythms and how they regulate sleep

- 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

![Graph showing circadian rhythm patterns for body temperature, melatonin, cortisol, and growth hormone over three days.]
Circadian rhythms and how they regulate sleep

➢ Sleep/wake cycle in humans controlled by genes

Partch CL et al., Trends in Cell Bio. 2014, PMC3946763
Circadian rhythms and how they regulate sleep

➢ Sleep/wake cycle in humans controlled by genes

Positive:
Promotes sleep
Activates PER/CRY

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Circadian rhythms and how they regulate sleep

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**Negative:**
Promotes wake
Inhibits CLOCK/BMAL

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PWS genes in Master Clock

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Devos et al., J Circ Rhythm 2011, PMC3278377

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➢ May result in lots of daytime sleepiness and mistimed sleep

Negate:

Promotes wake
Inhibits CLOCK/BMAL

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Devos et al., J Circ Rhythm 2011, PMC3278377

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Partch CL et al., Trends in Cell Bio. 2014, PMC3946763
Powell WT et al., Hum Mol Genet. 2013, PMC3792690
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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
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.
- Sleep disordered breathing was worse in individuals with PWS compared to their typically developing siblings.

Veatch et al., Pediatric Neurol. 2021, PMC8429141
Sleep problems in PWS may differ depending on genetic cause

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<td>Sleep time with SaO₂ below 90% (IQR), minute</td>
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Ozsezen et al., Resp. Med. 2021, PMID: 34411906
Sleep problems in PWS may differ depending on genetic cause.

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↓ Oxygen

↑ Central apneas (?) – small numbers need replicating to confirm

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|                          | (IQR)              |                      |                |       |
| Oxygen desaturation %    | 1.4 (0.3-6.4)      | 3 (0.9-12.6)         | 0.3            | 0.02  |
| AHI-total (IQR)          | 11.7 (6.3-16)      | 14.6                 | 6.7            | 0.04b |

|                          | (IQR)              |                      |                |       |
| Obstructive apnea index  | 0 (0-0.1)          | 0 (0-0.05)           | 0 (0-0.02)     | 0.9   |
| Central apnea index      | 2.6 (0.5-3.9)      | 3.4 (1.2-6.6)        | 0.5 (0.3-3)    | 0.06  |

|                          | (IQR)              |                      |                |       |
| Hypopnea index           | 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   |

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↓ Oxygen
↑ Central apneas (?) – small numbers need replicating to confirm
↑ Apnea hypopnea index

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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
Co-occurring conditions also impact sleep

- People with uniparental disomy may be more likely to have autism
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- Insomnia symptoms are common in individuals with autism (50-80%)
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

- Insomnia symptoms are common in individuals with autism (50-80%)

- Evidence for problems with melatonin production in autism
  Reviewed in Veatch et al., J Nat Sci. 2015
Conclusions

➢ Sleep is important for brain and body development
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➢ Sleep and wake timing are controlled by genetics
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Conclusions

- Sleep is important for brain and body development
- Sleep and wake timing are controlled by genetics
- Genes causing Prader-Willi syndrome also alter sleep and circadian biology
- There may be differences in the types of sleep problems seen when someone has a deletion vs uniparental disomy
➢ Sleep is important for brain and body development
➢ Sleep and wake timing are controlled by genetics
➢ Genes causing Prader-Willi syndrome also alter sleep and circadian biology
➢ There may be differences in the types of sleep problems seen when someone has a deletion vs uniparental disomy
➢ Finding connections between PWS and sleep may help us find better treatments for sleep problems