HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2020 January 10.

Published in final edited form as:

Am J Med Genet A. 2019 October ; 179(10): 1982–1986. doi:10.1002/ajmg.a.61307.

Objective Measures of Sleep Disturbances in Children with Potocki-Lupski Syndrome

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Abstract

Background: Potocki-Lupski syndrome (PTLS; MIM 610883) is a neurodevelopmental disorder caused by a micro-duplication, a 3.7 Mb copy number variant (CNV), mapping within chromosome 17p11.2, encompassing the dosage sensitive *RAI1* gene. Whereas *RAI1* triplosensitivity causes PTLS, haploinsufficiency of *RAI1* due to 17p11.2 microdeletion causes the clinically distinct Smith-Magenis Syndrome (SMS; MIM 182290). Most individuals with SMS have an inversion of the melatonin cycle. Subjects with PTLS have mild sleep disturbances such as sleep apnea with no melatonin abnormalities described. Sleep patterns and potential disturbances in subjects with PTLS have not been objectively characterized.

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DECLARATION of INTERESTS:

Kevin Kaplan: no conflicts of interest

Caroline McCool: No conflicts of interest

James R. Lupski: Baylor College of Medicine (BCM) and Miraca Holdings have formed a joint venture with shared ownership and governance of the Baylor Genetics (BG), which performs clinical microarray analysis and clinical exome sequencing. J.R.L. serves on the Scientific Advisory Board of the BG. J.R.L. has stock ownership in 23andMe, is a paid consultant for Regeneron pharmaceuticals, and is a co-inventor on multiple United States and European patents related to molecular diagnostics for inherited neuropathies, eye diseases, and bacterial genomic fingerprinting. The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from molecular genetic testing offered in the Baylor Genetics Laboratories.

Daniel Glaze: No conflicts of interest

Lorraine Potocki: The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from molecular genetic testing offered in the Baylor Genetics Laboratories.

WEB RESOURCES

OMIM Online Mendelian Inheritance in Man (https://www.omim.org/)

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Methods: We delineated sleep characteristics in 23 subjects with PTLS who underwent a polysomnogram at Texas Children's Hospital. 11 of these subjects (58%) completed the Child's Sleep Habits Questionnaire (CSHQ). Urinary melatonin was measured in one patient and published previously.

Results: While the circadian rhythm of melatonin in PTLS appears not to be disrupted, we identified significant differences in sleep efficiency, percentage of rapid eye movement (REM) sleep, oxygen nadir, obstructive apnea hypopnea index, and periodic limb movements between pre-pubertal subjects with PTLS and previously published normative data. Data from the CSHQ indicate that 64% (7/11) of parents do not identify a sleep disturbance in their children.

Conclusions: Our data indicate that younger individuals, <10 years, with PTLS have statistically significant abnormalities in five components of sleep despite lack of recognition of substantial sleep disturbances by parents. Our data support the contention that patients with PTLS should undergo clinical evaluations for sleep disordered breathing and periodic limb movement disorder (PLMD), both of which are treatable conditions.

Keywords

Potocki-Lupski Syndrome; sleep study; sleep characteristics; obstructive sleep apnea; periodic limb movement disorder; *RAI1*; duplication 17p11.2; genomic disorder

INTRODUCTION

Potocki-Lupski syndrome (PTLS; MIM 610883) is usually associated with duplication 17p11.2 and represents a neurodevelopmental disorder characterized by infantile hypotonia, failure to thrive, congenital cardiovascular anomalies, developmental delay, intellectual disability, and behavioral abnormalities including attention deficits and features of autism spectrum disorder [1, 2, 3, 4, 5] Clinically recognizable distinct craniofacial features are usually mild in individuals with PTLS, and often include a triangular shaped face, down-slanting palpebral fissures and mandibular hypoplasia [2, 6]. Most subjects reported with PTLS harbor a common, recurrent duplication of 3.7Mb within 17p11.2 that occurs *de novo* in association with the sporadic disease trait; however, both smaller and larger duplication copy number variants (CNVs) of this region will cause the PTLS phenotype [7].

The short arm of chromosome 17 is susceptible to genomic instability and prone to rearrangements due to the presence of low-copy repeats (LCRs), resulting in a number of conditions collectively known as "genomic disorders" [8]. Those relevant to this discussion include PTLS, Smith-Magenis (SMS) syndrome (MIM 182290) and Yuan-Harel-Lupski (YUHAL) syndrome (MIM 616652). The common PTLS duplication and the common SMS deletion are reciprocal recombination products [1, 9, 10]. Interestingly, these two disorders exhibit many clinical features that are on opposite ends of a given spectrum—so called "mirror traits" [6, 11]. The duplicated segment in YUHAL syndrome spans not only the PTLS region, but the CMT1A (MIM 118220) region as well, thus these individuals have a more severe neuromuscular phenotype and manifest clinical signs of distal symmetric polyneuropathy observed in Charcot-Marie-Tooth disease [12]. Importantly, the genomic region of each of these disorders contains the dosage sensitive *RAI1* gene. This gene is

deleted, or harbors a pathogenic single nucleotide variant (SNV) allele, resulting in protein loss-of-function, and haploinsufficiency in persons with SMS; the *RAI1* gene is duplicated in persons with PTLS and YUHAL syndromes.

Smith-Magenis syndrome is a multiple congenital anomalies disorder in which sleep abnormalities pose substantial clinical concern. Specific sleep disturbances include excessive daytime sleepiness, increased nocturnal awakenings, and diminished rapid eye movement (REM) sleep [13]. Inversion of the circadian rhythm of melatonin was first elucidated in SMS deletion patients [14] and corroborated by other investigators [13]. Haploinsufficiency of RA*I1* is implicated in the aberrant sleep phenotype in SMS as an inversion of the circadian rhythm of melatonin has also been observed in a person with SMS harboring a pathogenic variant in *RAI1* [15]. Circadian abnormalities in mouse models for SMS also implicate *RAI1* as being the major 'driver gene' contributing to SMS [16]

In contrast to the prevalence of sleep disturbances in SMS, most individuals with PTLS do not report abnormal sleep patterns [2]. Although individuals with PTLS do not typically exhibit sleep disturbances that are noted by parents or disrupt family dynamics, we have reported central and/or obstructive sleep apnea in a small cohort, n=10, of PTLS subjects who underwent a formal sleep assessment and polysomnography [2]. Mullegama et al., reported caregiver survey data on a cohort of 15 subjects which also supports dyssomnia in PTLS [17]. The study herein comprehensively delineates the sleep characteristics of the subjects (n=10) reported in Potocki et al., [2] and polysomnography results and sleep analyses in 13 additional subjects with PTLS.

MATERIAL and METHODS:

This research project was approved by the Institutional Review Board at Baylor College of Medicine in Houston, Texas. Records were reviewed from all subjects diagnosed with PTLS who were seen at Baylor College of Medicine and Texas Children's Hospital from 2003 through 2017. Of these subjects, 23 subjects had a nocturnal polysomnogram (PSG) performed as part of the research protocol; however, only 19 of these were available to review. Records from all subjects (n=23; 14 = male) with a genetic diagnosis of Potocki-Lupski syndrome at Baylor College of Medicine and Texas Children's Hospital from 2003 through 2017 were included in the study. Of the 23 subjects studied, 11 (58%) of the subject's parents completed the Child's Sleep Habits Questionnaire (CSHQ). Subjects on whom the information was collected were studied under a research protocol to obtain objective baseline data. Subjects were not screened for possible sleep disordered breathing before being referred for a polysomnogram. Informed consent was obtained from the parents of all subjects. All subjects received their sleep studies through the Children's Sleep Center at Texas Children's Hospital in Houston, Texas which is an accredited sleep center for pediatric patients. These studies were performed by a registered PSG technologist experienced in recording pediatric patients according to the standards of the American Academy of Sleep Medicine (AASM) for pediatric patients.

Measurements obtained on the night of the polysomnogram in all subjects included a 10–20 EEG montage, two ocular channels, a nasal flow sensor, a nasal thermistor, a chin and two

leg EMGs, a pulse oximeter, either end tidal or transcutaneous carbon dioxide sensor, a one lead EKG, and abdominal and thoracic respiratory inductance plethysmography belts. Sleep sessions also obtained time synchronized video and sound recorded to characterize snoring and behaviors during sleep. Study data were analyzed by sleep medicine physicians at Texas Children's Hospital using pediatric scoring practice guidelines established by the AASM [18, 19]. Study data included validated sleep questionnaires (CSHQ), parental reports on sleep quality, and results from polysomnograms.

The Child's Sleep Habits Questionnaire (CSHQ) is a 33 item clinically validated questionnaire which screens for sleep disturbances among several sleep disorder sub types; bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakening's, parasomnias, sleep disordered breathing, and daytime sleepiness. The measure has a total cut off score of 41, with subjects with a score above 41 indicating an underlying sleep disturbance. The responses indicate a frequency of the observed behavior in addition to identifying if that behavior is considered a problem [20].

For analysis of the polysomnographic data subjects were divided into two sub-groups; subjects over 10 years of age (n=3; age 11, 13, and 14 years) and subjects under 10 years of age (n=16; Median age of 4 years). Data for the remaining 4 polysomnograms were not available as the results were not documented in the report and the original data was unavailable for retrieval. This age cut-off division was delineated to minimize effects of hormonal change on study subjects. Sleep characteristics of the subjects were compared to previously published normative data [21] using independent sample T-tests to assess potential differences in sleep characteristics. Comparisons were made for sleep efficiency, percentage of REM sleep, oxygen nadir, carbon dioxide levels as measured either by end tidal or transcutaneous measurement, obstructive sleep apnea events, central sleep apnea events, apnea hypopnea index, respiratory disturbance index, limb movements, and arousals associated with limb movements.

RESULTS

The total values of the CSHQ Screen did not identify the presence of a sleep disturbance in the majority of subjects with PTLS with a total score of less than 41 (64% n=7/11 subjects). Few parents report sleep difficulties in their children (Table 1); however, despite normal screening for sleep disturbances, the polysomnogram data reveals evidence for physiological sleep perturbations in subjects with PTLS.

The sleep characteristics measured by polysomnogram in subjects with PTLS (Table 2) suggest that subjects with PTLS are affected by sleep disordered breathing. The differences between the pre-pubertal and post-pubertal results varied in the extent of statistical significance. The cause of the difference could be phenotypic or due to small sample size (post pubertal subjects n = 3). Because the sample size of the post-pubertal subjects is small our discussion focuses on the data from the pre-pubertal subjects.

The sleep characteristics of pre-pubertal PTLS subjects compared to previously published normative control data are shown in Table 2. Overall, pre-pubertal subjects with PTLS

showed statistically significant differences from previously published normative data in five of six measured sleep characteristics – sleep efficacy, REM sleep, oxygen nadir, obstructive apnea hypopnea index, and limb movements [21].

Sleep efficiency is the amount of time a subject was sleeping divided by the total amount of time the subject was recorded. Subjects with PTLS have a significantly decreased sleep efficiency when compared to control data (p=0.029). Subjects with PTLS had a sleep efficiency which was 8% lower when compared to previously published normative control data.

Sleep can be divided into two distinct stages; non rapid eye movement sleep (NREM) and REM sleep. REM is typically a dream state which is clustered in the second half of the sleep period. During REM sleep muscle tone is typically lost which can contribute to worsening of sleep apnea. REM is also essential to neurological development, learning, and memory consolidation. Subjects with PTLS have a decreased amount of REM sleep when compared to previously published normative control data (p=0.002), with subjects with PTLS having 7% less REM sleep on average.

The obstructive apnea hypopnea index (oAHI) is a measure of sleep apnea. It is calculated by adding the number of obstructive events and dividing by the total amount of sleep time. In pediatrics normal oAHI ranges from 0–1 events per hour. Mild obstructive sleep apnea ranges from >1–5 events per hour, moderate obstructive sleep apnea is >5–10 events per hour, and severe obstructive sleep apnea is greater than 10 events per hour. Central or obstructive events can be scored if they are preceded by either an arousal, a change in the EEG, or by a 3% or greater desaturation [22]. Subjects with PTLS have a higher obstructive apnea hypopnea index when compared to normative control data, having an elevated oAHI (p=0.034). Based on these data, subjects with PTLS were found to have a significantly higher incidence of obstructive sleep apnea.

In comparison to previously published normative control data subjects with PTLS have a 4% lower oxygen nadir (p=0.001). This finding is likely due to both the hypotonia associated with subjects with PTLS as well as the increased obstructive sleep apnea, as seen by the increased oAHI.

During a polysomnogram EMG leads are typically placed on one or both of the anterior tibialis muscles. For this study electrodes were placed on both limbs. These electrodes are able to detect and record muscle movements occurring during sleep. Subjects with PTLS have a significantly higher amount of limb movements when compared to previously published normative control data (p=0.007). In fact, subjects with PTLS had more than a ten-fold increase in the number of limb movements when compared to normative data. However, subjects with PTLS did not have a significantly higher amount of limb movements that were associated with arousals when compared to previously published normative control data (p=0.122).

DISCUSSION

Our findings indicate that younger subjects (<10 years) with PTLS have statistically significant sleep disordered breathing (n=10/16). Parents may not be able to identify the presence of sleep disorders in their children with PTLS as only 36% (4/11) of respondents identified a sleep disturbance prior to the sleep study using the CSHQ. Of the sleep disturbances reported using the CSHQ: bedtime resistance, sleep onset delay, and daytime sleepiness were the most frequently observed (Table 1). These objective abnormal findings include differences from previously published normative control data in sleep efficiency (lower), percentage of REM sleep (lower), oxygen nadir (lower), apnea hypopnea index (higher), and periodic limb movement index (higher) [21]. Most of the significant differences between the groups could be attributed to the finding of, on average, mild obstructive sleep apnea in subjects with PTLS (n=13/19; 68.4%). Obstructive sleep apnea is associated with lower sleep efficiency, a lower percentage of REM sleep, and a lower oxygen nadir. If the obstructive sleep apnea is treated in these subjects, these other significant differences could potentially also be corrected.

Although increased periodic limb movements can also be associated with obstructive sleep apnea, the degree of elevation in numbers of limb movements is unlikely to be solely caused by the underlying sleep disordered breathing. It has been shown that limb movements can be evident in the setting of periodic limb movement disorder (PLMD) or in restless leg syndrome (RLS). In contrast to PLMD, RLS is diagnosis based solely on clinical history of four criteria obtained by the patient: uncomfortable feelings in the legs, occurring while at rest, typically worse at night, and relieved by walking or movement [23]. Clinical diagnosis of RLS can be impeded in persons with cognitive impairment or communication disorders which are often features of PTLS. The underlying cause of this disorder is attributed to dysfunction in the dopamine pathway. Frequently there is evidence of low iron storage as reflected by a low serum ferritin plasma level. Iron is a cofactor in the dopamine pathway. Further studies are needed to characterize abnormalities in dopamine/iron storage in this disorder. These differences, when compared to normative data, became non-significant in the post pubertal subject group. This finding could be due to the small sample size of our older subject population (n=3). Iron studies were not performed as a part of this research protocol.

Our findings indicate that persons with PTLS should be evaluated for sleep disordered breathing and PLMD. Further research is needed to better evaluate the sleep characteristics of patients with PTLS and in regards to possible causes of the increased PLMs. Limitations to our study include a limited number of older subjects with PTLS. Further research is needed to better evaluate the sleep characteristics of people with PTLS across the lifespan. Such investigations should include serum iron studies, including ferritin levels, and nocturnal attended polysomnograms. Further research might also delineate the role of the dosage-sensitive *RAI1* gene in specific aspects of circadian disturbance in SMS and sleep disordered breathing and periodic limb movements in PTLS. Interestingly, *RAI1* was recently identified as a promising candidate gene for obstructive sleep apnea in a genome wide multiethnic meta-analysis of the quantitative measure of apnea- hypopnea index [24].

ACKNOWLEDGEMENTS:

We thank the patients and their families, for their willing and productive participation and sharing their clinical data. We acknowledge the generous referral from the many physicians and genetic professionals who helped identify subjects for these studies. This work was supported in part by National Institute of Child Health and Human Development grants K08 HD01149 (to L.P.), and the National Human Genome Research Institute, National Heart, Lung, and Blood Institute (NHGRI/NHLBI) grant UM1HG006542 to the Baylor Hopkins Center for Mendelian Genomics (BHCMG); National Institutes of Neurological Disorders and Stroke (NINDS) grant R35 NS105078 to JRL; National Institute of Child Health and Human Development (NICHD)U54HD083092 to IDDRC Clinical Translational Core.

REFERENCES

1. Potocki L, Chen KS, Park SS, Osterholm DE, Withers MA, Kimonis V, Summers AM, Meschino WS, Anyane-Yeboa K, Kashork CD, Shaffer LG, Lupski JR. Molecular mechanism for duplication 17p11.2 – the homologous recombination reciprocal of the Smith-Magenis microdeletion. Nat Genet 2000;24:84–7. [PubMed: 10615134]
2. Potocki L, Bi W, Treadwell-Deering D, Carvalho CM, Eifert A, Friedman EM, Glaze D, Krull K, Lee JA, Lewis RA, Mendoza-Londono R, Robbins-Furman P, Shaw C, Shi X, Weissenberger G, Withers M, Yatsenko SA, Zackai EH, Stankiewicz P, Lupski JR. Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. Am J Hum Genet 2007;80:633–49. [PubMed: 17357070]
3. Soler-Alfonso C, Motil KJ, Turk CL, Robbins-Furman P, Friedman EM, Zhang F, Lupski JR, Fraley JK, Potocki L. Potocki-Lupski syndrome: a microduplication syndrome associated with oropharyngeal dysphagia and failure to thrive. J Pediatr 2011;158:655–59. [PubMed: 21168152]
4. Jefferies JL, Pignatelli RH, Martinez HR, Robbins-Furman PJ, Liu P, Gu W, Lupski JR, Potocki L. Cardiovascular findings in duplication 17p11.2 syndrome. Genet Med 2012;14:90–4. [PubMed: 22237436]
5. Treadwell-Deering DE, Powell MP, Potocki L. Cognitive and behavioral characterization of the Potocki-Lupski syndrome (duplication 17p11.2). J Dev Behav Pediatr 2010;31:137–43. [PubMed: 20110824]
6. Neira-Fresneda J, Potocki L. Neurodevelopmental disorders associated with abnormal gene dosage: Smith-Magenis and Potocki-Lupski syndromes. J Pediatr Genet 2015;4:159–67. [PubMed: 27617127]
7. Zhang F, Potocki L, Sampson JB, Liu P, Sanchez-Valle A, Robbins-Furman P, Navarro AD, Wheeler PG, Spence JE, Brasington CK, Withers MA, Lupski JR. Identification of uncommon recurrent Potocki-Lupski syndrome-associated duplications and the distribution of rearrangement types and mechanisms in PTLS. Am J Hum Genet 2010;86:462–70. [PubMed: 20188345]
8. Shchelochkov OA, Cheung SW, Lupski JR. Genomic and clinical characteristics of microduplications in chromosome 17. Am J Med Genet 2010;152A:1101–10. [PubMed: 20425816]
9. Chen KS, Manian P, Koeuth T, Potocki L, Zhao Q, Chinault AC, Lee CC, Lupski JR. Homologous recombination of a flanking repeat gene cluster is a mechanism for a common contiguous gene deletion syndrome. Nat Genet 1997;17:154–63. [PubMed: 9326934]
10. Liu P, Lacaria M, Zhang F, Withers M, Hastings PJ, Lupski JR. Frequency of nonallelic homologous recombination is correlated with length of homology: evidence that ectopic synapsis precedes ectopic crossing-over. Am J Hum Genet 2011;89:580–588. [PubMed: 21981782]
11. Lupski JR. Structural variation mutagenesis of the human genome: Impact on disease and evolution. Environ Mol Mutagen 2015;56:419–436. [PubMed: 25892534]
12. Yuan B, Harel T, Gu S, Liu P, Burglen L, Chantot-Bastaraud S, Gelowani V, Beck CR, Carvalho CMB, Cheung SW, Coe A, Malan V, Munnich A, Magoulas PL, Potocki L, Lupski JR. Nonrecurrent 17p11.2p12 rearrangement events that result in two concomitant genomic disorders: the PMP22-RAI1 contiguous gene duplication syndrome. Am J Hum Genet 2015;97:691–707. [PubMed: 26544804]
13. De Leersnyder H, De Blois MC, Claustrat B, Romana S, Albrecht U, Von Kleist-Retzow JC, Delobel B, Viot G, Byonnet S, Vekemans M, Munnich A. Inversion of the circadian rhythm of melatonin in the Smith-Magenis syndrome. J Pediatr 2001;139:111–6. [PubMed: 11445803]

14. Potocki L, Glaze D, Tan DX, Park SS, Kashork CD, Shaffer LG, Reiter RJ, Lupski JR. Circadian rhythm abnormalities of melatonin in Smith-Magenis syndrome. J Med Genet 2000;37:428–33. [PubMed: 10851253]
15. Boone PM, Reiter RJ, Glaze DG, Tan DX, Lupski JR, Potocki L. Abnormal circadian rhythm of melatonin in Smith-Magenis syndrome patients with RA*I1* point mutations. Am J Med Genet 2011;155A:2024–7. [PubMed: 21739587]
16. Lacaria M, Gu W, Lupski JR. Circadian abnormalities in mouse models of Smith–Magenis syndrome: Evidence for involvement of RAI1. Am J Med Genet Part A 2013;61A:1561–1568.
17. Mullegama SV, Alaimo JT, Fountain MD, Burns B, Balog AH, Chen L, Elsea SH. *RAI1* Overexpression Promotes Altered Circadian Gene Expression and Dyssomnia in Potocki-Lupski Syndrome J Pediatr Genet. 2017 9;6(3):155–164. doi: 10.1055/s-0037-1599147. Epub 2017 Mar 7. [PubMed: 28794907]
18. Berry R, Brooks R Gamaldo C, Harding S, Lloyd R, Marcus C, and Vaughn B. The AASM Manual for the Scoring of Sleep and Associated Events; rules, terminology, and technical specifications. Version 2. 2007.
19. Rechtschaffen A, Kales A, editors. Los Angeles: Brain Information Service/Brain Research Institute, University of California; A manual of standardized terminology, techniques and scoring system of sleep stages in human subjects. 1968.
20. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep 2000;23(8): 1043–51. [PubMed: 11145319]
21. Scholle S, Waiter A, Scholle HC. Normative values of polysomnographic parameters in childhood and adolescence: cardiorespiratory parameters. Sleep Med 2011;12:988–96 [PubMed: 22036104]
22. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22:667–89. [PubMed: 10450601]
23. American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed Darien, IL: American Academy of Sleep Medicine, 2014.
24. Chen H, Cade BE, Gleason KJ, Bjonnes AC, Stilp AM, Sofer T, Conomos MP, Ancoli-Israel S, Arens R, Azarbarzin A, Bell GI, Below JE, Chun S, Evans DS, Ewert R, Frazier-Wood AC, Gharib SA, Haba-Rubio J, Hagen EW, Heinzer R, Hillman DR, Johnson WC, Kutalik Z, Lane JM, Larkin EK, Lee SK, Liang J, Loredo JS, Mukherjee S, Palmer LJ, Papanicolaou GJ, Penzel T, Peppard PE, Post WS, Ramos AR, Rice K, Rotter JI, Sands SA, Shah NA, Shin C, Stone KL, Stubbe B, Sul JH, Tafti M, Taylor KD, Teumer A, Thornton TA, Tranah GJ, Wang C, Wang H, Warby SC, Wellman DA, Zee PC, Hanis CL, Laurie CC, Gottlieb DJ, Patel SR, Zhu X, Sunyaev SR, Saxena R, Lin X, Redline S. Multiethnic Meta-Analysis Identifies RAI1 as a Possible Obstructive Sleep Apnea-related Quantitative Trait Locus in Men. Am J Respir Cell Mol Biol. 2018 3;58(3):391–401. [PubMed: 29077507]
25. PTLS sleep dataset. Kaplan K, McCool C, Lupski J, Glaze D, Potocki L; 2018, PTLS Sleep Characteristics. Baylor College of Medicine Encrypted Servers.

Table 1.

Results from the CSHQ

Subscale	Problem Reported by Parent (Parental responses identifying a problem in their child's sleep)
bedtime resistance	13.6%
sleep onset delay	27%
sleep duration	6%
sleep anxiety	9%
night awakenings	0%
parasomnias	9%
sleep disordered breathing	3%
daytime sleepiness	17%

Table 2.

Sleep Characteristics of Pre-Pubertal and Post-Pubertal Subjects with PTLS Compared to Normalized Data

Sleep Characteristic	Pre Pubertal Median n=16 (IQR)	Pre Pubertal p-value	Post Pubertal Median n=3 (IQR)	Post Pubertal p-value	Normative data
Sleep Efficacy (% of time asleep)	82 (16)	0.029*	88 (20.65)	0.07	90
% REM sleep (% of total sleep time in rapid eye movement sleep)	13 (8.9)	0.002*	19 (20.1)	0.36	20
O_2 Nadir (lowest oxygen level)	86 (8)	0.001*	90 (12.5)	0.15	90
oAHI (Obstructive apnea hypopnea index: events per hour of sleep)	7.99 (6.9)	0.034*	2.7 (23.41)	0.1	1
Limb Movements (periodic limb movements observed per hour of sleep)	44 (202)	0.007*	7 (36)	0.48	5
Limb Movements Associated with Arousal (periodic limb movements observed per hour of sleep associated with a change in brain wave activity)	3.8 (20.3)	0.1228	4 (17.63)	0.57	5

P-values for comparing six sleep characteristics of 16 pre-pubertal and 3 post-pubertal subjects with PTLS to previously published normalized data are reported above. Prepubertal subjects showed significant differences from normalized data in five of six characteristics. Asterisk indicates statistical significant.