Case Report

Unraveling Leptin's Influence: Sleep Abnormalities in Obesity-Related Neurogenetics

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DOI: 10.71332/cv0z6g31

Abstract: The role of early-onset obesity-related genetic predisposition and leptin receptor variants have been previously studied. However, studies involving sleep-related disorders linked to a genetic predisposition, leading to obesity, and how leptin could play a role in sleep-related disorders have been limited. In this study, we explore a case of how leptin receptor variants could play a role in the relationship between obesity and sleep-related disorders. We present a case of a morbidly obese (BMI of 62.87 kg/m2) Puerto Rican teenage female with a past medical history of type 2 diabetes mellitus, hypothyroidism, essential primary hypertension, and obstructive sleep apnea (OSA), who was evaluated due to complications regarding sleeping difficulties, despite being on Continuous Positive Airway Pressure (CPAP) treatment. Genetic studies performed to assess the causes of obesity revealed BBS9 heterozygous gene for a sequence variant defined as c.396GC and heterozygous *LEPR* gene for a sequence variant defined as c.658GA, which has been associated with an increased predisposition to obesity. This case report emphasizes the value of genetic research in figuring out the root causes of obesity and its comorbidities, especially in cases of early-onset obesity and co-occurring disorders such as OSA. The discovery of genetic variations in *LEPR* and *BBS9* genes offers crucial information on potential mechanisms underlying the clinical phenotype of the patient.

Keywords: leptin receptor variants; early-onset diabetes; obstructive sleep apnea.

1. Introduction

Obesity is a complex, multifaceted condition with a rising global incidence that poses a risk for severe problems and comorbidities [1]. The regulation of calorie intake, hunger, and physical activity are all involved in the etiology of obesity [2]. Although the availability of healthcare, socioeconomic position, and underlying hereditary and environmental factors could be present, research suggests that obesity-related genetic variables account for between 40% and 70% (monogenic and polygenic causes) of obesity in humans, according to family and twin studies [4]. Previous studies have explored the role of leptin receptor variants and genetic predispositions in the early development of obesity [5]. However, studies involving sleep disorders related to a genetic predisposition leading to obesity and how leptin could play a role in sleep-related disorders have been limited. In this case, we report clinical findings and genetic analysis of an 18-year-old female patient with early-onset obesity and co-occurring disorders such as treatment-resistant Obstructive Sleep Apnea (OSA). Furthermore, we explore how leptin receptor variants could play a role in the relationship between obesity and sleep-related disorders.

Editor-in-Chief: Wilfredo De Jesús Rojas, MD, FAAP, MSc, ATSF

Received: 6/24/2024
Revised: 10/16/2024
Accepted: 11/1/2024
Published: 7/14/2025

2. Case Presentation

Case of an 18-year-old female patient with early-onset obesity and co-occurring disorders such as treatment-resistant Obstructive Sleep Apnea (OSA). Polysomnography (PSG) was performed to assess the severity of OSA in this patient (**Figure 1**).

Figure 1: 18-year-old female with early-onset obesity, significant facial and central adiposity, large neck circumference, and pronounced submental fat, also displaying acanthosis nigricans.

Respiratory disturbances were associated with oxygen desaturation down to a nadir of 68% during sleep. The mean oxygen saturation during the study was 91%. The cumulative time under 88% oxygen saturation was 13.4 minutes (**Table 1-4**). Prior to starting CPAP therapy, the patient had an apnea/hypopnea index (AHI) of 22.7 events per hour. During titration, the AHI was 2.1 events per hour, and the Respiratory Disturbance Index (RDI) was 2.1 events per hour. The most appropriate setting of CPAP was 8cm H2O, with a sleep efficiency of 96.8%. There were no significant findings for central sleep apnea nor periodic leg movements (PLMs) during sleep (**Appendix 1**).

Table 1. Sleep Architecture

Lights Out Time: 21:02:19		**Lights On Time: 04:47:18**	
Total Recording Time (Min.): 465.0		# of REM Episodes:	
	Time (min.)	% of Total Sleep Time	Normal %
Stage N1 (Drowse)	5.5	3.6	5-10%

Stage N2 (Mod. Depth)	86.5	56.4	45-55%
Stage N3 (Deep/Slow Wave)	61.5	40.1	0-21%
REM (Dream)	0.0	0.0	17-28%
Total Sleep Time (Min.)	153.5	100%	>360 Min.
Latency to Sleep Onset	5.0	-	<30 Min.
Latency to Stage N2	1.0		<10 Min. from onset
Latency to REM Sleep	-		80-110 Min. (approx)
Wake After Sleep Onset	0.5		-
Sleep Efficiency*	94.8		>85-90%

This table outlines the distribution of sleep stages during the total recording time of 465 minutes. Time spent in each stage includes N1 (5.5 min, 3.6%), N2 (86.5 min, 56.4%), N3 (61.5 min, 40.1%), with no REM sleep recorded. The total sleep time was 153.5 minutes, with a sleep efficiency of 94.8%. Sleep onset latency was 5.0 minutes, latency to stage N2 was 1.0 minute, and wake after sleep onset was 0.5 minutes.

Table 2. Sleep Architecture, Titration Section

Lights Out Time: 23:44:49		**Lights On Time: 04:47:18**	
Total Recording Time (Min.): 302.5		# of REM Episodes:	
		CPAP Titration	
	Normal %	TIME (min.)	% Total Sleep Time
Total Recording	-	302.5	-
Stage N1 (Drowse)	5-10%	6.0	2.1
Stage N2 (Mod. Depth)	45-55%	157.5	53.8
Stage N3 (Deep/Slow Wave)	0-21%	26.0	8.9
Stage REM (Dream)	17-28%	103.0	35.2
Total Sleep Time (Min.)	>360 Min.	292.5	100%
Latency to Sleep Onset	<30 Min.	1.0	
Latency to Stage N2		1.0	-
Latency to REM Sleep	80-100 Min. (approx)	21.0	
Wake After Sleep Onset	-	9.0	
Sleep Efficiency*	>85-90%	96.7	

This table outlines the sleep architecture during a CPAP titration study. The total recording time was 302.5 minutes, with sleep divided into stages: N1 (6.0 min, 2.1%), N2 (157.5 min, 53.8%), N3 (26.0 min, 8.9%), and REM (103.0 min, 35.2%). Latencies to sleep onset, stage N2, and REM sleep were 1.0, 1.0, and 21.0 minutes, respectively. Sleep efficiency was 96.7%, with 9.0 minutes of wake time after sleep onset.

Table 3. Respiratory Summary

	By Sleep Stage		**By Position**		**TOTAL**
	NREM	REM	Supine	Non-Supine	
Sleep Time (Min.)	153.5	0.0	153.5	0.0	153.5
APNEA					
Obstructive	0	0	0	0	0
Mixed	0	0	0	0	0
Central	0	0	0	0	0
Total Apnea	0	0	0	0	0
Apnea Index	0.0	0.0	0.0	0.0	0.0
HYPOPNEA	58	0	58	0	58
Total Apneas and Hypopneas	58	0	58	0	58
AHI*	22.7	0.0	22.7	0.0	22.7
Flow Limitation Events (RERA)	0	0	0	0	0
RDI	22.7	0.0	22.7	-	22.7

This table details the number of apneas and hypopneas during sleep, broken down by sleep stage (NREM, REM) and body position (Supine, Non-Supine). No apneas were recorded, while 58 hypopneas occurred, all during NREM sleep in the supine position. The Apnea-Hypopnea Index (AHI) was 22.7, and the Respiratory Disturbance Index (RDI) was also 22.7. No flow limitation events (RERA) were noted.

Table 4. Respiratory Summary

TIME BETWEEN	**NREM**	**REM**	**TOTAL (SLEEP)**
90+%	2:14:38.0	0:00:0.0	2:14:38.0
80-89%	0:13:18.0	0:00:0.0	0:13:18.0
70-79%	0:01:39.0	0:00:0.0	0:00:0.0
60-69%	0:00:3.0	0:00:0.0	0:00:3.0
<60%	0:00:0.0	0:00:0.0	0:00:0.0
SAO2 NADIR	68%	-%	68%

This table summarizes the time spent at different oxygen saturation levels (SpO2) during non-REM (NREM) and REM sleep stages. The time is divided into intervals of SpO2: 90+%, 80-89%, 70-79%, 60-69%, and <60%. The nadir (lowest) SpO2 recorded during sleep was 68%.

Since this patient had a history of treatment-resistant OSA due to morbid obesity, genetic testing was performed to assess the causes of obesity (**Table 5**). This patient is heterozygous in the *BBS9* gene for a sequence variant defined as c.396GC, which is predicted to result in the amino acid substitution p.Gln132His.

Furthermore, this patient is heterozygous in the *LEPR* gene for a sequence variant defined as c.658GA, which is predicted to result in the amino acid substitution p.Val220Ile.

Table 5. Summary of Genetic Testing Results for Obesity-Related Gene Variants (*BBS9* and *LEPR*) and their Clinical Significance

Gene Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
***BBS9*, NM_198428.2**	AR, 607968	c.396G>C, p.Gln132His, Heterozygous	841915	0.042% Latino	Damaging	UNCERTAIN
LEPR, NM_002303.5	AR, 601007	c.658G>A, p.Val220Ile, Heterozygous	917428	0.13%, African	Tolerated	UNCERTAIN

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive =AR, X-Linked=XL, ClinVar ID: Variant accession, GnomAD: Allele Frequency registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v.2.0 (The "Other" population is excluded). Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via Poly Phen-2, SIFT, Mutation Taster, and FATHMM.

Additionally, leptin levels were measured, and genetic testing was performed on the patient's parents. The father's leptin level was 34.2 ng/mL (Male: 1.8-19.9 ng/mL). Genetic analysis showed the father is heterozygous in the *BBS9* gene, heterozygous in the *LEPR* gene, and heterozygous in the *DNMT3A* gene (**Table 6**). On the other hand, the mother's leptin level was 64.6 ng/mL (Female: 8-38 ng/mL), and she was negative for genetic variants (**Figure 2)**.

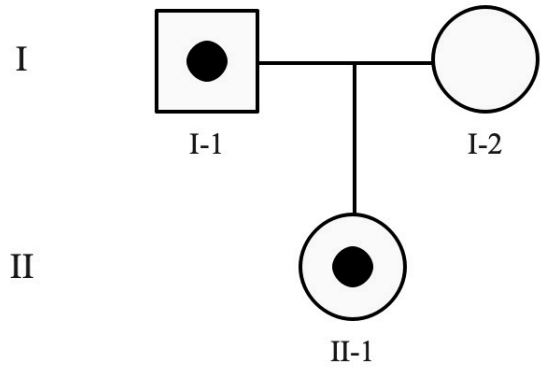
Table 6. Summary of Genetic Testing Results for Obesity-Related Gene Variants (BBS9 and LEPR) and their Clinical Significance in the Patient's Father

Gene Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
***BBS9*, NM_198428.2**	AR, 607968	c.396G>C, p.Gln132His, Heterozygous	841915	0.042% Latino	Damaging	UNCERTAIN
***LEPR*, NM_002303.5**	AR, 601007	c.658G>A, p.Val220Ile, Heterozygous	917428	0.13%, African	Tolerated	UNCERTAIN
***DNMT3A*, NM_175629.2**	AD, 602769	c.835G>A, p.Asp279Asn, Heterozygous	1190119	0.0029%, Latino	Conflicting	UNCERTAIN

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive =AR, X-Linked=XL , ClinVar ID: Variant accession (www.ncbi.nlm.nih.gov/clinvar), GnomAD: Allele Frequency

registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v.2.0 (The "Other" population is excluded).
Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via Poly Phen-2, SIFT, Mutation Taster, and FATHMM [6].

Figure 2. Pedigree of Genetic Testing Results for Obesity-Related Gene Variants (*BBS9* and *LEPR*)



The pedigree shows the inheritance pattern of BBS9 and LEPR variants. I-1 (filled square) carries the identified variants, while I-2 (empty circle) has no known variants. II-1 (filled circle) represents the child with the variants, indicating a potential autosomal recessive inheritance pattern related to early-onset obesity.

3. Discussion

This case report presents the clinical and genetic findings of an 18-year-old female patient with early-onset obesity and co-occurring disorders such as treatment-resistant. What is significant about this case is how these genes could play a role in mutations of the leptin receptor gene (*LEPR*) and Bardet-Biedl syndrome 9 (*BBS9*) and how it could be related to the patient's obesity and accompanying comorbidities [7-8, 9].

The *LEPR* gene variant identified in this patient is a heterozygous sequence variant (c.658GA), resulting in the amino acid substitution p.Val220Ile. Leptin, a hormone primarily released by adipose tissue, is crucial in regulating energy balance and body weight by acting on its receptor, encoded by the *LEPR* gene [10-11]. Mutations in this variant leading to loss of function or resistance has been reported in the heterozygous state in an individual with severe obesity [12], and this variant is reported in 0.13% of alleles in individuals of African descent in GnomAD. Although we suspect that this variant may be benign, at this time, the clinical significance of this variant is uncertain due to the absence of conclusive functional and genetic evidence. Pathogenic variants in *LEPR* are associated with autosomal recessive obesity and hypogonadotropic hypogonadism due to leptin receptor deficiency [13-14]. For instance, genetic variations of the *LEPR* gene have been described in Puerto Rican children of Hispanic descent, as is the case with our patient [15].

Emerging research supports the function of leptin and its receptor in controlling energy balance and body weight, even though other genetic and environmental factors contribute to its development [5]. Leptin is primarily released by adipose tissue and circulates in the bloodstream, passing the blood-brain barrier (BBB) and acting in the brain. When leptin binds to its receptor, signaling pathways involved in energy balance and body weight control are activated [11]. Several factors (energy balance, calorie intake, adipose tissue mass, insulin levels, stress, sleep duration and quality, etc.) regulate leptin levels, particularly acute changes in energy intake [16]. In addition, rare genetic causes of severe early-onset obesity with disturbed signaling and consequent leptin resistance have been previously

reported as leptin receptor variants [7-8]. Furthermore, leptin has been previously reported to be elevated in obesity-related sleep breathing disorders such as OSA. Some research has shown that plasma leptin levels are increased in newly diagnosed, otherwise healthy individuals with untreated sleep apnea, surpassing the levels observed in similarly obese control subjects without sleep apnea [17].

Moreover, our patient carries a heterozygous sequence variant (c.396GC) in the *BBS9* gene, which has been reported in a family where individuals presented with Bardet-Biedl syndrome (BBS) [18]. BBS is a rare autosomal recessive ciliopathy characterized by retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties, and hypogonadism [19]. Although two additional variants in BBS1 were identified, the study did not provide segregation data to support their pathogenicity [20]. This variant is reported in 0.042% of alleles in individuals of Latino descent in gnomAD. In general, heterozygous carriers of pathogenic variants of autosomal recessive diseases present asymptomatic. The occurrence of symptomatic heterozygosity in autosomal diseases is exceptionally uncommon and has primarily been documented through individual case reports. However, certain extensive studies have indicated an elevated risk for specific diseases among individuals with one copy of the mutated gene [21]. Furthermore, BBS is characterized by notable clinical and genetic diversity. While initially conceptualized as a purely recessive trait, recent findings have revealed an oligogenic mode of disease transmission. In certain families, genetic interactions between mutations at distinct BBS loci have been identified, contributing to the causation and/or modification of the syndrome's phenotype [22]. Although heterozygous, this patient presents with a milder phenotype presentation of BBS. It has been demonstrated that a wide range of Mendelian diseases, variants traditionally considered to be recessive can cause milder phenotypes in heterozygous carriers [21].

The co-occurrence of genetic variants associated with obesity in this patient suggests a synergistic effect that can be clinically observed. Previous studies have demonstrated that certain individuals carry heterozygous mutations in multiple genes associated with interconnected biological pathways. Individually, each mutation's heterozygosity holds no clinical significance. However, when present concurrently, the heterozygosity exhibits synergy, leading to clinically relevant biochemical abnormalities. This concept of "synergistic heterozygosity" proves valuable in understanding complex phenotypes, such as seen in our patient [23].

Genetic testing was also done on the patient's parents to evaluate the inheritance pattern of the discovered variations. The *LEPR* and *BBS9* mutations found in the patient's father are indicative of an autosomal dominant or autosomal recessive inheritance pattern. The patient's mother, on the other hand, did not carry any of the detected variations yet still had an elevated leptin level, indicating that she may have developed leptin resistance without any genetic mutation. Leptin resistance is defined as the failure of leptin to promote anticipated salutary metabolic outcomes in states of over-nutrition or obesity [24]. This phenomenon has been described to be induced by multiple conditions. In general, leptin resistance can be classified based on different etiologies; like high fat diet (HFD) induced leptin resistance, inflammation induced leptin resistance, pregnancy/lactation induced leptin resistance, etc. [25]. With these findings, it can be inferred that the patient's obesity may have a paternal genetic component, as well as an environmental component.

Sleep breathing disorders associated with obesity, such as OSA, result in intermittent hypoxia during sleep, a potent inducer of oxidative stress. Elevated levels of leptin and the development of leptin resistance might enhance the production of reactive oxygen species, accelerating oxidative stress and fostering inflammation. Consequently, some studies have suggested a potential connection between leptin and oxidative stress in the development of sleep-breathing disorders [25]. Our patient presented with a treatment-resistant OSA, which could

be explained by multifactorial genetic and environmental components that have led her to chronically elevated leptin levels and obesity.

This case report emphasizes the value of genetic research in figuring out the root causes of obesity and its comorbidities, especially in cases of early-onset obesity and co-occurring disorders such as OSA. The discovery of genetic variations in the *LEPR* and *BBS9* genes offers crucial new information on putative mechanisms underlying the clinically presentable phenotype of the patient. These variations' precise clinical significance and impact on the patient's condition are still unknown. It is necessary to conduct more research, including functional investigations and extensive genetic analysis, to clarify the genotype-phenotype relationship and provide individualized treatment plans for people with obesity and related comorbidities.

4. Conclusions

Leptin dysregulation has been associated with an increased predisposition to obesity, which could lead to sleep-related disorders, such as OSA. What is novel about our case is that our patient has a *LEPR* gene heterozygous variant, leading to an increase in leptin levels, greater increase in metabolic dysregulation and increased body weight; thus, worsening her OSA. At the same time, research has shown that conditions such as OSA also increase leptin levels, which could worsen her OSA and prognosis. Further research is needed to assess *LEPR* and its role in OSA, especially in Hispanic populations, where research is limited.

Supplementary Materials: None

Author Contributions: All authors significantly contributed to the study's conception and design, clinical data acquisition, analysis, and interpretation, as well as manuscript drafting and revision, and approved the final version for publication.

Acknowledgements: None

Funding: This research received no external funding.

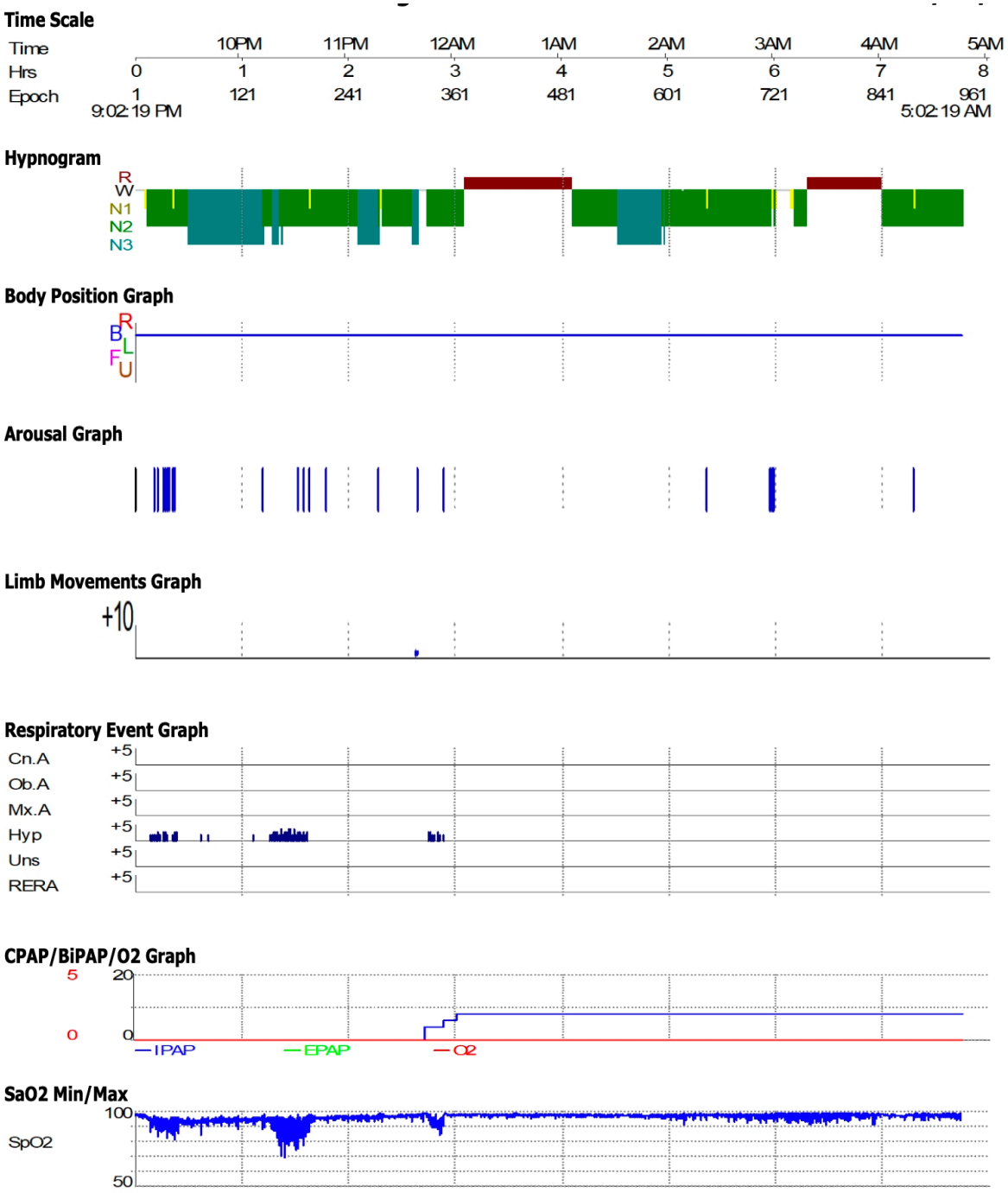
Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Ponce Health Sciences University on July 27, 2022, protocol code 2207110163.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data analyzed for this case report are included in this published article.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix 1. Polysomnography Report with Sleep Architecture, Arousals, and Respiratory Events



Time Scale

- **Time:** Shows the hour of the night (10 PM to 5 AM).
- **Hrs:** Number of hours since the start of the recording.
- **Epoch:** Consecutive time intervals since the start of the recording.

Hypnogram

- **R:** REM sleep.
- **W:** Wake.
- **N1:** Non-REM stage 1 sleep.

- **N2:** Non-REM stage 2 sleep.
- **N3:** Non-REM stage 3 sleep.

Body Position Graph

- **B:** Back.
- **L:** Left side.
- **R:** Right side.
- **F:** Face down.
- **U:** Unknown position.

Arousal Graph

- **Vertical lines:** Indicate arousal events during sleep.

Limb Movements Graph

- **+10:** Indicates the occurrence of limb movements.

Respiratory Event Graph

- **Cn.A:** Central Apneas.
- **Ob.A:** Obstructive Apneas.
- **Mx.A:** Mixed Apneas.
- **Hyp:** Hypopneas.
- **Uns:** Unspecified events.
- **RERA:** Respiratory Effort-Related Arousals.

CPAP/BiPAP/O2 Graph

- **IPAP:** Inspiratory Positive Airway Pressure.
- **EPAP:** Expiratory Positive Airway Pressure.
- **O2:** Oxygen levels.

SaO2 Min/Max

- **SpO2:** Blood oxygen saturation levels (ranging from 50% to 100%).

References

1. Apovian, C. M. (2016). Obesity: definition, comorbidities, causes, and burden. *The American Journal of Managed Care*, *22*(7 Suppl), s176-85. PMID: 27356115.

2. Schwartz, M. W., Seeley, R. J., Zeltser, L. M., Drewnowski, A., Ravussin, E., Redman, L. M., & Leibel, R. L. (2017). Obesity Pathogenesis: An Endocrine Society Scientific Statement. *Endocrine Reviews*, *38*(4), 267–296. https://doi.org/10.1210/er.2017-00111

3. Lin, X., & Li, H. (2021). Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Frontiers in Endocrinology*, *12*, 706978. https://doi.org/10.3389/fendo.2021.706978

4. Wu, Y., Duan, H., Tian, X., Xu, C., Wang, W., Jiang, W., Pang, Z., Zhang, D., & Tan, Q. (2018). Genetics of Obesity Traits: A Bivariate Genome-Wide Association Analysis. *Frontiers in Genetics*, *9*, 179. https://doi.org/10.3389/fgene.2018.00179

5. Obradovic, M., Sudar-Milovanovic, E., Soskic, S., Essack, M., Arya, S., Stewart, A. J., Gojobori, T., & Isenovic, E. R. (2021). Leptin and Obesity: Role and Clinical Implication. *Frontiers in Endocrinology*, *12*, 585887. https://doi.org/10.3389/fendo.2021.585887

6. Liu, X., Wu, C., Li, C., & Boerwinkle, E. (2016). dbNSFP v3.0: A One-Stop Database of Functional Predictions and Annotations for Human Nonsynonymous and Splice-Site SNVs. *Human Mutation*, *37*(3), 235–241. https://doi.org/10.1002/humu.22932

7. Park, H.-K., & Ahima, R. S. (2014). Leptin signaling. *F1000prime Reports*, *6*, 73. https://doi.org/10.12703/P6-73

8. Perakakis, N., Farr, O. M., & Mantzoros, C. S. (2021). Leptin in Leanness and Obesity: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*, *77*(6), 745–760. https://doi.org/10.1016/j.jacc.2020.11.069

9. Pomeroy, J., Krentz, A. D., Richardson, J. G., Berg, R. L., VanWormer, J. J., & Haws, R. M. (2021). Bardet-Biedl syndrome: Weight patterns and genetics in a rare obesity syndrome. *Pediatric Obesity*, *16*(2), e12703. https://doi.org/10.1111/ijpo.12703

10. Nunziata, A., Funcke, J.-B., Borck, G., von Schnurbein, J., Brandt, S., Lennerz, B., Moepps, B., Gierschik, P., Fischer-Posovszky, P., & Wabitsch, M. (2019). Functional and Phenotypic Characteristics of Human Leptin Receptor Mutations. *Journal of the Endocrine Society*, *3*(1), 27–41. https://doi.org/10.1210/js.2018-00123

11. Courbage, S., Poitou, C., Le Beyec-Le Bihan, J., Karsenty, A., Lemale, J., Pelloux, V., Lacorte, J.-M., Carel, J.-C., Lecomte, N., Storey, C., De Filippo, G., Coupaye, M., Oppert, J.-M., Tounian, P., Clément, K., & Dubern, B. (2021). Implication of Heterozygous Variants in Genes of the Leptin-Melanocortin Pathway in Severe Obesity. *The Journal of Clinical Endocrinology and Metabolism*, *106*(10), 2991–3006. https://doi.org/10.1210/clinem/dgab404

12. Clément, K., Vaisse, C., Lahlou, N., Cabrol, S., Pelloux, V., Cassuto, D., Gourmelen, M., Dina, C., Chambaz, J., Lacorte, J. M., Basdevant, A., Bougnères, P., Lebouc, Y., Froguel, P., & Guy-Grand, B. (1998). A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature*, *392*(6674), 398–401. https://doi.org/10.1038/32911

13. Farooqi, I. S., Wangensteen, T., Collins, S., Kimber, W., Matarese, G., Keogh, J. M., Lank, E., Bottomley, B., Lopez-Fernandez, J., Ferraz-Amaro, I., Dattani, M. T., Ercan, O., Myhre, A. G., Retterstol, L., Stanhope, R., Edge, J. A., McKenzie, S., Lessan, N., Ghodsi, M., … O'Rahilly, S. (2007). Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *The New England Journal of Medicine*, *356*(3), 237–247. https://doi.org/10.1056/NEJMoa063988

14. Kleinendorst, L., van Haelst, M. M., & van den Akker, E. L. T. (2017). Young girl with severe early-onset obesity and hyperphagia. *BMJ Case Reports*, *2017*. https://doi.org/10.1136/bcr-2017-221067

15. Melendez-Montañez, J. M., & De Jesus-Rojas, W. (2024). The Tip of the Iceberg: Genotype of Puerto Rican Pediatric Obesity. *Genes*, *15*(4), 394. https://doi.org/10.3390/genes15040394

16. Phillips, B. G., Kato, M., Narkiewicz, K., Choe, I., & Somers, V. K. (2000). Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *American Journal of Physiology. Heart and Circulatory Physiology*, *279*(1), H234-7. https://doi.org/10.1152/ajpheart.2000.279.1.H234

17. Suárez-González, J., Seidel, V., Andrés-Zayas, C. *et al.* Novel biallelic variant in *BBS9*causative of Bardet–Biedl syndrome: expanding the spectrum of disease-causing genetic alterations. *BMC Med Genomics* 14, 91 (2021). https://doi.org/10.1186/s12920-021-00943-w

18. Forsythe, E., & Beales, P. L. (2013). Bardet-Biedl syndrome. *European Journal of Human Genetics : EJHG*, *21*(1), 8–13. https://doi.org/10.1038/ejhg.2012.115

19. Chen, J., Smaoui, N., Hammer, M. B. H., Jiao, X., Riazuddin, S. A., Harper, S., Katsanis, N., Riazuddin, S., Chaabouni, H., Berson, E. L., & Hejtmancik, J. F. (2011). Molecular analysis of Bardet-Biedl syndrome families: report of 21 novel mutations in 10 genes. *Investigative Ophthalmology & Visual Science*, *52*(8), 5317–5324. https://doi.org/10.1167/iovs.11-7554

20. Barton, A. R., Hujoel, M. L. A., Mukamel, R. E., Sherman, M. A., & Loh, P.-R. (2022). A spectrum of recessiveness among Mendelian disease variants in UK Biobank. *American Journal of Human Genetics*, *109*(7), 1298–1307. https://doi.org/10.1016/j.ajhg.2022.05.008

21. Katsanis, N. (2004). The oligogenic properties of Bardet-Biedl syndrome. *Human Molecular Genetics*, *13 Spec No 1*, R65-71. https://doi.org/10.1093/hmg/ddh092

22. Kalyta, K., Stelmaszczyk, W., Szczęśniak, D., Kotuła, L., Dobosz, P., & Mroczek, M. (2023). The Spectrum of the Heterozygous Effect in Biallelic Mendelian Diseases-The Symptomatic Heterozygote Issue. *Genes*, *14*(8). https://doi.org/10.3390/genes14081562

23. Myers, M. G., Heymsfield, S. B., Haft, C., Kahn, B. B., Laughlin, M., Leibel, R. L., Tschöp, M. H., & Yanovski, J. A. (2012). Challenges and opportunities of defining clinical leptin resistance. *Cell Metabolism*, *15*(2), 150–156. https://doi.org/10.1016/j.cmet.2012.01.002

24. Liu, J., Lai, F., Hou, Y., & Zheng, R. (2022). Leptin signaling and leptin resistance. *Medical Review (Berlin, Germany)*, *2*(4), 363–384. https://doi.org/10.1515/mr-2022-0017

25. Berger, S., & Polotsky, V. Y. (2018). Leptin and Leptin Resistance in the Pathogenesis of Obstructive Sleep Apnea: A Possible Link to Oxidative Stress and Cardiovascular Complications. *Oxidative Medicine and Cellular Longevity*, *2018*, 5137947. https://doi.org/10.1155/2018/5137947