



Case Report

<http://wjpn.ssu.ac.ir>**First Report of Concurrent Homozygous LEP and PKHD1 Pathogenic Variants in a Child with Early-Onset Obesity and Renal Microlithiasis**Somayeh Talaeipour^{1,2}, Seyedeh Zalfa Modarresi^{2,3*}, Elham Shafighii⁴¹ Mother and Newborn Health Research Center, Comprehensive Research Institute for Maternal and Child Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran² Children Growth Disorder Research Center, Comprehensive Research Institute for Maternal and Child Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran³ Department of Pediatrics, School of Medicine, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran⁴ Children and Adolescents Health Research Center, Research Institute of Cellular and Molecular Science in Infectious Diseases, Zahedan University of Medical Sciences, Zahedan, Iran

Received: 11 October 2025

Revised: 04 November 2025

Accepted: 11 November 2025

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Keywords:Leptin,
Deficiency,
PKHD1,
Nephrocalcinosis,
Consanguinity,
Whole-exome sequencing**ABSTRACT****Background:** Severe early-onset obesity with hyperphagia may be caused by a monogenic disorder involving the leptin–melanocortin pathway. Leptin (LEP) deficiency is a known cause of congenital obesity, whereas PKHD1 mutations are associated with autosomal recessive polycystic kidney disease (ARPKD).**Case Presentation:** We report a 20-month-old boy born to consanguineous parents with rapid weight gain since birth (current body weight of 25 kg), extreme hyperphagia, truncal obesity, acanthosis nigricans, dyslipidemia, and renal microlithiasis or nephrocalcinosis. Results of endocrine and thyroid function tests were unremarkable. Renal ultrasonography revealed multiple echogenic foci, with no cystic dilatation or sonographic evidence of impaired renal function. Whole exome sequencing identified homozygous pathogenic variants in both LEP and PKHD1, consistent with autosomal recessive inheritance.**Interpretation:** The LEP variant explains the early-onset severe obesity, hyperphagia, and metabolic abnormalities observed in this patient, as seen in congenital leptin deficiency. The PKHD1 variant likely accounts for the atypical renal phenotype of nephrocalcinosis without overt cystic disease and may result in a truncating frameshift. To our knowledge, this is the first report of simultaneous pathogenic LEP and PKHD1 variants in an individual.**Conclusion:** The case underscores the clinical and diagnostic value of whole-genome analysis in early-onset obesity, particularly in consanguineous families where two or more recessive conditions can co-occur by chance. More comprehensive genetic evaluation should be encouraged in atypical or multisystem obesity in children to uncover composite molecular etiologies.

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Introduction

Early childhood obesity is increasingly recognized as a multifactorial condition, and in some cases may reflect monogenic or syndromic disease, particularly when severe obesity and hyperphagia present early in life. Monogenic obesity results from rare, highly penetrant mutations in a single gene, typically affecting hunger regulation, energy homeostasis, or fat-signaling pathways (e.g., the leptin–melanocortin axis)^{1,2}. While environmental and polygenic factors account for most cases in the general population, identifying monogenic causes is crucial due to their implications for treatment, diagnosis, and genetic counseling.

Leptin (LEP) deficiency plays a central role in congenital obesity caused by monogenic disorders. Leptin, secreted by adipocytes in proportion to fat mass, suppresses appetite, increases energy expenditure, and modulates endocrine axes by acting on hypothalamic neurons. Loss-of-function mutations of LEP disrupt this negative feedback, leading to uncontrolled appetite, overeating, and severe obesity at a very early age³. Clinically, patients with LEP deficiency present with infantile obesity, hyperphagia, normal birth weight, and variable endocrine manifestations, including hypogonadotropic hypogonadism or pituitary hormone deficiencies in about one-third of cases. A recent systematic review identified approximately 86 reported cases of LEP deficiency worldwide, though genetic modeling suggests underdiagnosis, with an estimated prevalence of ~1.34 per million in Europe.³

Apart from obesity, LEP-deficient patients present with a syndrome of metabolic derangements, including insulin resistance, dyslipidemia, hepatic steatosis, and acanthosis nigricans.⁴ Given the presence of ligand- level dysfunction, recombinant leptin therapy (e.g., metreleptin) demonstrates high efficacy, unlike in LEPR deficiency, and may therefore be integrated into treatment regimens together with supportive care.⁵

On the renal side, *PKHD1* is the classical gene for autosomal recessive polycystic kidney disease (ARPKD), a fibrocystic hepatorenal syndrome classically presenting that typically presents in perinatal or neonatal life with echogenic, enlarged kidneys, deranged renal function, and hepatic fibrosis^{6,7}. Genotype-phenotype correlation, however, reveals that *PKHD1* truncating mutations may lead to severe perinatal or neonatal phenotypes, while hypomorphic or non-truncating mutations may lead to atypical or mild renal phenotypes, sometimes with minimal cystic change, isolated tubular dysfunction, nephrocalcinosis, or even an adult-onset presentation, "hybrid phenotypes"⁸. Indeed, cases with biallelic *PKHD1* variants in the absence of overt cystic kidney disease have been reported, supporting a broader phenotypic spectrum than that of classic ARPKD⁹.

In this case report, we describe a 20-months-old boy with severe early-onset obesity, hyperphagia, dyslipidemia, and renal microlithiasis from consanguineous parents, in whom whole exome sequencing identified homozygous pathogenic variants in both *LEP* and *PKHD1*. To our knowledge, concomitant pathogenic defects in both *LEP* and *PKHD1* have not previously been reported.

Case Presentation:

A 20-months-old boy was presented with severe early-onset obesity, hyperphagia, and respiratory distress. Rapid weight gain began in early infancy. He was the first child of consanguineous parents with a birth weight of 3900 grams, with NVD delivery without a history of NICU admission. There was no known family history of obesity, renal, or other systemic illness.

Physical Examination:

Vital signs were within normal limits except for mild tachypnea. The patient was extremely obese with truncal predominance of fat distribution. No edema or cushingoid facial features were noted. Acanthosis nigricans of

the neck and axillae, a round face, small hands and feet, and mild hypotonia were observed. Genitalia were normal for the age, and no dysmorphic features were noted. These findings, in combination with hyperphagia and early-onset severe obesity, raised suspicion of a monogenic obesity syndrome, most particularly a leptin deficiency mutation.

Detailed paraclinical evaluation for the patient are is presented in Table 1. Key

paraclinical findings included severe mixed dyslipidemia, hypochromic microcytic anemia, microscopic hematuria without proteinuria, and bilateral renal microlithiasis with medullary nephrocalcinosis on ultrasound, despite preserved renal function and no cystic changes. Thyroid, adrenal, and glucose homeostasis were normal. Mild left ventricular hypertrophy was noted on echocardiography, consistent with obesity burden.

Table 1. Clinical, Laboratory, Imaging and Genetic Findings at 20 Months of Age

Category	Parameter	Value	Reference Range	Comment
Anthropometry	Weight/ Height / BMI	25 kg/ 85 cm/ 37 kg/m ²	—	Severe early-onset obesity
	BMI z-score	+11.5 SD (>99.9th percentile)	—	Extremely high
Hematology	Hb/ MCV/ MCH/ MCHC/RDW	9.3 g/dL/ 47.5 fL/ 13.4 pg / 26.2 g/dL / 17.7%	Hb >11, MCV >70	Microcytic hypochromic anemia
Biochemistry	WBC/ Platelets	13,600/μL / 573,000/μL	—	Moderate thrombocytosis
	FBS	91 mg/dL	<100	Normal
	Total chol/ LDL / HDL/ TG	263/ 173/ 37/ 269mg/dL	<170/ <110/ >40 / <150	Severe mixed dyslipidemia
	AST / ALT / ALP	35/ 45/ 779 U/L	ALP <500	Markedly elevated ALP
	Urea/ Creatinine	7/ 0.7 mg/dL	—	Currently normal renal function
	Calcium/ Phosphorus	10.3/ 3.9 mg/dL	Ca 8.8–10.8	Upper-normal calcium
	25(OH)Vitamin D/ Ferritin	41.5 ng/mL/ 28 ng/mL	Vit D >30/ Ferritin >20	Sufficient Vit D, low-normal ferritin
Thyroid & adrenal	TSH/ Free T4/ Morning cortisol	2.25 μIU/mL/ 1.33 ng/dL/ 11.1 μg/dL	Normal	All normal
Urinalysis	Specific gravity	1.006	—	Low
	RBC/ WBC/ Protein	10–15/ 4–6/ Negative	—	Microscopic hematuria
Renal ultrasound	Kidney size (R/L)	96/ 99 mm	Normal for age	Normal size at present
	Cortex thickness / CMD	13–14 mm/ preserved	—	Preserved
	Findings	Multiple 1.5–2 mm echogenic foci + medullary nephrocalcinosis	—	Microlithiasis + medullary nephrocalcinosis
Liver ultrasound	Size/ Echotexture	Normal/ Normal	—	No hepatic fibrosis or cysts
Echocardiography	Findings	Mild LVH, trivial AI	—	Early obesity-related left ventricular hypertrophy + trivial aortic insufficiency
Genetic (WES + Sanger)	LEPR variant	NM_002303.5: c.2357T>C (p.Leu786Pro) homozygous	—	Pathogenic → complete leptin receptor dysfunction → congenital leptin signaling defect
	PKHD1 variants	NM_138694.4: c.5895G>A (p.Leu1965=) + c.107C>T (p.Thr36Met) compound heterozygous	—	Likely pathogenic/ hypomorphic alleles → mild or juvenile form of ARPKD at the moment

Genetic Analysis

Whole exome sequencing (WES) revealed homozygous pathogenic variants in *LEP* (Leptin gene) and *PKHD1* (Polycystic Kidney and Hepatic Disease 1 gene), both of which were inherited in an autosomal recessive (AR) pattern. Parental testing was consistent with heterozygosity for the same variants in each parent.

Treatment:

He went under lifestyle modification and conservative treatment.

Discussion

In this case presentation, we report the first case of concurrent pathogenic variants in *LEP* and *PKHD1*, identified by WES in a 20-month-old boy from consanguineous parents presenting with extreme early onset obesity and renal microlithiasis and nephrocalcinosis.

The homozygous pathogenic *LEP* variant (c.313C>T, p.Gln105Ter) is fully responsible for the typical manifestations of congenital leptin deficiency: normal birth weight, excessive hyperphagia in the first months of life, rapid weight gain, acanthosis nigricans, dyslipidemia, and mild hypotonia.^{4, 10, 11} Disrupted leptin signaling interferes with the hypothalamic melanocortin pathway, causing insatiable hunger and early onset of severe obesity.

The homozygous *PKHD1* variant c.5895dupA is considered pathogenic, with a probable truncating frameshift effect. Though *PKHD1* is the major gene for ARPKD, truncating allelic combinations have been known to cause severe phenotypes, including early nephrocalcinosis or perinatal disease.¹²⁻¹⁴

The medullary nephrocalcinosis and microlithiasis observed in the absence of cysts or renal impairment at this age are consistent with such an early *PKHD1*-related disease.^{15, 16} Severe obesity and associated metabolic stress (insulin resistance, altered urinary solute excretion) may further enhance calcium deposition in the kidneys, which has already been rendered susceptible by fibrocystin dysfunction.¹⁷

Dual biallelic pathogenic variants in *LEP* and *PKHD1*, to the best of our knowledge, have not been previously reported. This dual molecular diagnosis underlines the critical value of unbiased comprehensive genomic testing by WES in consanguineous families presenting with multisystem or atypical early-onset obesity, since more than one recessive condition can coexist, or more children will be affected.¹⁸

Clinically, recognition of both disorders is essential to ensure appropriate management and surveillance. The patient has been recommended on recombinant leptin therapy (metreleptin) for *LEP* deficiency,¹⁹ intensive lifestyle intervention, potassium citrate and hydration for nephrocalcinosis, and statin and metformin therapy for dyslipidemia and metabolic control. Long-term multidisciplinary follow-up is planned to monitor metabolic complications, renal disease progression, including cyst development, potential hepatic fibrosis, stone-related sequelae, and genetic counseling.

Conclusion

This case represents the first description of simultaneous *LEP* and *PKHD1* pathogenic variants and underscores the critical role of WES in consanguineous families with atypical or multisystem presentations of early-onset obesity. Recognition of dual molecular diagnoses is essential for accurate prognosis, personalized management, and appropriate genetic counseling.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgments

The authors express their gratitude to the patient's family for their cooperation during this study.

Funding

The authors declare that no funding was received for this research.

Ethical Considerations

The study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences.

(Code: IR.SSU.REC.1404.132)

Author's Contribution

Patient evaluation, data collection and initial drafting of the case presentation, S.T.; Literature review, discussion writing, and manuscript editing, S.ZM.; Genetic interpretation, study supervision, and critical revision of the manuscript, E.Sh.

How to Cite: Talaeipour S, Modarresi SZ, Shafighii E. First Report of Concurrent Homozygous LEP and PKHD1 Pathogenic Variants in a Child with Early-Onset Obesity and Renal Microlithiasis. *World J Peri & Neonatol* 2024; 7(2): 104-9. DOI: 10.18502/wjpn.v7i2.20452

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