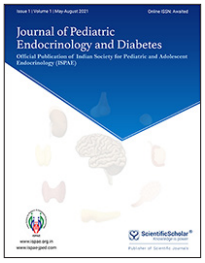
ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ispae-jped.com/

Journal of Pediatric Endocrinology and Diabetes



Case Report

Congenital leptin receptor deficiency: A novel leptin receptor gene mutation in an Indian family producing severe early-onset monogenic obesity

Prashant Prakash Patil[1], Sakina Rajagara[2], Sachin Dhamankar[2], Maroti Yalamgonde[2], Pratik Thakare[3]

[1]Department of Pediatrics, Division of Pediatric Endocrinology, Society for Rehabilitation of Crippled Children-Narayana Health Hospital, [2]Department of Pediatrics, Seth V.C. Gandhi and M.A. Vora Municipal General Hospital, [3]Division of Genetic, Life Cell international Pvt. Limited, Mumbai, Maharashtra, India.

***Corresponding author:**
Prashant Prakash Patil, Division of Pediatric Endocrinology, Society for Rehabilitation of Crippled Children-Narayana Health Hospital, Mumbai, Maharashtra, India.

dr_prash4u@yahoo.com

Received: 26 February 2023
Accepted: 16 July 2023
Published: 05 September 2023

DOI
10.25259/JPED_5_2023

Quick Response Code:

ABSTRACT

Congenital leptin receptor (LEPR) deficiency is a rare autosomal recessive condition producing early-onset severe monogenic obesity with around 90 cases reported worldwide to date. It is associated with early-onset obesity, hyperphagia, and various hormone deficiencies. We describe siblings born to consanguineous parents with progressive early-onset obesity associated with hyperphagia. Genetic analysis revealed a novel homozygous mutation in *LEPR* (c.1752G>A) gene on chromosome 1p31. Both parents were heterozygous carriers for the same mutation. This is only the second reported case from India where siblings have been affected with *LEPR* gene mutation. This will provide further insight into the physiologic role of leptin and its receptor LEPR in monogenic obesity.

Keywords: Leptin receptor gene, Monogenic obesity, Setmelanotide

INTRODUCTION

The prevalence of pediatric obesity has reached epidemic proportions worldwide affecting developed and developing nations alike. As per the World Health Organization (WHO) 2017 report, approximately 41 million children who are <5 years old are overweight and obese [http://www.who.int/topics/obesity/en.]. Obesity is an end result of the complex interaction between various environmental factors and genetic factors. Most infantile early-onset obesity is caused by a mutation of a single gene also known as monogenic obesity. Genetic defects which affect the leptin (LEP)-melanocortin pathway ultimately lead to an imbalance in food intake and energy homeostasis, resulting in early-onset obesity and extreme hyperphagia.[1,2] LEP is produced by white adipocytes in the body and it acts through its receptor LEP receptor (LEPR) and controls energy expenditure and food intake through a specialized set of hypothalamic neurons.[3] The mutation in *LEP* and *LEPR* genes is one of the most common causes of early-onset obesity with a prevalence of as high as 10–20% monogenic obesity especially where the consanguinity is common.[4] The mutation of the *LEPR* gene results in early-onset obesity with sudden and severe weight gain and endocrine problems such as hypothyroidism, hypogonadotropic hypogonadism, diabetes mellitus, and recurrent respiratory tract infection.[5] Discovery of novel mutations by Whole Exome Sequencing (WES) having a pathogenic role in early-onset obesity is a relatively recent approach in comparison to genome-wide association studies and will help formulate a specific treatment plan.

CASE REPORT

An 8-year-old Indian girl and her 1.5-year-old brother [Figure 1] born out of consanguineous parentage came for concern about excessive weight gain in our obesity clinic. The proband and her brother were second and fifth in birth order, respectively, with the eldest boy with severe obesity who succumbed at 1.5 years of age due to respiratory tract infection [Figure 2]. Both children had a normal birth weight of around 3 kg with a typical history of excessive weight gain after 3–6 months of life. The elder girl was apparently alright till 3 months of life; thereafter, she started to put on excessive weight (at 3 months weight 10.3 kg; WHO weight Standard Deviation Score [SDS] +4.77) reaching 19 kg (WHO weight SDS +7.01) at 11 months of age. Due to her excessive weight, comorbidities such as immobility and type 2 diabetes mellitus, and lack of specific diagnosis, she underwent bariatric surgery twice; first at 11 months of age and later at 7 years (weight - 49 kg and WHO weight SDS +3.31). The elder girl was already operated on twice before visiting our clinic without any genetic evaluation performed due to non-affordability. Her younger brother too had sudden weight gain post 4 months of life, his present weight at 1.5 years is 18 kg (WHO weight SDS: +4.73) and length 80 cm (WHO length SDS score: –0.83) with weight for height for age and gender is beyond 99th percentile of the WHO chart (WHO weight for length SDS: +6.82). He had a history of repeated admissions with respiratory ailments. Both children were developmentally normal without any developmental delay with normal genitalia without any dysmorphic features typical of any known syndrome. Both of them had hyperphagia with compulsive eating. Investigation revealed dyslipidemia and very high serum LEP levels. Blood glucose, cortisol, thyroid profile, gonadotropin levels, creatinine, liver enzymes, and fasting insulin were normal [Table 1].

Figure 1: Clinical image of the index case and sibling.

Considering monogenic obesity as a diagnosis, WES was performed from peripheral blood isolated genomic deoxyribonucleic acid, and its reporting and classification of variants were carried out according to the latest ACMG guidelines.[6] Protein coding region sequencing of approximately 30 Mb of human exome was performed using Illumina Next-Generation Sequencing systems. Sention's HaplotypeCaller module was used to detect the clinically significant variants and variant annotations were done using published databases such as OMIM, GWAS, GNOMAD, and 1000Genome. It showed a novel homozygous mutation in the *LEPR* (c.1752G>A) gene on exon 12 at chromosome 1p31 suggestive of congenital LEPR deficiency [Figure 3]. Sanger sequencing of both parents confirmed the heterozygous carrier state with identical mutation. Parents were counseled about the genetic nature of obesity. Due to the non-availability of setmelanotide, extreme hyperphagia and persistent weight gain, the younger sibling at 2 years and 2 months of age also underwent bariatric surgery with sleeve gastrectomy. The child tolerated the procedure well

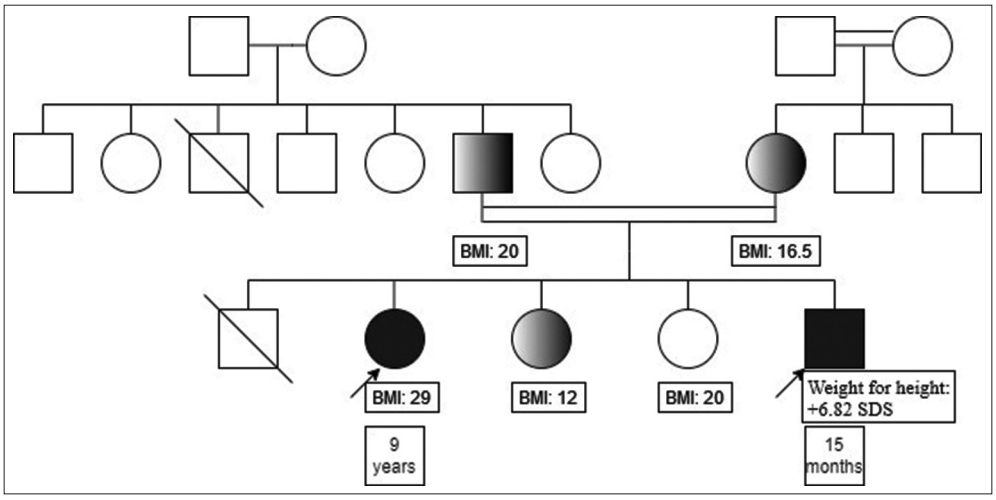


Figure 2: Pedigree chart of the affected family.

and currently post 3 months of surgery his weight at 2.5 years is stabilized at around 20.5 kg (WHO weight for age SDS +3.86), length of 91.5 cm (WHO BMI SDS +5.67) with a hypocaloric and controlled diet.

DISCUSSION

Congenital LEPR deficiency is a rare autosomal recessive disorder with estimated prevalence ranging from 0% to 3% to as high as 10% where consanguinity is very common as described in previous obesity cohort studies worldwide.[4,7] Approximately 90 cases have been reported to date from approximately 60 families of this rare condition. Congenital LEPR deficiency is characterized by severe, infantile obesity associated with selective deposition of fat mass. Unlike congenital LEP deficiency, phenotypic features in LEPR deficiency are less severe.[8] Children with *LEPR* gene deficiency have hyperphagia with *ad libitum* energy intake starting from early infancy without much deficit in basal energy expenditure. Both cases exhibited typical clinical characteristics of LEPR deficiency like rapid weight gain during infancy with severe hyperphagia. They had normal fasting blood glucose and insulin levels. Our case is similar to the case report previously described by Clément *et al.* in 1998.[9] These children exhibit near-normal linear growth with normal insulin-like growth factor 1 levels during childhood. However, the final adult height is often short due lack of a pubertal growth spurt. Adults with LEPR deficiency are known to have hypogonadotropic hypogonadism with delayed development of secondary sexual characteristics. We could not examine the gonadal axis since both were in the prepubertal stage. Children with *LEPR* gene mutations often have reduced CD4+ T-cell count with higher compensatory B-cell count indicating the role of LEP on the immune system.[10] Impaired respiratory reserve due to severe obesity coupled with decreased proliferation and altered cytokine release from lymphocytes in response to antigen-specific stimuli leads to early deaths. The younger boy had a history of repeated lower respiratory tract infections which could be attributed to the dysfunction of T-cells.

In our case, WES reported a novel synonymous variant NM_002303.6 (LEPR):c.1752G>A (p.Lys584=) which has never been reported as a pathogenic variant before but also not reported as a benign variant either [Figure 3]. The p.Lys584= variant is novel in the gnomAD database, a repository for large-

Table 1: Investigation chart of index case and sibling.

Parameter	Sibling (9 years)	Index case (15 months)	Reference range
Triglycerides (mg/dL)	**253**	**283**	Upto 200
Total cholesterol (mg/dL)	**158**	**204**	110-230
HDL-cholesterol (mg/dL)	**28**	**23**	>35
Glucose (mg/dL)	98	**128**	70-110
Insulin (µU/mL)	3.5	3.2	2.6-24.9
Serum leptin (ng/mL)	**58.4**	**60.2**	
	Ref: (1.7-2.2)	Ref (2.5-7.15)	
TSH (µU/mL)	1.4	2.0	0.7-5.5
Free T3 (pg/mL)	3.2	2.7	2-5
Free T4 (pg/mL)	1.2	1.2	0.7-1.8
Cortisol (µg/dL)	7.1	6.4	6.2-19.4

Bold values indicate presence of dyslipidemia with higher levels of serum leptin in both index case and sibling.

Figure 3: Whole exome sequencing of the affected siblings with homozygous variant c.1752G>A, carrier parents and sister with heterozygous variant c.1752G>A and normal sibling with no change.

scale sequencing projects globally. The nucleotide c.1752 in LEPR is predicted as conserved by Genomic Evolutionary Rate Profiling++ and PhyloP which measures evolutional constraints at individual alignment sites across 100 vertebrates. The phyloP scores represent logarithmic value (*P*-value) under a null hypothesis of neutral evolution and indicate both accelerated and evolutionary conservation. The variant was found to be segregating in two affected boys and an elder girl whose levels of serum LEP were significantly higher which is a salient biochemical feature of this condition. Parents and an unaffected girl were heterozygous carriers, whereas another unaffected girl did not have the given variant. Therefore, this variant (p.Lys584=) was classified as pathogenic in our case. This, in fact, is only the second reported case in India with *LEPR* gene mutation with the first reported from the western part of India.[11]

The elder girl had undergone bariatric surgery twice without favorable outcome. Previously, failure of various bariatric surgery procedures in cases of syndromic obesity caused by *LEPR* gene mutation has been reported.[12]

Setmelanotide is a disulfide cyclic octapeptide that acts as a melanocortin-4 receptor (MC4R) agonist which activates a transmembrane G-protein receptor (MC4R) located in the hypothalamus which regulates appetite and energy expenditure. It reduces calorie intake and increases the expenditure of energy.[13]

It is the only available drug which is approved by the United States Food and Drug Administration in November 2020 for genetically proven monogenic obesity with *LEPR* gene mutation in children of age 6 years and older. Apart from LEPR deficiency, it is also approved for use in genetically proven POMC and PCSK1 mutation in children who are 6 years and older.[13] It is a subcutaneous injection with daily dosing of 1–3 mg in the early morning, depending on patient's age, and the dose is titrated as per therapeutic response.

In an open-label single-arm, multicentric phase 3 clinical trial from ten different centers worldwide, five out of 11 participants (45%) with LEPR mutation who were enrolled, achieved at least 10% weight loss and reduction in mean hunger score by −43.7% after 52 weeks of treatment.[14] Overall, setmelanotide was well tolerated and the most common adverse reactions noted were nausea, vomiting, injection site reactions, and hyperpigmentation. At present, this new drug is unavailable in India but could be used in the future as a potential therapeutic option in such cases of monogenic obesity.

Diagnosis in such cases has several implications especially for the caregiver of these children, specifically in terms of genetic counseling of the affected families regarding the nature of the disease and in terms of novel therapeutic options acting on the LEP-melanocortin pathway which could have a favorable response in them.

CONCLUSION

Monogenic obesity is an important condition that warrants an early diagnosis since most of them require specialized treatment and a multidisciplinary approach. *LEPR* gene mutation is associated with severe infantile-onset obesity, pituitary hormonal abnormalities, and repeated respiratory tract infection due to T-cell defects. Measurement of circulating serum LEP might help to differentiate it from LEP mutation. Our case underscores the significance of timely and precise newer genetic diagnostics in patients with severe, infantile obesity to circumvent extensive diagnostic tests and failed, and often disappointing therapeutic measures especially where consanguineous marriages are prevalent. Utilizing genetic testing as a tool and improving overall awareness will assist such children with severe monogenic obesity to have early access to novel pharmacotherapy such as setmelanotide.

Acknowledgement

We would like to acknowledge Life Cell Pvt Limited for doing Whole Exome Sequencing and Sanger confirmation free of cost for academic interest. We also sincerely thank Dr Vidya Thakur Medical Superintendent of Rajawadi Hospital and Social Worker Mr Jaydeep Gite for extending their support for diagnosis and management of case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: Clinical approach and current treatments in 2016. Obes Facts 2016;9:158-73.
2. Moustafa JS, Froguel P. From obesity genetics to the future of personalized obesity therapy. Nat Rev Endocrinol 2013;9:402-13.
3. Gill R, Cheung YH, Shen Y, Lanzano P, Mirza NM, Ten S, *et al*. Whole-exome sequencing identifies novel LEPR mutations in individuals with severe early onset obesity. Obesity (Silver Spring) 2014;22:576-84.
4. Saeed S, Bonnefond A, Manzoor J, Shabbir F, Ayesha H, Philippe J, *et al*. Genetic variants in LEP, LEPR, and MC4R explain 30% of severe obesity in children from a consanguineous population. Obesity (Silver Spring) 2015;23:1687-95.

5. Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, *et al*. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med 2007;356:237-47.
6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al*. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
7. Kleinendorst L, Abawi O, van der Kamp HJ, Alders M, Meijers-Heijboer HE, van Rossum EF, *et al*. Leptin receptor deficiency: A systematic literature review and prevalence estimation based on population genetics. Eur J Endocrinol 2020;182:47-56.
8. Gibson WT, Farooqi IS, Moreau M, Keogh JM, Lawrence E, Agwu C, *et al*. Congenital leptin deficiency due to homozygosity for the Delta133G mutation: Report of another case and evaluation of response to four years of leptin therapy. J Clin Endocrinol Metab 2004;89:4821-6.
9. Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, *et al*. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998;392:398-401.
10. Ozata M, Ozdemir IC, Licinio J. Human leptin deficiency caused by a missense mutation: Multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. J Clin Endocrinol Metab 1999;84:3686-95.
11. Bhatt A, Purani C, Bhargava P, Patel K, Agarbattiwala T, Puvar A, *et al*. Whole exome sequencing reveals novel LEPR frameshift mutation in severely obese children from Western India. Mol Genet Genomic Med 2019;7:e00692.
12. Nunziata A, Funcke JB, Borck G, von Schnurbein J, Brandt S, Lennerz B, *et al*. Functional and phenotypic characteristics of human leptin receptor mutations. J Endocr Soc 2018;3:27-41.
13. Trapp CM, Censani M. Setmelanotide: A promising advancement for pediatric patients with rare forms of genetic obesity. Curr Opin Endocrinol Diabetes Obes 2023;30:136-40.
14. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, *et al*. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: Single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol 2020;8:960-70.

How to cite this article: Patil PP, Rajagara S, Dhamankar S, Yalamgonde M, Thakare P. Congenital leptin receptor deficiency: A novel leptin receptor gene mutation in an Indian family producing severe early-onset monogenic obesity. J Pediatr Endocrinol Diabetes 2023;3:29-33.