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Case Series

Monogenic obesity in a familial cluster: insights into laurence-moon-bardet-biedl syndrome and leptin deficiency associated with genetic variants in BBS12 and LEPR genes

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ABSTRACT

Monogenic obesity is a rare but clinically significant condition characterized by excessive weight gain due to genetic mutations that affect appetite regulation and energy balance. This case series explores the clinical presentation and genetic underpinnings of monogenic obesity in a familial cluster, focusing on Laurence-Moon-Bardet-Biedl Syndrome (LMBBS) and leptin deficiency associated with genetic variants in the BBS1 and LEPR genes. The index patient, an 11-year-old female, presented with progressive weight gain since infancy, accompanied by acanthosis nigricans on the neck and axillary region. Genetic testing revealed mutations in both the BBS1 and LEPR genes, confirming a monogenic etiology of obesity. Remarkably, her two siblings and a cousin from the paternal side exhibited similar clinical profiles and shared the same genetic variants. This report shows the significance of genetic testing in diagnosing monogenic obesity disorders and highlights the familial clustering observed in such cases. The findings emphasize the need for heightened awareness and consideration of genetic factors in the evaluation of obesity, particularly in pediatric patients with a family history suggestive of monogenic obesity.

Keywords: Monogenic obesity, BBS-12, LEPR, LMBBS

INTRODUCTION

Monogenic obesity, characterized by aberrant eating behavior and endocrine abnormalities, is an uncommon and severe form of early-onset obesity.[1] It follows a Mendelian pattern of inheritance, with patients typically exhibiting severe obesity due to mutations in specific genes.[2] Only a few genes are known to cause the development of severe obesity in early childhood, with autosomal recessive mutations being predominantly accountable.[3] Children born into consanguineous marriages are primarily affected by Laurence-Moon-Bardet-Biedl syndrome (LMBBS), a rare ciliopathic, pleiotropic autosomal recessive disease. Twelve genes (BBS1 through BBS12) that create proteins essential for cilia function are affected by BBS, resulting in defects in both structure and function. Among the known genetic variables linked to monogenic obesity are variations in the Bardet-Biedl syndrome 12 (BBS12) gene.[4] A monogenic form of obesity, also characterized by hyperphagia and fast weight gain beginning in the first few months of life, is brought on by mutations in the LEPR gene. Globally, at least 88 patients have been documented with at least 38 human LEPR mutations described.[5,6] In the leptin-melanocortin pathway, essential for the hypothalamic modulation of food intake, leptin specifically binds to LEPR in the hypothalamus, producing α-melanocyte-stimulating hormone, which

then activates the melanocortin-4 receptor (MC4R) to induce satiety thus reducing food intake and increasing energy consumption.[7,8] Typically, Obesity caused by damaging mutations in LEP and LEPR displays an autosomal recessive mode of inheritance.[9]

Autosomal recessive mutations, including variants in BBS12 and leptin receptor (LEPR) genes, are mostly accountable for the onset of obesity and are among the known genetic factors associated with monogenic obesity. Herein, we present a case series of a familial cluster of monogenic obesity as shown in figure 1, with variants in both BBS12 and LEPR genes, observed in the Endocrinology Department of the National Institute of Child Health Hospital, Karachi Pakistan.

CASE SERIES

The pedigree represents a family with a history of consanguineous marriage. The parents, who are first cousins, have seven children's, among which one daughter and two brother is affected. Additionally, one cousin from the paternal family is also affected.

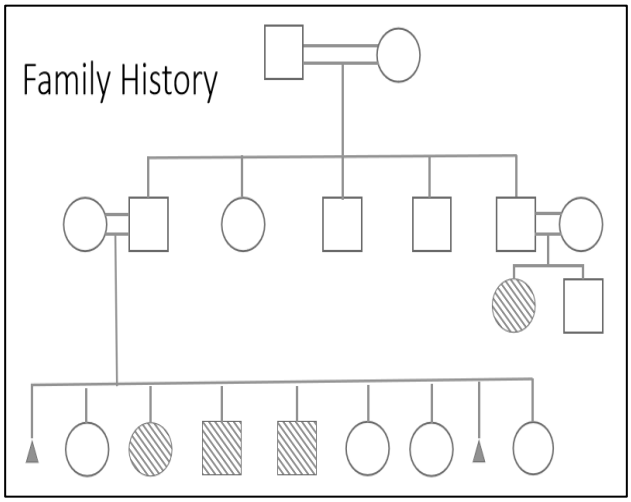

Figure 1: Family pedigree of the cases.

Case 1

The index patient, an 11-year-old girl from Dadu, Sindh, presented to the pediatric endocrinology OPD with a history of progressive weight gain since the age of 4 months. Despite her severe obesity, she displayed no syndromic facial features and was hemodynamically stable. Anthropometric measurements revealed significant adiposity, with her BMI exceeding +3 SDS (Figure 2). Clinical examination revealed acanthosis nigricans in the neck and axillary regions, a common feature associated with insulin resistance in obesity (Figure 2). Genetic testing identified homozygous variants in both the variant c.571G>C (p.Gly191Arg) for BBS1 and c.1232A>G (p.Tyr411Cys) for LEPR genes as shown in Figure 3, suggesting a monogenic origin of her obesity 3. Notably, physical examinations across the affected cohort revealed no signs of retinitis pigmentosa or fundus dystrophy, typically associated with BBS, indicating an absence of ocular manifestations. However, the presence of acanthosis nigricans in all affected individuals highlights the metabolic consequences of monogenic obesity. Systemic examinations, including cardiovascular, abdominal, and neurological evaluations, were largely unremarkable apart from changes related to obesity. While the genetic findings of positive variants in the BBS1 and LEPR genes confirmed the diagnosis of monogenic obesity.

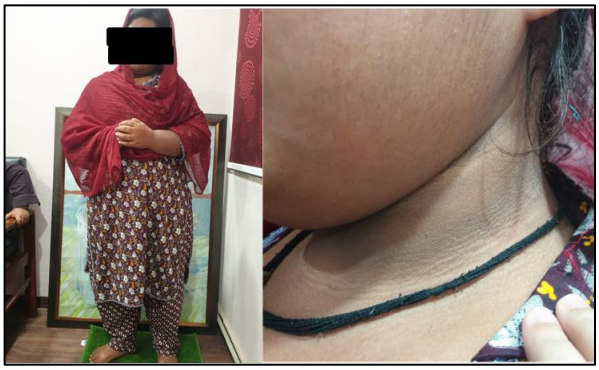

Figure 2: Clinical phenotypes of case 1, Acanthosis nigricans noted on the neck region.

RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BBS12	c.571G>C (p.Gly191Arg)	homozygous	Uncertain Significance
LEPR	c.1232A>G (p.Tyr411Cys)	homozygous	Uncertain Significance

About this test

This diagnostic test evaluates 68 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Figure 3: Genetic report of case 01. Identification of homozygous variants in bbs12 and lEPR genes.

RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BBS12	c.571G>C (p.Gly191Arg)	heterozygous	Uncertain Significance
LEPR	c.1232A>G (p.Tyr411Cys)	homozygous	Uncertain Significance

About this test

This diagnostic test evaluates 2 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Figure 4: Genetic analysis of case 03. Detection of a homozygous variant in the lEPR gene and a heterozygous variant in the BBS12 gene.

Case 2

The sibling of the index patient, a 7-year-old male, was also evaluated in the endocrinology OPD for concerns about his weight and growth. His anthropometric measurements indicated a weight of 54 kg (+2.09 SDS), height of 123.5 cm (-2.68 SDS), and a BMI of 35.4 (+3.13 SDS, Class 2). Examination revealed acanthosis nigricans in the neck and axillary regions, suggestive of insulin resistance commonly associated with obesity. Additionally, a buried penis was noted on genital examination.

Figure 5: Clinical phenotypes of cases 02, 03, and 04. Siblings and a cousin exhibiting obesity similar to the index case (Case 01).

Genetic testing identified variants in both the BBS1 and LEPR genes, pointing to a monogenic cause of obesity. Ophthalmic evaluation showed no signs of retinitis pigmentosa or fundus dystrophy, and there was no evidence of polydactyly. Systemic evaluations, including cardiovascular, abdominal, and neurological assessments, were unremarkable aside from obesity-related findings. The genetic results confirmed the monogenic origin of obesity, consistent with the diagnosis established in his sister.

Case 3

The sibling of the index patient, an 8-year-old male, was also referred to the endocrinology OPD due to concerns regarding his weight and associated health issues. Like his cousin, he exhibited significant adiposity, with a BMI exceeding +3 SDS (Figure 5) Weight: 46 kg (+2.25 SDS) Height: 123.5 cm (-0.85 SDS) BMI: 30.4 (2.96, Class 1), Similarly clinical examination revealed acanthosis nigricans in the neck and axillary regions, along with male genitalia and buried penis.

Genetic testing revealed homozygous variant c1232 A>G (p.Tyr411Cys in the LEPR gene and carrier heterozygous variant c.571G>C(p. Gly191Arg) for BBS as shown in Figure 5, indicating a monogenic etiology of obesity like his sister. Ophthalmic examination did not reveal any evidence of retinitis pigmentosa or fundus dystrophy and polydactyly is noted that is typical of Bardet-Biedl syndrome (BBS).

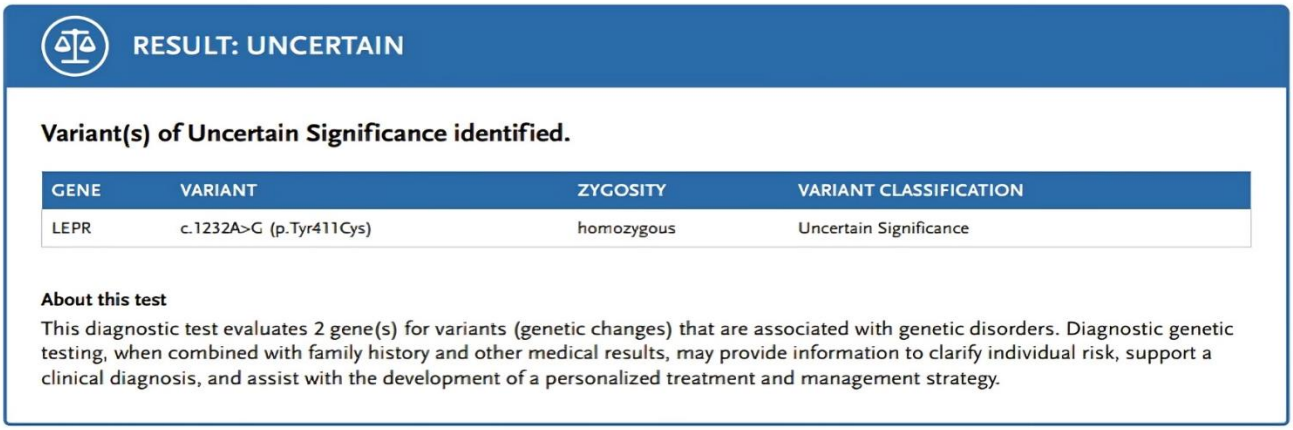

Figure 6: Genetic analysis of case 04. Identification of a homozygous variant exclusively in the lEPR gene in a cousin of the index patient (Case 01).

Case 4

The Paternal cousin of the index patient, a 3-year-old female was also evaluated due to similar concerns about his weight and related health issues. she displayed marked adiposity, with a BMI exceeding +3 SDS (Figure 4). Additionally, he exhibited acanthosis nigricans in the neck and axillary regions, suggestive of underlying insulin resistance commonly associated with obesity.

Genetic analysis uncovered homozygous variant c1232 A>G (p.Tyr411Cys) mutation in LEPR only as shown in Figure 6, suggesting a monogenic basis for his obesity similar to his sibling. Ophthalmic examination did not reveal any evidence of retinitis pigmentosa or fundus dystrophy & genetic variant in BBS12 gene typical of Bardet-Biedl syndrome (BBS). Nonetheless, the presence of acanthosis nigricans alongside genetic findings supported the diagnosis of monogenic obesity.

Besides obesity-related changes, systemic evaluations, including cardiovascular, abdominal, and neurological assessments, did not yield significant abnormalities. Confirmation of positive variants in LEPR genes through genetic testing provided conclusive evidence for the monogenic nature of obesity in this patient, consistent with his sibling's diagnosis.

Outcomes

The 68 genes that are linked to monogenic obesity were assessed using sequential analysis and deletion/duplication testing as part of the diagnostic gene testing (panel for monogenic obesity). Illumina technology was utilized to sequence the patient's genomic sample after it had been enriched for certain regions through a hybridization-based process. All targeted regions were sequenced at a depth of ≥50x or supplemented with further analysis. Consequently, two Novel variations were found in the LEPR and BBS12 genes. In the LEPR gene, the sequences identified as c.1232A>G (p.Tyr411Cys) and c.571G>C (p.Gly191Arg) replace glutamine with cytosine at codon 571 of the BBS-12 protein. At codon 1232 of the LEPR protein, this variant substitute cytosine for trypsine. The identified variants in both genes are not previously reported in population database (gnom AD frequency) and the reported literature of the individual affected with LEPR and BBS12 related conditions.

In case 01, the index patient displayed homozygous variants in both the BBS12 and LEPR genes, suggesting a potential dual genetic contribution to the observed phenotype. In case 03, the index patient's brother, a homozygous variant was identified in the LEPR gene, along with a heterozygous variant in the BBS12 gene. In case 04, a cousin of the index patient, a homozygous variant was exclusively detected in the LEPR gene. These findings indicate a shared genetic alteration within the family, with the LEPR gene variants being a common factor in both the index patient and their cousin.

DISCUSSION

Monogenic obesity, while infrequent, highlights the significant role of genetic factors in the development of obesity. Laurence-Moon- Bardet-Biedl syndrome (LMBBS) exemplifies a type of non-motile ciliopathy, encompassing a broad range of conditions due to primary cilium (PC) dysfunction. This autosomal recessive disorder is notably characterized by rod-cone dystrophy, postaxial polydactyly, obesity, kidney malformations, and hypogonadism.[10] Less commonly, it may also present with hearing loss, dental abnormalities, congenital heart defects, diabetes mellitus, and hepatic fibrosis.[11]

Insulin resistance is a frequent feature in patients with Bardet-Biedl syndrome (BBS), but the progression to type 2 diabetes mellitus is not exceptionally high according to existing literature. Diabetes prevalence varies, with 15.8% in patients averaging 33 years of age, and 6% and 48% in those aged 26.3 and 43 years,

respectively. Approximately 75% of mutations in BBS families are linked to the 14 identified BBS genes, ranging from BBS1 to BBS14. However, mutations in BBS12 have been noted to result in a very mild phenotype, which may not be detectable using the current diagnostic criteria.[10,12]

Furthermore, mutations in the LEPR gene are associated with hyperphagia, leading to severe obesity that often presents before the age of five, sometimes as early as infancy.[13,14] The initial pathogenic mutation in LEPR was identified at the splice donor site of exon 16.[15,16] To date, pathogenic mutations in LEPR have been documented in 22 patients across 13 families. Recent studies also suggest that both common and rare polymorphisms near LEPR may impact susceptibility to obesity.[16]

In this case series, two variants in the LEPR and BBS12 genes e.g. c.1232A>G (p.Tyr411Cys) in the LEPR gene and c.571G>C (p.Gly191Arg) in the BBS12 gene were identified. These variants have not been reported in population databases (gnom AD frequency) or existing literature of individuals with LEPR and BBS12 gene or related conditions, making them Novel. The findings highlight a potential dual genetic contribution to the obesity phenotype observed in the family, the index patient is presented with homozygous variants in both genes. The presence of these variants, especially in the LEPR gene, aligns with known associations of leptin deficiency with extreme early-onset obesity and hyperphagia. Notably, the homozygous variant of BBS12 gene's contribution appears to be less pronounced in terms of phenotypic expression, suggesting that mutations in BBS12 may result in milder clinical manifestations of obesity compared to those seen with LEPR gene mutations. In cases 03 and 04, similar patterns of genetic alterations were observed. Case 03, 04, the index patient's brothers, exhibited a homozygous variant in the LEPR gene and a heterozygous variant in BBS12, while case 04, a cousin from paternal side showed a homozygous variant exclusively in the LEPR gene. These shared genetic alterations within the family underscore the role of the LEPR gene in this familial obesity syndrome. Remarkably, this case series is the first to report concurrent homozygous mutations in both LEPR and BBS12 genes, a combination that has not been previously documented. This unique genetic profile suggests a dual contribution to the obesity phenotype observed in familiar cluster.

Clinical evaluations revealed that all affected individuals exhibited significant obesity and acanthosis nigricans in the neck and axillary regions, but no ocular symptoms typically associated with BBS were noted. This supports the notion that mutations in the BBS12 gene generally exhibit a mild phenotypic impact, as observed in this case series and in previously reported cases.[10,12] The phenotypic effects of BBS12 mutations appear to be subtle and may not be readily detectable using standard diagnostic criteria.

CONCLUSION

This case series introduces novel genetic variants associated with monogenic obesity, specifically in the LEPR and BBS12 genes. The findings highlight the significant role of leptin deficiency in the development of obesity. Additionally, the BBS12 gene mutations, although present, appear to contribute to a milder phenotype compared to LEPR gene mutations. These results underscore the importance of comprehensive genetic testing and thorough clinical correlation in the accurate diagnosis and management of monogenic obesity disorders.

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