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Case report

A Rare Case of Monogenic Obesity due to a Novel Variant in the ADCY3 Gene: Challenges in Follow-up and Treatment

ÖZCABI B et al. A Novel Variant in ADCY3: How to Manage the Case?

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What is already known on this topic?
The ADCY3 gene alterations have been previously found to be associated with obesity.
Only a small number of cases with homozygous mutations were reported in litterature. Besides early-onset severe obesity, hyperphagia, insulin resistance, hyperlipidemia, anosmia/hypoosmia and intellectual disability may occur.
The follow up and treatment options -especially in young children- are still unclear.

What this study adds?
In patients with homozygous ADCY3 mutations, severe obesity and insulin resistance may occur as from infantile period.
These cases should be followed and supported in term of neuromotor developmental delay; and serious complications of obesity may be exhibited in young ages.
The treatment is challenging especially in young children and more data is needed.

Abstract
Adenylate cyclase 3 (*ADCY3*) gene alterations have been found to be associated with obesity. However, few patients with homozygous mutations have been reported so far, and the follow-up procedure and treatment options have not been clarified. A 10-month-old female presented with increased appetite and weight gain. She was born from a consanguineous marriage. Weight, height, head circumference measurements and standard deviation scores (SDS) were 19 kg (+6.98 SDS), 82 cm (+3.53 SDS), and 49 cm (+3.07 SDS), respectively. Laboratory tests revealed a fasting glucose level of 103 mg/dL (5.7 mmol/L), insulin level of 25.39 µIU/mL, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) value of 6.43. Whole-exome sequencing revealed a novel, homozygous c.1102G>A(p.Asp368Asn) variant in *ADCY3*. Her parents and healthy sister were heterozygous for the variant. At the age of 2.5 years, neurodevelopmental delay was observed. At the age of 3.5 years, the patient's weight, height, and body mass index values were 49.5 kg (+8.16 SDS), 111 cm (+2.59 SDS), and 40.18 kg/m^2 (+6.48 SDS), respectively. Signs of Blount's disease and acanthosis nigricans were distinctive, and she had hyperphagia. She was undergoing speech therapy. Homozygous *ADCY3* variants may present with early onset, severe obesity, insulin resistance, and neurodevelopmental delay in children. Severe complications may occur even at young ages. More data regarding the follow-up process and treatment of these patients are needed.
Keywords: ADCY3 gene, hyperphagia, insulin resistance, monogenic obesity

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Introduction
Monogenic obesity (MO) is a severe, early onset form of obesity caused by a single gene mutation that leads to dysfunction in the leptin–melanocortin pathway controlling energy balance (1). During the past 30 years, more than a dozen genes have been identified in the leptin–melanocortin pathway and the tyrosine kinase receptor B–brain-derived neurotrophic factor signalling system. However, alterations in previously defined genes account for only 5% to 30% of cases of MO, and melanocortin 4 receptor (MC4R) deficiency is the most common cause of MO (1,2).
ADCY3 gene alterations were recently found to have effects on severe obesity (1,3-14). The *ADCY3* gene (OMIM*600291) is located on the short arm of chromosome 2 (2p23.3) and encodes ADCY3 (13). This gene product has a pseudosymmetric structure of two transmembrane and two cytoplasmic domains. Nine isoforms of ADCY3 are expressed in various human tissues, such as adipose tissue and the hypothalamus. ADCY3 catalyses the synthesis of cyclic adenosine monophosphate (cAMP), which plays a role in intracellular signal transduction. In paraventricular nucleus of hypothalamus, ADCY3 colocalizes with MC4R and inhibition of its signaling at the primary cilia of these neurons, is concluded with increased body weight (1,13). ADCY3–cAMP signalling also controls the metabolic processes of carbohydrates and lipids; and appears to regulate the proliferation and differentiation of adipocytes (10). Some anorexigenic peptides, such as glucagon-like peptide-1 (GLP-1), act centrally to control appetite by upregulating cAMP formation (1,13,15-17). Apart from its effects on appetite and body weight, ADCY3 seems to be linked to olfactory signal transduction based on the finding that disruption of ADCY3 causes peripheral and behavioural anosmia (15). Only 12 patients with homozygous *ADCY3* alterations have been reported in large cohorts to date, and severe obesity, anosmia/hyposmia, hyperlipidaemia, and insulin resistance were common conditions in these patients (7,10) (Table 1). Although the association between ADCY3 deficiency and obesity has been established, few patients with homozygous variants have been reported in the literature. Additionally, follow-up and treatment data are lacking. We herein describe a child who presented with early-onset and severe obesity due to a novel mutation in *ADCY3*, assess the follow up data, and discuss the treatment options, especially in young children.

Case Presentation

A 10-month-old female infant presented with increased appetite and weight gain. She had been born from a consanguineous marriage at 38 weeks of gestation, and her birth weight was 3050 g (−0.08 standard deviation score [SDS]). Her mother had been diagnosed with insulin resistance and required a specific diet during pregnancy. The infant's medical records revealed that her weight at the age of 2 months and 7 months was 6.5 kg (+2.03 SDS) and 14 kg (+5.06 SDS), respectively. She was still breastfeeding and had not yet been successfully transitioned to complementary feeding. No steroids or other medications were being used.–Physical examination at the age of 10 months revealed that her weight, height, and head circumference were 19 kg (+6.98 SDS), 82 cm (+3.53 SDS), and 49 cm (+3.07 SDS), respectively. Her weight age was 5.3 years, weight-for-height centile was 213%, and body mass index (BMI) was 28.26 kg/m^2 (+4.81 SDS) (18). Her target height was 155 cm (−1.38 SDS). She was at Tanner stage 1. She was able to sit up without support. The patient's appearance and height, weight, and BMI measurements are plotted in a chart in Figure. 1. Laboratory tests revealed a fasting glucose level of 103 mg/dL (5.7 mmol/L), insulin concentration of 25.39 µIU/mL, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) value of 6.43 (>2.22) (calculated as fasting blood glucose × fasting insulin / 22.5) (19). Thyroid function test results were within the reference ranges. The insulin-like growth factor-1 level was 44 ng/mL (reference range: 40.8–93.6 ng/mL) (20). The basal cortisol level was 5.9 µg/dL, and the peak level stimulated by a low-dose adrenocorticotrophic hormone (1 µg/kg intravenous cosyntropin) stimulation test was 18.4 µg/dL, with an adrenocorticotrophic hormone level of 20.1 pg/mL. A leptin level test could not be performed. The ophthalmologic examination and echocardiography findings were normal.

The patient was diagnosed with MO based on the presence of early onset and severe obesity, hyperphagia, normal height without dysmorphic/syndromic features, birth from a consanguineous marriage, and a family history of insulin resistance and obesity. After an MO panel for known common obesity-related genes was found to be normal, whole-exome sequencing analysis was performed and a novel homozygous c.1102G>A(p.Asp368Asn) variant was found (Figure 2). This variant had not been previously reported and was classified as a variant of unknown significance with a high pathogenicity score according to the American College of Medical Genetics classification. The patient's pedigree is shown in Figure 2. Her mother was heterozygous for the variant c.1102G>A(p.Asp368Asn) and had obesity and insulin resistance. Her father was also a heterozygous carrier of the mutation but was of normal weight. The patient's brother and sister had been diagnosed with ulcerative colitis, but only the sister was a heterozygous carrier of this variant (Figure 2).

At the age of 2.5 years, the patient's weight, height, and BMI were 34 kg (+8.42 SDS), 103 cm (+3.06 SDS), and 32.05 kg/m^2 (+6 SDS), respectively. Her weight age was 10.3 years (18). She had hyperphagia. She was unable to say two consecutive words. The Denver II Developmental Screening Test revealed that she was delayed in two domains: personal-social (13.5 months) and language (8.5 months). Her audiometry results were within the normal range. She was referred for speech therapy.

At the age of 3.5 years, the patient's weight, height, and BMI were 49.5 kg (+8.16 SDS), 111 cm (+2.59 SDS), and 40.18 kg/m^2 (+6.48 SDS), respectively. Her weight age was 12.9 years (18). Signs of Blount's disease and acanthosis nigricans were distinctive. She had hyperphagia. The patient's clinical features and height, weight, and BMI measurements are plotted in a chart in Figure 1. Laboratory testing showed that her fasting glucose level was 86 mg/dL (4.8 mmol/L), fasting insulin level was 20.9 µIU/mL, c-peptide level was 3.27 ng/mL, and HOMA-IR value was 4.44 (19). Thyroid function test results, uric acid and alanine aminotransferase levels, and a lipid profile were within normal ranges. She was undergoing treatment of metformin at a dosage of 250 mg/day, but this treatment was withdrawn in a short time, as it did not show any effect on improving insulin levels and insulin resistance. An operation for Blount's disease was planned. Her parents reported that she was able to smell and react to pleasant and unpleasant odours. An odour identification test was planned to rule out hyposmia but had to be postponed because of speech delay.

The written informed consent was obtained from the parents of the patient.

Discussion

ADCY3 catalyses the formation of cAMP and mediates G_S signalling from G protein-coupled receptors. It colocalises in the primary cilia of paraventricular nucleus neurons with MC4R (a type of G protein-coupled receptor), which transduces anorexigenic signals. Additionally, cAMP seems to be involved in intracellular signalling of anorexigenic peptides such as GLP-1, and GLP-1 upregulates ADCY3 (1,3-14). Specific inhibition of ADCY3 activity in MC4R-expressing neurons was found to be associated with obesity in mice (21). Wang et al. (21) showed that *ADCY3*-knockout mice might exhibit not only severe obesity but also hyperphagia, low locomotor activity, and hypogonadism. Several studies of different populations have also supported the association between *ADCY3* and severe obesity in humans (3-5,7-9,11-13). Three population-based genetic studies showed that *ADCY3* variants are also associated with type 2 diabetes (3,7,11). In 2018, patients with homozygous variants in the *ADCY3* gene were finally reported. Grarup et al. (7) identified seven patients with homozygous c.2433-1G>A variant in a large cohort of the Greenland population (n = 4,217): the affected individuals had a 7.3-kg/m^2 higher BMI, an 8.1% higher body fat mass, a 17-cm larger waist circumference, and higher fasting glucose and 2-hour plasma glucose concentrations than the rest of the study group. Saeed et al. (10) reported three homozygous mutations in four patients with severe obesity from three unrelated Pakistani families, as well as a compound heterozygous mutation in a Euro-American child. The mutations and phenotypes of previously reported patients and our patient are summarised in Table 1. Our patient had more severe obesity with a higher BMI than the previously described patients. Also, she had a prominent insulin resistance defined in younger ages than two patients reported by Saeed et al. (6 and 15 years of age). Hyperphagia was present in all previously reported patients, as in our patient (10). Anosmia was reported in three patients and the other two patients had hyposmia (10). We observed that our patient was able to smell; however, we could not rule out hyposmia because the patient's age and speech delay prevented the performance of an odour identification test. Neurodevelopmental delay is not a rare condition in monogenic obesity (1). However, it was not previously mentioned in cases with ADCY3 gene variants. Intellectual disability has been previously reported in two patients, but their neurological development was not described in details (10). The association between neurogical development and ADCY3 gene alterations is not well defined; but an animal model showed that loss of type 3 adenylyl cyclase in mice led to decreased neuronal activity, altered sleep pattern, and depression-like behaviors (22).

Additionally, although our patient exhibited complications of obesity, including Blount's disease at a young age, such data are not shown in the previously reported cases (10).

No clear follow-up procedure for patients with homozygous *ADCY3* mutations has been established. Insulin resistance and complications of obesity, including Blount's deformity, were exhibited early in our patient. Additionally, speech delay was distinct and neuromotor developmental delay was a major problem for the patient and her family. Another important feature reported in an animal study was hypogonadism (21). Saeed et al. (10) reported secondary amenorrhoea in their adolescent proband with a normal profile of serum gonadotropins and oestradiol. We suggest close follow-up of these children in terms of obesity and its complications, neurological development, puberty, and other additional features not previously detected.

The mother, father, and sister of our patient were heterozygous carriers of the c.1102G>A(p.Asp368Asn) mutation in *ADCY3*. The mother had obesity and insulin resistance, but the father and the sister were of normal weight. Some heterozygous carriers of *ADCY3* gene variants may not exhibit obesity or insulin resistance (10). Interestingly, the brother and sister of our patient had been diagnosed with ulcerative colitis. Inflammatory bowel diseases have been found to be associated with *ADCY3* variants (23). However, only the sister was a carrier; therefore, we plan to perform further genetic analyses for ulcerative colitis in the brother and sister of our patient.

Although there are previously reported treatments for children with monogenic obesity, the treatment in patients with ADCY3 variants are not well-defined. Setmelanotide is an MC4R agonist that is 20 times more potent than endogenous melanocortin-stimulating hormone. It was approved in 2020 for the treatment of MO syndromes affecting the proximal leptin signal pathway in adults and children aged ≥ 6 years (24). ADCY3 plays a role in correct function of the MC4R. Because ADCY3 does not work properly in patients with MO, whether setmelanotide

would be effective in this condition remains questionable. However, setmelanotide forces MC4R activity. The MC4R pathway appears to be a modifiable system, and another question is therefore whether it can be effectively utilised for overcoming and improving ADCY3 dysfunction by regulating food intake and preference. Liraglutide is a GLP-1 analogue approved in children aged > 12 years with type 2 diabetes and obesity; it is also the subject of ongoing clinical trials for children aged 7–12 years (25). Liraglutide was found to be effective in increasing hepatic AC3 mRNA and protein levels, and serum AC3 levels, in mice, as well as upregulating ADCY3 (26). Liraglutide has also been useful for regulating appetite in diabetic patients with hypothalamic hyperphagia and obesity (27). In one study of adolescents with obesity, the use of liraglutide with lifestyle therapy reportedly led to a significantly greater reduction in the BMI SDS. However, this drug has also been found to be associated with some serious complications such as pancreatitis (25). Unfortunately, the treatment options for MO are limited and our patient was younger than other children treated with these agents. ADCY3 has recently been proposed as a target for anti-obesity agents (28). The main safety concern regarding such agents is the risk of malignancy because the upregulation of ADCY3 may lead to an increase in the tumorigenic potential of cells via activation of the cAMP-response element binding protein (CREB) pathway (29).

Conclusion

Homozygous *ADCY3* variants may lead to early onset severe obesity, insulin resistance, and neurodevelopmental delay in children. Severe complications may occur in the early stages. More follow-up and treatment data are needed for optimal management of these patients beginning at young ages.

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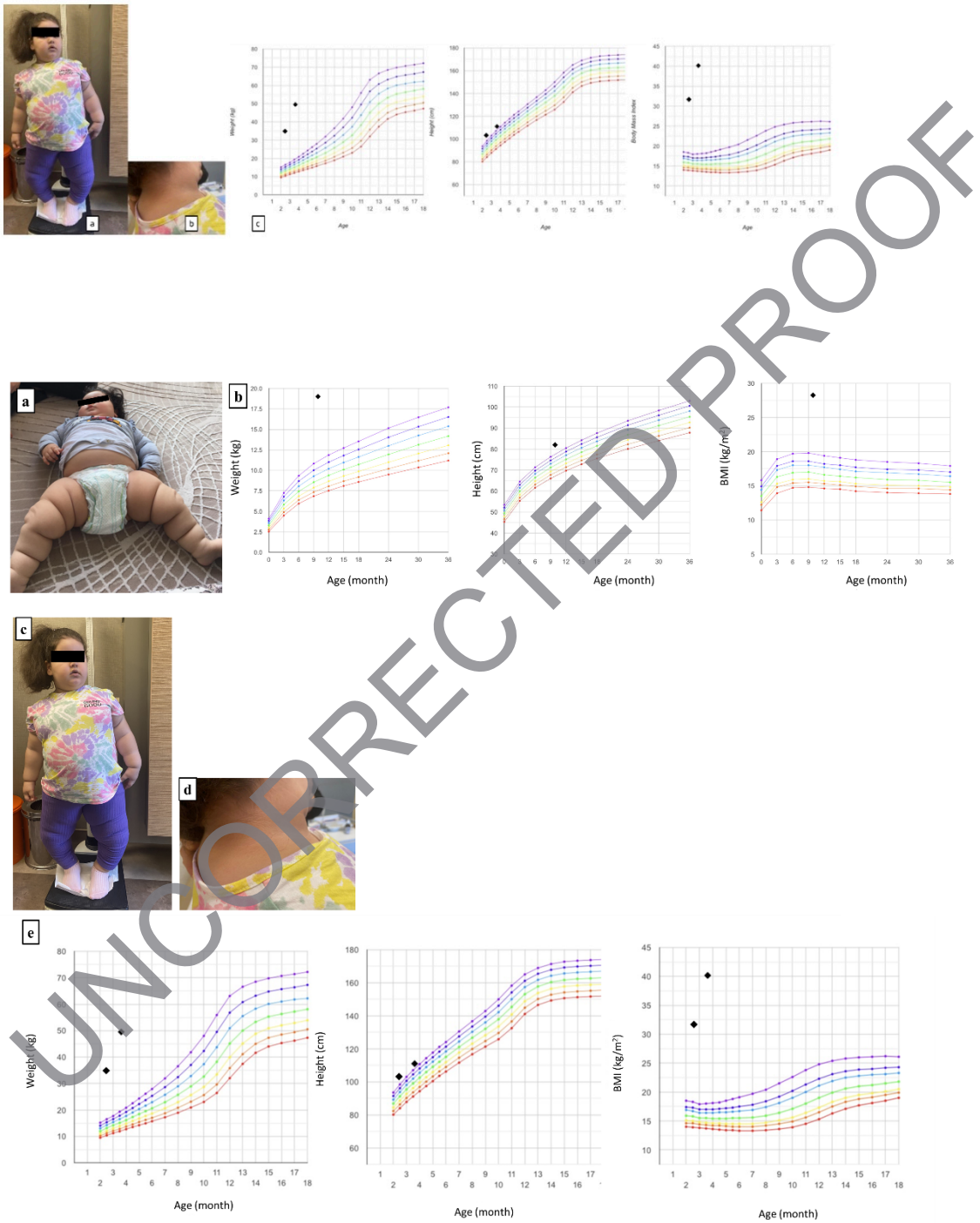

Figure 1: a) appearance of the patient at the age of 10 month b) height, weight and body mass index measurements plotted on the chart of the patient at the age of 10 month. c) appearence of the patient at the age of 3.5 year d) acanthosis nigricans e) height, weight and body mass index plotted on the chart of the patient at the age of 3.5 year

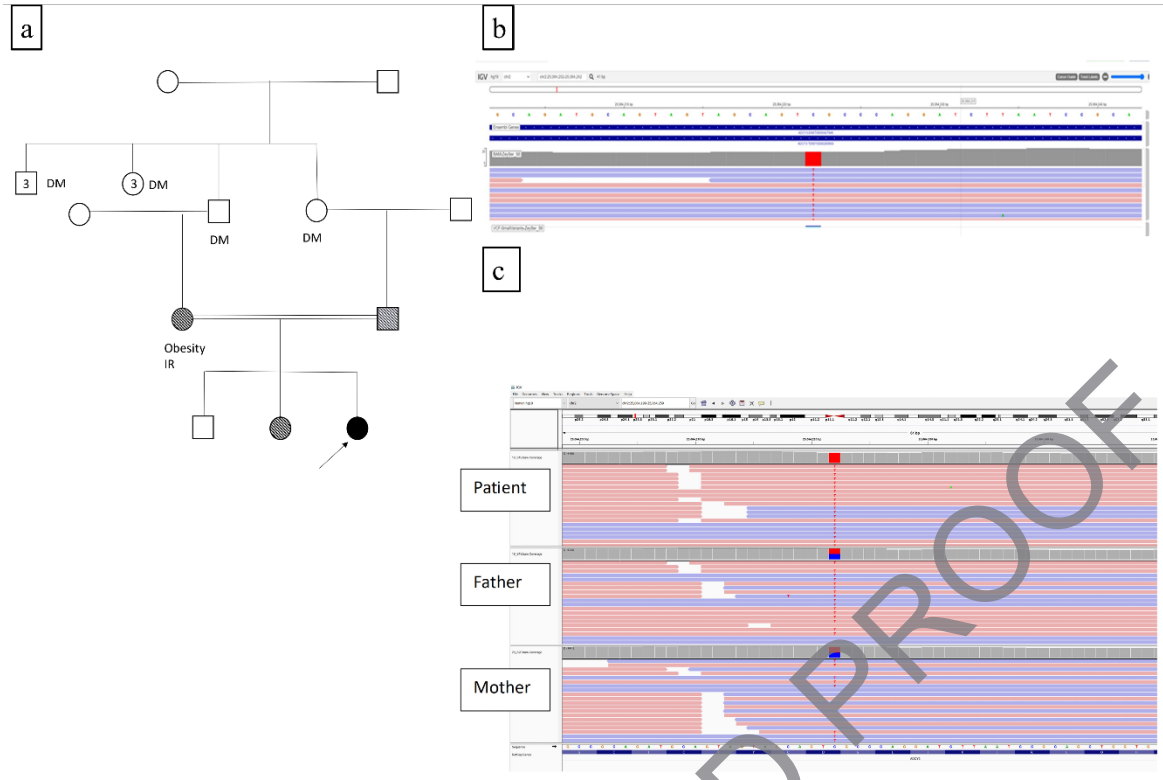

Figure 2: a) The pedigree of the patient b) Homozygous ADCY3 c.1102G>A (p.Asp368Asn) variant detected in the case c) Sanger sequencing confirmation of the patient and segregation analsis of the variant in parents

Table 1: The mutations in the ADCY3 gene and the phenotypes of the previously reported cases and our patient

Patients	**Age (year)**	**Sex**	**Genetic evaluation**	**Clinical evaluation**
1-7 (7)	NA	NA	Homozygous c.2433-1G>A	3 cases: type 2 DM 1 case: impaired glucose tolerance 1 case: impaired fasting glucose 2 cases: normal
8 (10)	15	F	Homozygous c.3315del (frameshift mutation) (p.Ile1106Serfs*3)	87 kg/150 cm (BMI: 38.7) (BMI SDS: +3.5 SDS) Hyperphagia Anosmia Slight to moderate intellectual disability Secondary amenorrhea (menarche: 14 y) Dyslipidemia, IR
9 (10)	6	M	Homozygous c.2578-1G>A (splicing mutation)	52 kg/137 cm (BMI:28) (BMISDS: +6.5) Hyperphagia Anosmia Obesity in parents
10 (10)	6	M	Homozygous c.191A>T (a nonsynonymous missense mutation) (p.Asn64Ile)	49 kg/132 cm (BMI: 28.1) (BMISDS: +6.5) Hyperphagia Hypoosmia
11 (10)	NA	F	Homozygous c.191A>T (a nonsynonymous missense mutation)	BMI: 32.8 kg/m2 Hyperphagia Hypoosmia
12 (10)	11	M	Compound heterozygous c.1268del (frameshift mutation) (p.Gly423Alafs*19) c.3354_3356del (an amino acid deletion mutation)	89 kg/154 cm (BMI: 37.8) (BMI SDS: +4.6) Hyperphagia Anosmia

			(p.Phe1118del)	
13 (our patient)	0.9	F	Homozygous c.1102G>A(p.Asp368Asn)	Early onset severe obesity Hyperphagia Insulin resistance Neuromotor developmental delay Blount's disorder

NA: Not available, M:male, F: female; BMI: body mass index, DM: diabetes mellitus, IR: insulin resistance, SDS: standart deviation score