CASE REPORT

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

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What is already known on this topic?

Adenylate cyclase 3 (*ADCY3*) gene alterations have been previously found to be associated with obesity. However, only a small number of cases with homozygous mutations have been reported. Besides early-onset severe obesity, hyperphagia, insulin resistance, hyperlipidemia, anosmia/hypo-osmia and intellectual disability may occur. The follow up and treatment options, especially in affected young children, are still unclear.

What this study adds?

In patients with homozygous *ADCY3* mutations, severe obesity and insulin resistance may occur from infancy. These cases should be followed and supported in term of neuromotor developmental delay. Moreover, serious complications of obesity may be exhibited at very young ages. The treatment is challenging, especially in young children, and so more data is needed.

Abstract

Adenylate cyclase 3 (*ADCY3*) gene alterations have been reported to be associated with obesity. However, few patients with homozygous mutations have been described to date and the follow-up procedure and treatment options are unclear. A 10-month-old female presented with increased appetite and weight gain. She was born from a consanguineous marriage. Weight, height, and 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 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 disease and acanthosis nigricans were evident, 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 in terms of the optimal treatment and follow-up process 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 be associated with severe obesity (1,3-14). The *ADCY3* gene (OMIM*600291) is located on the short arm of chromosome 2 (2p23.3) and encodes the adenylate cyclase 3 enzyme (ADCY3) (13). This protein 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 the paraventricular nucleus of hypothalamus, *ADCY3* co-localizes with MC4R and inhibition of signaling at the primary cilia of these neurons results in increased body weight (1,13). *ADCY3*-cAMP signaling 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 (1,13,15,16,17). 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 behavioral anosmia (15). To date, only 12 patients with homozygous *ADCY3* alterations have been reported in large cohorts, and severe obesity, anosmia or hypo-osmia, hyperlipidemia, and insulin resistance were common features in these individuals (Table 1) (7,10).

Nevertheless, data on long-term follow-up and treatment strategies in these patients remain limited, despite the well-established link between *ADCY3* deficiency and obesity. Here, we report a child with early-onset and severe obesity caused by a novel homozygous *ADCY3* mutation. We present follow-up data and discuss potential treatment approaches, with a particular focus on management in young children.

Case Report

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 with a standard deviation score (SDS) of -0.08. Her mother had been diagnosed with insulin resistance and required dietary intervention during pregnancy. The infant's medical records revealed that her weight at the age of two months and seven months were 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 showed a weight, height, and head circumference of 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, together with height, weight, and BMI measurements on a growth chart are shown in Figure 1a, 1b. Laboratory testing found 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 (ACTH) stimulation test with 1 µg/kg intravenous cosyntropin was 18.4 µg/dL, with an ACTH 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 reported as normal, whole-exome sequencing analysis was performed and a novel homozygous c.1102G>A (p.Asp368Asn) variant in *ADCY3* 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 (21).

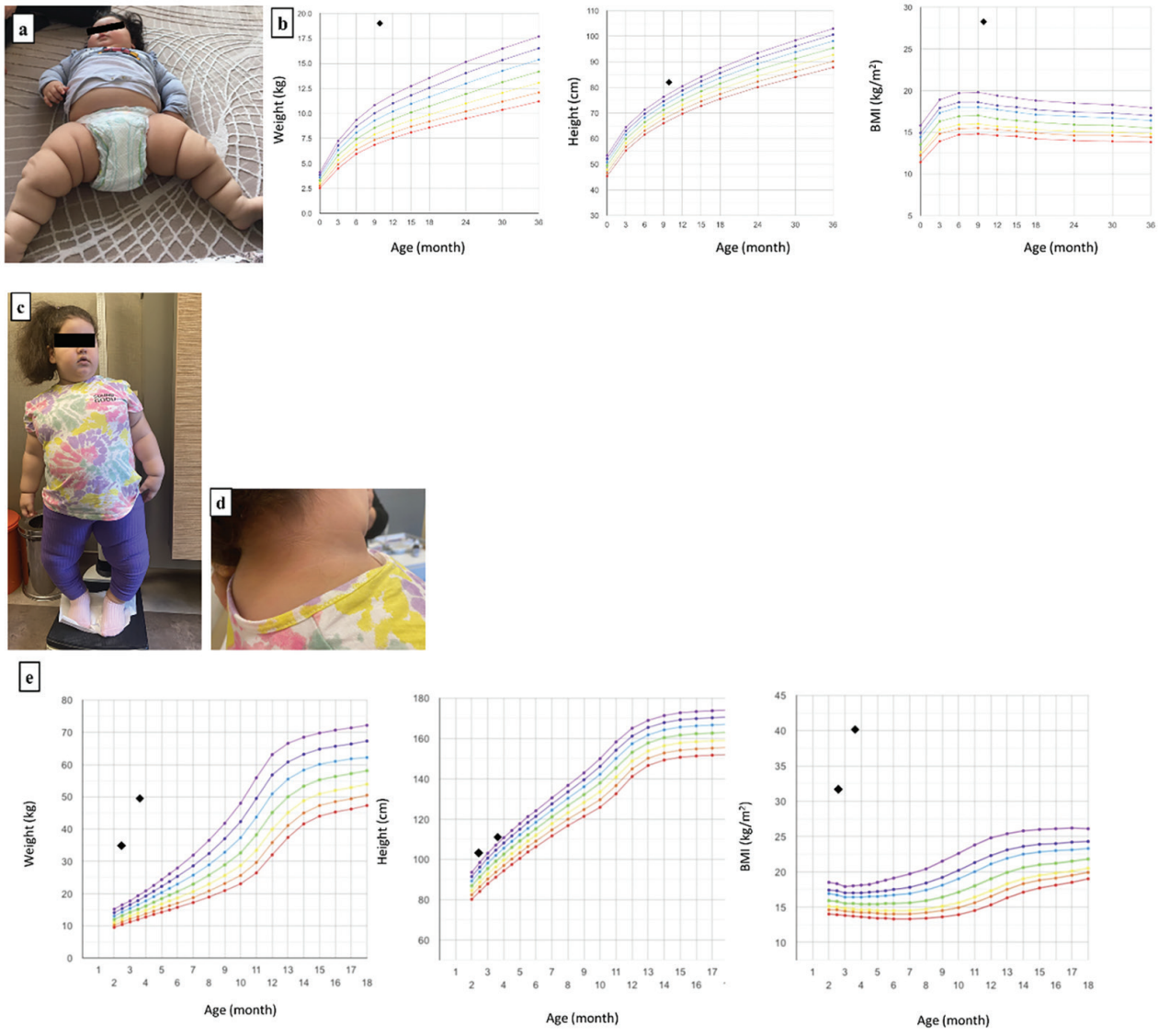

Figure 1. (a) Appearance of the patient at the age of 10 months; b) height, weight and body mass index measurements plotted on a growth chart at the age of 10 months; c) appearence of the patient at the age of 3.5 years; d) acanthosis nigricans; e) height, weight and body mass index plotted on a growth chart at the age of 3.5 year

DM: diabetes mellitus, IR: insulin resistance

The patient's pedigree is shown in Figure 2. Her mother was heterozygous for the same 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.

One year later 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 disease

and acanthosis nigricans were evident. She continued to be hyperphagic. The patient's clinical features and height, weight, and BMI measurements are also shown on the growth chart shown 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. Metformin was initiated at a dose of 250 mg/day, but was promptly discontinued as it had no significant effect on insulin levels or insulin resistance. An operation for Blount disease was planned. Her parents reported that she was able to smell and react to pleasant and unpleasant odors. An odor identification test was planned, to rule out hypo-osmia but was postponed because of speech delay.

The patient's parents provided written informed consent for publication.

Discussion

ADCY3 catalyses the formation of cAMP and mediates G_S signalling from G protein-coupled receptors. It co-localises in the primary cilia of the paraventricular nucleus neurons with MC4R (a type of G protein-coupled receptor), which transduces anorexigenic signals. In addition, cAMP seems to be involved in intracellular signaling 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 (22). Wang et al. (22) showed that *ADCY3*-knockout mice may exhibit both severe obesity and hyperphagia, low locomotor activity, and hypogonadism. Several studies in different populations have also supported the association between *ADCY3* and severe obesity in humans (3,4,5,7,8,9,11,12,13). Three population-based genetic studies have demonstrated

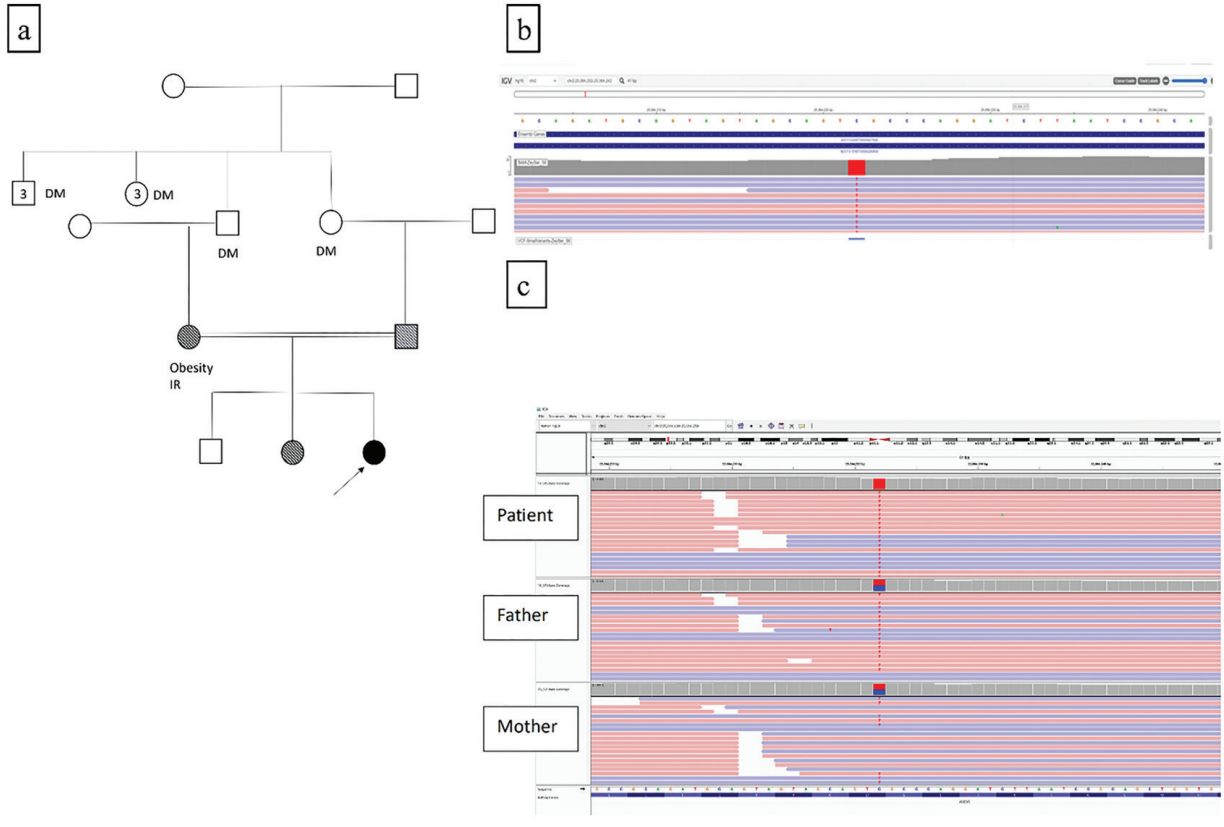

Figure 2. (a) The pedigree of the patient; b) homozygous *ADCY3* c.1102G > A(p.Asp368Asn) variant detected in the case; c) Sanger sequencing confirmation of the patient and segregation analysis of the variant in parents

DM: diabetes mellitus, IR: insulin resistance

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) (BMI SDS: +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) (BMI SDS: +6.5) Hyperphagia Hypoosmia Slight to moderate intellectual disability
11 (10)	NA	F	Homozygous c.191A > T (a nonsynonymous missense mutation)	BMI: 32.8 kg/m^2 Hyperphagia Hypoosmia
12 (10)	11	M	Compound heterozygous c.1268del (frameshift mutation) (p.Gly423Alafs*19) c.3354_3356del (an amino acid deletion mutation) (p.Phe1118del)	89 kg/154 cm (BMI: 37.8) (BMI SDS: +4.6) Hyperphagia Anosmia
13 (the current case)	0.9	F	Homozygous c.1102G > A(p.Asp368Asn)	Early onset severe obesity Hyperphagia Insulin resistance Neuromotor developmental delay Blount disorder

NA: not available, M: male, F: female, y: year, BMI: body mass index, DM: diabetes mellitus, IR: insulin resistance, SDS: standard deviation score

that *ADCY3* variants are also associated with type 2 diabetes (3,7,11). In 2018, patients with homozygous variants in the *ADCY3* gene were first 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 the presented case are summarized in Table 1. The girl presented here had more severe obesity with a higher BMI than previously described patients. Moreover, she had prominent insulin resistance defined at a younger age than two patients reported by Saeed et al. (10) (6 and 15 years of age). Hyperphagia was present in all previously reported patients, as in the current patient. Anosmia was reported in three patients and two others had hypo-osmia (10). The patient described in this report was able to smell but hypo-osmia could not be ruled out because the patient's age and speech delay prevented the performance of an odor identification test. While neurodevelopmental delay is relatively common in monogenic forms of obesity (MO) (1), it has not been previously documented in association with *ADCY3* gene variants. Intellectual disability was reported in two earlier cases; however, detailed information regarding their neurodevelopmental progress was not provided. The association between neurological 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 behavior (23). Of note, although the currently presented patient exhibited complications of obesity, including Blount disease at a young age, such findings have not been described 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 deformity, were exhibited early in our patient. Furthermore, speech delay was marked and neuromotor developmental delay was a major problem for the patient and her family. Another important feature reported in an animal study was hypogonadism (22). Saeed et al. (10) reported secondary

amenorrhoea in the 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 the index case 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 have previously been reported to 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 associated with *ADCY3* variants (24). 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 MO, the treatment in patients with *ADCY3* variants are not established. 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 (25). The ADCY3 protein plays a role in correct function of MC4R. As ADCY3 does not function correctly in patients with MO due to variants in *ADCY3*, whether setmelanotide would be effective in this condition remains questionable. However, setmelanotide increases MC4R activity. The MC4R pathway appears to be a modifiable system, and another question is therefore whether it can be effectively used 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 and is also the subject of ongoing clinical trials in children aged 7-12 years (26). 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* (17). Liraglutide has also been useful for regulating appetite in diabetic patients with hypothalamic hyperphagia and obesity (16). 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 (26). Unfortunately, the treatment options for MO are limited and the presented patient was younger than other children treated with these agents. *ADCY3* has recently been proposed as a target for anti-obesity agents (27). 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 pathway (28).

Conclusion

Homozygous *ADCY3* variants may lead to very early onset severe obesity, insulin resistance, and neurodevelopmental delay in children. Severe complications may occur in the early stages. More evidence is needed to determine optimal management of these patients beginning at young ages.

Ethics

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: Bahar Özcabı, Concept: Bahar Özcabı, Samim Özen, Design: Bahar Özcabı, Samim Özen, Data Collection or Processing: Bahar Özcabı, Asude Durmaz, Ayça Aykut, Hasan Önal, Samim Özen, Analysis or Interpretation: Bahar Özcabı, Asude Durmaz, Ayça Aykut, Hasan Önal, Samim Özen, Literature Search: Bahar Özcabı, Asude Durmaz, Ayça Aykut, Hasan Önal, Samim Özen, Writing: Bahar Özcabı, Asude Durmaz, Ayça Aykut, Samim Özen.

Conflict of Interest: One author of this article, Samim Özen, is member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, he was not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions.

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References

1. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022;23:120-133. Epub 2021 Sep 23.
2. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med. 2003;348:1085-1095.
3. Nordman S, Abulaiti A, Hilding A, Långberg EC, Humphreys K, Ostenson CG, Efendic S, Gu HF. Genetic variation of the adenylyl cyclase 3 (AC3) locus and its influence on type 2 diabetes and obesity susceptibility in Swedish men. Int J Obes (Lond). 2008;32:407-412. Epub 2007 Sep 25.
4. Wang H, Wu M, Zhu W, Shen J, Shi X, Yang J, Zhao Q, Ni C, Xu Y, Shen H, Shen C, Gu HF. Evaluation of the association between the AC3 genetic polymorphisms and obesity in a Chinese Han population. PLoS One. 2010;5:e13851.

5. Stergiakouli E, Gaillard R, Tavaré JM, Balthasar N, Loos RJ, Taal HR, Evans DM, Rivadeneira F, St Pourcain B, Uitterlinden AG, Kemp JP, Hofman A, Ring SM, Cole TJ, Jaddoe VW, Davey Smith G, Timpson NJ. Genome-wide association study of height-adjusted BMI in childhood identifies functional variant in *ADCY3*. Obesity (Silver Spring). 2014;22:2252-2259. Epub 2014 Jul 21.

6. Siljee JE, Wang Y, Bernard AA, Ersoy BA, Zhang S, Marley A, Von Zastrow M, Reiter JF, Vaisse C. Subcellular localization of MC4R with *ADCY3* at neuronal primary cilia underlies a common pathway for genetic predisposition to obesity. Nat Genet. 2018;50:180-185. Epub 2018 Jan 8.

7. Grarup N, Moltke I, Andersen MK, Dalby M, Vitting-Seerup K, Kern T, Mahendran Y, Jørsboe E, Larsen CVL, Dahl-Petersen IK, Gilly A, Suveges D, Dedoussis G, Zeggini E, Pedersen O, Andersson R, Bjerregaard P, Jørgensen ME, Albrechtsen A, Hansen T. Loss-of-function variants in *ADCY3* increase risk of obesity and type 2 diabetes. Nat Genet. 2018;50:172-174. Epub 2018 Jan 8.

8. Andersen MK, Hansen T. Genetics of metabolic traits in Greenlanders: lessons from an isolated population. J Intern Med. 2018;284:464-477. Epub 2018 Aug 12.

9. Turcot V, Lu Y, Highland HM, Schurmann C, Justice AE, Fine RS, Bradfield JP, Esko T, Giri A, Graff M, Guo X, Hendricks AE, Karaderi T, Lempradl A, Locke AE, Mahajan A, Marouli E, Sivapalaratnam S, Young KL, Alfred T, Feitosa MF, Masca NGD, Manning AK, Medina-Gomez C, Mudgal P, Ng MCY, Reiner AP, Vedantam S, Willems SM, Winkler TW, Abecasis G, Aben KK, Alam DS, Alharthi SE, Allison M, Amouyel P, Asselbergs FW, Auer PL, Balkau B, Bang LE, Barroso I, Bastarache L, Benn M, Bergmann S, Bielak LF, Blüher M, Boehnke M, Boeing H, Boerwinkle E, Böger CA, Bork-Jensen J, Bots ML, Bottinger EP, Bowden DW, Brandslund I, Breen G, Brilliant MH, Broer L, Brumat M, Burt AA, Butterworth AS, Campbell PT, Cappellani S, Carey DJ, Catamo E, Caulfield MJ, Chambers JC, Chasman DI, Chen YI, Chowdhury R, Christensen C, Chu AY, Cocca M, Collins FS, Cook JP, Corley J, Corominas Galbany J, Cox AJ, Crosslin DS, Cuellar-Partida G, D'Eustacchio A, Danesh J, Davies G, Bakker PIW, Groot MCH, Mutsert R, Deary IJ, Dedoussis G, Demerath EW, Heijer M, Hollander AI, Ruijter HM, Dennis JG, Denny JC, Di Angelantonio E, Drenos F, Du M, Dubé MP, Dunning AM, Easton DF, Edwards TL, Ellinghaus D, Ellinor PT, Elliott P, Evangelou E, Farmaki AE, Farooqi IS, Faul JD, Fauser S, Feng S, Ferrannini E, Ferrieres J, Florez JC, Ford I, Fornage M, Franco OH, Franke A, Franks PW, Friedrich N, Frikke-Schmidt R, Galesloot TE, Gan W, Gandin I, Gasparini P, Gibson J, Giedraitis V, Gjesing AP, Gordon-Larsen P, Gorski M, Grabe HJ, Grant SFA, Grarup N, Griffiths HL, Grove ML, Gudnason V, Gustafsson S, Haessler J, Hakonarson H, Hammerschlag AR, Hansen T, Harris KM, Harris TB, Hattersley AT, Have CT, Hayward C, He L, Heard-Costa NL, Heath AC, Heid IM, Helgeland Ø, Hernesniemi J, Hewitt AW, Holmen OL, Hovingh GK, Howson JMM, Hu Y, Huang PL, Huffman JE, Ikram MA, Ingelsson E, Jackson AU, Jansson JH, Jarvik GP, Jensen GB, Jia Y, Johansson S, Jørgensen ME, Jørgensen T, Jukema JW, Kahali B, Kahn RS, Kähönen M, Kamstrup PR, Kanoni S, Kaprio J, Karaleftheri M, Kardia SLR, Karpe F, Kathiresan S, Kee F, Kiemeney LA, Kim E, Kitajima H, Komulainen P, Kooner JS, Kooperberg C, Korhonen T, Kovacs P, Kuivaniemi H, Kutalik Z, Kuulasmaa K, Kuusisto J, Laakso M, Lakka TA, Lamparter D, Lange EM, Lange LA, Langenberg C, Larson EB, Lee NR, Lehtimäki T, Lewis CE, Li H, Li J, Li-Gao R, Lin H, Lin KH, Lin LA, Lin X, Lind L, Lindström J, Linneberg A, Liu CT, Liu DJ, Liu Y, Lo KS, Lophatananon A, Lotery AJ, Loukola A, Luan J, Lubitz SA, Lyytikäinen LP, Männistö S, Marenne G, Mazul AL, McCarthy MI, McKean-Cowdin R, Medland SE, Meidtner K, Milani L, Mistry V, Mitchell P, Mohlke KL, Moilanen L, Moitry M, Montgomery GW, Mook-Kanamori DO, Moore C, Mori TA, Morris AD, Morris AP, Müller-Nurasyid M, Munroe PB, Nalls MA, Narisu N, Nelson CP, Neville M, Nielsen SF, Nikus K, Njølstad PR, Nordestgaard BG, Nyholt DR, O'Connel JR, O'Donoghue ML, Olde Loohuis LM, Ophoff RA, Owen KR, Packard CJ, Padmanabhan S, Palmer CNA, Palmer ND, Pasterkamp G, Patel AP, Pattie A, Pedersen O, Peissig PL, Peloso GM, Pennell CE, Perola M, Perry JA, Perry JRB, Pers TH, Person TN, Peters A, Petersen ERB, Peyser PA, Pirie A, Polasek O, Polderman TJ, Puolijoki H, Raitakari OT, Rasheed A, Rauramaa R, Reilly DF, Renström F, Rheinberger M, Ridker PM, Rioux JD, Rivas MA, Roberts DJ, Robertson NR, Robino A, Rolandsson O, Rudan I, Ruth KS, Saleheen D, Salomaa V, Samani NJ, Sapkota Y, Sattar N, Schoen RE, Schreiner PJ, Schulze MB, Scott RA, Segura-Lepe MP, Shah SH, Sheu WH, Sim X, Slater AJ, Small KS, Smith AV, Southam L, Spector TD, Speliotes EK, Starr JM, Stefansson K, Steinthorsdottir V, Stirrups KE, Strauch K, Stringham HM, Stumvoll M, Sun L, Surendran P, Swift AJ, Tada H, Tansey KE, Tardif JC, Taylor KD, Teumer A, Thompson DJ, Thorleifsson G, Thorsteinsdottir U, Thuesen BH, Tönjes A, Tromp G, Trompet S, Tsafantakis E, Tuomilehto J, Tybjaerg-Hansen A, Tyrer JP, Uher R, Uitterlinden AG, Uusitupa M, Laan SW, Duijn CM, Leeuwen N, van Setten J, Vanhala M, Varbo A, Varga TV, Varma R, Velez Edwards DR, Vermeulen SH, Veronesi G, Vestergaard H, Vitart V, Vogt TF, Völker U, Vuckovic D, Wagenknecht LE, Walker M, Wallentin L, Wang F, Wang CA, Wang S, Wang Y, Ware EB, Wareham NJ, Warren HR, Waterworth DM, Wessel J, White HD, Willer CJ, Wilson JG, Witte DR, Wood AR, Wu Y, Yaghootkar H, Yao J, Yao P, Yerges-Armstrong LM, Young R, Zeggini E, Zhan X, Zhang W, Zhao JH, Zhao W, Zhao W, Zhou W, Zondervan KT; CHD Exome+ Consortium; EPIC-CVD Consortium; ExomeBP Consortium; Global Lipids Genetic Consortium; GoT2D Genes Consortium; EPIC InterAct Consortium; INTERVAL Study; ReproGen Consortium; T2D-Genes Consortium; MAGIC Investigators; Understanding Society Scientific Group; Rotter JI, Pospisilik JA, Rivadeneira F, Borecki IB, Deloukas P, Frayling TM, Lettre G, North KE, Lindgren CM, Hirschhorn JN, Loos RJF. Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity. Nat Genet. 2018;50:26-41. Epub 2017 Dec 22.

10. Saeed S, Bonnefond A, Tamanini F, Mirza MU, Manzoor J, Janjua QM, Din SM, Gaitan J, Milochau A, Durand E, Vaillant E, Haseeb A, De Graeve F, Rabearivelo I, Sand O, Queniat G, Boutry R, Schott DA, Ayesha H, Ali M, Khan WI, Butt TA, Rinne T, Stumpel C, Abderrahmani A, Lang J, Arslan M, Froguel P. Loss-of-function mutations in *ADCY3* cause monogenic severe obesity. Nat Genet. 2018;50:175-179. Epub 2018 Jan 8.

11. Loid P, Mustila T, Mäkitie RE, Viljakainen H, Kämpe A, Tossavainen P, Lipsanen-Nyman M, Pekkinen M, Mäkitie O. Rare variants in genes linked to appetite control and hypothalamic development in early-onset severe obesity. Front Endocrinol (Lausanne). 2020;11:81.

12. AbouHashem N, Zaied RE, Al-Shafai K, Nofal M, Syed N, Al-Shafai M. The spectrum of genetic variants associated with the development of monogenic obesity in Qatar. Obes Facts. 2022;15:357-365. Epub 2022 Jan 13.

13. Toumba M, Fanis P, Vlachakis D, Neocleous V, Phylactou LA, Skordis N, Mantzoros CS, Pantelidou M. Molecular modelling of novel *ADCY3* variant predicts a molecular target for tackling obesity. Int J Mol Med. 2022;49:10. Epub 2021 Nov 25.

14. Manco L, Pereira J, Fidalgo T, Cunha M, Pinto-Gouveia J, Padez C, Palmeira L. Next-generation sequencing of 12 obesity genes in a Portuguese cohort of patients with overweight and obesity. Eur J Med Genet. 2023;66:104728. Epub 2023 Feb 10.

15. Wong ST, Trinh K, Hacker B, Chan GC, Lowe G, Gaggar A, Xia Z, Gold GH, Storm DR. Disruption of the type III adenylyl cyclase gene leads to peripheral and behavioral anosmia in transgenic mice. Neuron. 2000;27:487-497.

16. Ando T, Haraguchi A, Matsunaga T, Natsuda S, Yamasaki H, Usa T, Kawakami A. Liraglutide as a potentially useful agent for regulating appetite in diabetic patients with hypothalamic hyperphagia and obesity. Intern Med. 2014;53:1791-1795. Epub 2014 Aug 15.

17. Li Z, Liang Y, Xia N, Lai Y, Pan H, Zhou S, Jiang F, He Y. Liraglutide reduces body weight by upregulation of adenylate cyclase 3. Nutr Diabetes. 2017;7:e265.

18. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol. 2015;7:280-293.
19. Kurtoğlu S, Hatipoğlu N, Mazıcıoğlu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. J Clin Res Pediatr Endocrinol. 2010;2:100-106. Epub 2010 Aug 2.
20. Yüksel B, Özbek MN, Mungan NÖ, Darendeliler F, Budan B, Bideci A, Çetinkaya E, Berberoğlu M, Evliyaoğlu O, Yeşilkaya E, Arslanoğlu İ, Darcan Ş, Bundak R, Ercan O. Serum IGF-1 and IGFBP-3 levels in healthy children between 0 and 6 years of age. J Clin Res Pediatr Endocrinol. 2011;3:84-88. Epub 2011 Jun 8.
21. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; 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. Epub 2015 Mar 5.
22. Wang Z, Li V, Chan GC, Phan T, Nudelman AS, Xia Z, Storm DR. Adult type 3 adenylyl cyclase-deficient mice are obese. PLoS One. 2009;4:e6979.
23. Chen X, Luo J, Leng Y, Yang Y, Zweifel LS, Palmiter RD, Storm DR. Ablation of type III adenylyl cyclase in mice causes reduced neuronal activity, altered sleep pattern, and depression-like phenotypes. Biol Psychiatry. 2016;80:836-848. Epub 2015 Dec 19.
24. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Dayani NE, Franke L, Fuyuno Y, Hart A, Juyal RC, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JY, Malekzadeh R, Westra HJ, Yamazaki K, Yang SK; International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium; Barrett JC, Alizadeh BZ, Parkes M, Bk T, Daly MJ, Kubo M, Anderson CA, Weersma RK. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet. 2015;47:979-986. Epub 2015 Jul 20.
25. Trapp CM, Censani M. Setmelanotide: a promising advancement for pediatric patients with rare forms of genetic obesity. Curr Opin Endocrinol Diabetes Obes. 2023;30:136-140. Epub 2023 Feb 1.
26. Cornejo-Estrada A, Nieto-Rodríguez C, León-Figueroa DA, Moreno-Ramos E, Cabanillas-Ramirez C, Barboza JJ. Efficacy of liraglutide in obesity in children and adolescents: systematic review and meta-analysis of randomized controlled trials. Children (Basel). 2023;10:208.
27. Wu L, Shen C, Seed Ahmed M, Östenson CG, Gu HF. Adenylate cyclase 3: a new target for anti-obesity drug development. Obes Rev. 2016;17:907-914. Epub 2016 Jun 3.
28. Hong SH, Goh SH, Lee SJ, Hwang JA, Lee J, Choi IJ, Seo H, Park JH, Suzuki H, Yamamoto E, Kim IH, Jeong JS, Ju MH, Lee DH, Lee YS. Upregulation of adenylate cyclase 3 (*ADCY3*) increases the tumorigenic potential of cells by activating the CREB pathway. Oncotarget. 2013;4:1791-1803.