

CASE REPORT

Treatment of hypoglycemia due to a rare pathogenic variant in *AKT2* with waxy maize heat-modified starch

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Key Clinical Message

The gain-of-function *AKT2* c.49G>A variant causes hypoketotic hypoglycemia with variable associated features. Due to lack of effective medications, treatment is primarily supportive. This report suggests waxy maize heat is a viable treatment option.

Abstract

The serine–threonine kinase *AKT2* is a critical mediator of insulin's anabolic effects, particularly cellular glucose uptake. The gain-of-function c.49G>A, p.(Glu17Lys) *AKT2* variant results in hypoketotic hypoglycemia with suppressed insulin and free fatty acid levels due to constitutive activation of the insulin signaling cascade. Although biochemical similarities exist among the eight individuals identified to date, the associated phenotype varies considerably. Treatment of these patients remains challenging, consisting primarily of frequent feeds with uncooked cornstarch. We describe a female with hemihypertrophy, developmental delay, and dysmorphic features who presented to our center with hypoglycemic seizures at age 6 months. Critical sample revealed hypoketotic hypoglycemia, undetectable insulin, and suppressed free fatty acids. Molecular testing confirmed a pathogenic c.49G>A, p.(Glu17Lys) *AKT2* mutation. Glycemic control was initially difficult to establish, with recurrent hypoglycemia despite high glucose infusion rates. Following in-hospital administration of waxy maize heat-modified starch at age 4-years, she remained euglycemic overnight, despite a previous report showing no benefit compared to uncooked cornstarch in an infant with the same mutation. Our report suggests waxy maize heat-modified starch is a viable treatment option for patients with activating c.49G>A *AKT2* mutations and provides further evidence of a broad phenotypic spectrum.

KEYWORDS

AKT2, hyperinsulinism, hypoglycemia, overgrowth, starch

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1 | INTRODUCTION

Insulin's crucial role in energy metabolism is coordinated by a post-receptor signaling cascade resulting in activation of Akt2, a serine–threonine kinase. Expressed predominantly in insulin-sensitive tissue, Akt2 promotes glucose uptake by regulating translocation of the glucose transporter-4 (GLUT4) from cytoplasm to the cell membrane.¹ Further, Akt2 mediates insulin's metabolic effects by suppressing gluconeogenesis¹ and lipolysis,² and stimulating lipogenesis.³

A growing body of evidence supports the clinical relevance of AKT2. Although rare, gain-of-function mutations in *AKT2* have been described in eight individuals with hypoketotic hypoglycemia.^{4–8} Despite undetectable insulin levels, their biochemical profiles closely resemble hyperinsulinemic hypoglycemia due to constitutive activation of the insulin signaling cascade. Additional reported features include accelerated linear growth, hemihypertrophy, and polyhydramnios.^{4,6} Other features have been variably reported including characteristic facies, acanthosis nigricans, developmental delay, and intellectual disability.^{5,6}

Given the detrimental neurodevelopmental impact of hypoglycemia in infancy and childhood, achieving euglycemia is critical. Management consists of frequent carbohydrate-rich feedings, often including uncooked cornstarch.⁵ However, with this approach, euglycemia is achieved at the expense of excess weight gain and impaired quality of life.⁷ Due to the anticipated lifelong duration of treatment, alternate therapeutic approaches are needed. An encouraging option is modified waxy maize heat-modified starch (WMHMS) which demonstrates improved tolerability and longer duration of action than uncooked cornstarch.⁹

We report a patient with an activating *AKT2* mutation managed with WMHMS, providing additional insight into the phenotypic spectrum.

2 | CLINICAL PRESENTATION

The proband is a 4-year-old female born large-for-gestational age at 38 weeks to healthy, non-consanguineous Caucasian parents. She was born via spontaneous vaginal delivery complicated by a 3-min shoulder dystocia with Apgar scores of 4 at 1 min, 7 at 5 min and 8 at 10 min. Birth weight was 4.14 kg (+2.6 SD), length 56 cm (+3.68 SD), and head circumference 36.5 cm (+2.7 SD). Pregnancy was remarkable only for a thickened nuchal fold and bilateral choroid plexus cysts on prenatal ultrasound. Amniocentesis was offered, but ultimately declined.

Shortly after birth, she developed mild hypoglycemia with a lowest documented blood glucose of 2.6 mmol/L.

Hypoglycemia was treated with a 10% dextrose infusion for the first 24 h of life, with a maximal glucose infusion rate (GIR) of 4.2 mg/kg/min. The presence of bilateral proptosis, periorbital edema, subtle left facial hypertrophy, and central hypotonia prompted evaluation for Beckwith-Wiedemann syndrome (BWS), which returned negative. Newborn metabolic screen was unremarkable, and microarray demonstrated a normal, female result. The hypoglycemia resolved spontaneously and was not investigated further.

At 6 months of age, she presented with a 5-min, generalized tonic–clonic seizure. At presentation, her blood glucose was 1.9 mmol/L and only transiently responsive to two 10% dextrose boluses. A 10% dextrose infusion was started, and she was admitted to hospital for further treatment and investigation. History was significant for several 1–2-min episodes of “staring” and decreased responsiveness occurring in the preceding 2 weeks. All episodes occurred in the morning, following periods of fasting overnight. Examination again revealed bilateral proptosis, periorbital edema, and central hypotonia (Figure 1). Auxology demonstrated weight 9.77 kg (+2.1 SD), length 78.3 cm (+5.1 SD), and head circumference 46 cm (+2.6 SD).

During admission, a critical sample was drawn due to ongoing hypoglycemia, which demonstrated hypoketotic hypoglycemia with a laboratory glucose of 1.8 mmol/L and undetectable serum beta-hydroxybutyrate. Cortisol was 207 nmol/L, considered inappropriate in the context



FIGURE 1 The proband's facial features including bilateral proptosis, periorbital edema, and subtle left facial hemihypertrophy.

of hypoglycemia. To exclude adrenal insufficiency, a standard dose ACTH stimulation test was performed and returned normal. The insulin level, acylcarnitine profile, urine organic acids, and plasma amino acids were not immediately available, as they are processed at an outside laboratory (Table 1).

A standard dose glucagon challenge was performed immediately following critical sample collection, resulting in an increase in bedside capillary glucose from 1.9 to 4.4 mmol/L. This is in keeping with hyperinsulinism, as an increment of at least 1.7 mmol/L suggests suppression of hepatic glycogenolysis by excess insulin.¹⁰ Given this glucagon response and hypoketotic hypoglycemia, a presumptive diagnosis of congenital hyperinsulinism was made. Although not initially available, the serum free fatty acid level returned suppressed at 227 μ mol/L, further supporting the initial diagnosis.

Initial stabilization was achieved with a bolus of 10% dextrose followed by continuous infusion. Despite GIR exceeding 15 mg/kg/min, she experienced recurrent episodes of hypoglycemia requiring repeated boluses of 10% dextrose. The insulin level subsequently returned undetectable, with no evidence of hemolysis or sample degradation causing an artifactual reduction in measured insulin. Octreotide and diazoxide were separately trialed given her persistent hypoglycemia and biochemical profile otherwise suggestive of hyperinsulinism. She was unable to tolerate a wean of intravenous dextrose or pauses in the infusion exceeding 30 min, despite octreotide doses of up to 20 μ g/kg/day or diazoxide of 15 mg/kg/day. Both medications were eventually discontinued, and she successfully transitioned to continuous nasogastric feeds providing a GIR of 13 mg/kg/min before discharge home.

Given the severity and persistence of hypoglycemia, a comprehensive panel for genes implicated in hypoglycemia, hyperinsulinemia, and ketone metabolism was

performed on peripheral blood leukocytes. This demonstrated a pathogenic heterozygous variant in *AKT2*, c.49G>A, p.(Glu17Lys) previously reported in other individuals with gain-of-function *AKT2* variants.^{4–8} To assess for possible mosaicism, DNA from skin fibroblasts was subsequently analyzed and found to be positive for the mutation.

Based on the glucose requirements reported in other cases,⁷ feeds were changed to three times daily followed by uncooked cornstarch at 1.5–2 g/kg to maintain euglycemia between feeds, in addition to an overnight continuous feed which provided an overall GIR of 4–5 mg/kg/min. More recently, a 4.3 g/kg dose of WMHMS (1.5 packets of Glycosade®, VitaFlo USA, NJ) was trialed in hospital with successful maintenance of overnight euglycemia without the addition of a continuous feed (Figure 2).

Currently, at 4 years of age, the hypoglycemia is well-controlled on her current regimen. She continues to exhibit central hypotonia, mild ataxia, and moderate global developmental delay. Owing to these features, a non-contrast brain MRI was performed which demonstrated subtle white matter loss in the parietal region without evidence of cystic change favored to be sequelae of previous ischemic insult. Investigations for metabolic causes of developmental delay returned negative including serum ammonia, copper, ceruloplasmin, homocysteine, amino acid and acylcarnitine profiles, as well as urine organic acids, oligosaccharides, sialic acid, uric acid, mucopolysaccharide screen, and creatine. In view of the constitutive insulin pathway activation, serial abdominal ultrasounds have been performed for tumor surveillance which have been unremarkable including liver and kidneys normal in size for her age.

3 | GENETIC TESTING

BWS testing was performed using methylation sensitive, multiplex ligation-dependent probe amplification at the 11p15 locus and Sanger sequencing of *CDKN1C*.

The gene panel for hypoglycemia, hyperinsulinemia, and ketone metabolism is a commercially available panel (Blueprint Genetics, Seattle, WA) and included next-generation sequencing of the following genes: *ABCC8*, *ACAT1*, *ACSF3*, *AGL*, *AKT2*, *ALDOA*, *ALDOB*, *DIS3L2*, *ENO3*, *EPM2A*, *FBP1*, *G6PC*, *GAA*, *GBE1*, *GCK*, *GLUD1*, *GPC3*, *GYG1*, *GYS1*, *GYS2*, *HADH*, *HMGCL*, *HMGCS2*, *HNF1A*, *HNF4A*, *INSR*, *KCNJ11*, *KDM6A*, *KMT2D*, *LAMP2*, *LDHA*, *MPV17*, *NHLRC1*, *NSD1*, *OXCT1*, *PC*, *PCK1*, *PDX1*, *PFKM*, *PGAM2*, *PGK1*, *PGM1*, *PHKA1*, *PHKA2*, *PHKB*, *PHKG2*, *PIK3CA*, *PIK3R2*, *PRKAG2*, *PRKAG3*, *PTF1A*, *PYGL*, *PYGM*, *RBCK1*, *SLC16A1*, *SLC2A2*, *SLC37A4*, and *UCP2*.

TABLE 1 Critical sample at presentation.

	Results	Reference range
Glucose, mmol/L	1.8	3.3–5.5
Serum ketones, mmol/L	<0.1	0.0–0.6
Urine ketones	Negative	–
Serum insulin, pmol/L	<14.4	43.0–194.0
Cortisol, nmol/L	207	133.0–537.0
Growth hormone, μ g/L	6.09	0.00–8.00
Free fatty acids, μ mol/L	227.0	100.0–900.0
Acylcarnitine	Normal	–
Plasma amino acids	Normal	–
Urine organic acids	Normal	–

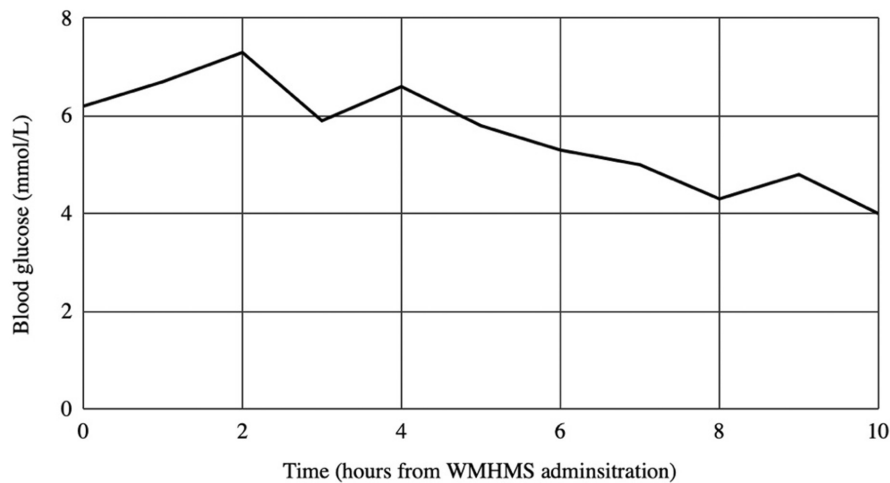


FIGURE 2 Overnight blood glucose following WMHMS administration.

TABLE 2 Summary of the clinical features of individuals with c.49G>A *AKT2* mutations.

Clinical features	Our patient	Hussain et al.			Garg et al.	Arya et al.	Dushar et al. ^a		Ochoa Molina, et al.
		M _A	M _B	F _C	M	F	M _A	M _B	M
Acanthosis nigricans					X		X _A		
Developmental Delay	X				X		X _A	X _B	X
Dysmorphic features ^b	X		X _B		X		X _A	X _B	X
Hemihypertrophy	X	X _A		X _C		X	X _A	X _B	
Hypoinsulinemic hypoglycemia	X	X _A	X _B	X _C	X	X	X _A	X _B	X
Hypoglycemic seizures	X	X _A		X _C	X		X _A	X _B	X
Hypotonia	X		X _B				X _A	X _B	
Macrosomia	X	X _A	X _B	X _C	X	X	X _A	X _B	
Polyhydramnios in utero			X _B		X			X _B	

^aThe older male proband is designated A and the younger B.

^bFacial features = exophthalmos, periorbital puffiness, proptosis, low-set ears, tented mouth, flat nasal bridge.

4 | DISCUSSION

In this case report, we describe a young female with hypoketotic hypoglycemia and dysmorphic features secondary to an activating *AKT2* mutation.

AKT2 is a serine/threonine kinase in the insulin signaling pathway. Insulin activates a transmembrane tyrosine kinase receptor, which phosphorylates insulin receptor substrate (IRS) proteins, leading to activation of phosphatidylinositol-3-kinase (PI3K).¹¹ PI3K in turn generates phosphatidylinositol (3,4,5)-trisphosphate which activates AKT.¹² Several AKT isoforms exist, of which AKT2 has been shown to mediate the metabolic actions of insulin.¹ The *AKT2* c.49G>A variant has been reported as de novo in patients with a similar clinical picture as our patient (Table 2). This gain-of-function *AKT2* variant leads to independent, constitutive activation of the insulin pathway in target tissues including liver, adipose, and skeletal muscle.⁷ Consequently, the biochemical profile resembles hyperinsulinism with suppressed free fatty

acids and ketones.¹³ However, insulin levels are undetectable due to negative feedback from the constitutively active signaling cascade.¹⁴

Despite variable clinical features, our patient's presentation overlaps considerably with previous reports, including growth parameters reflective of excess insulin action. The near universal presence of hemihypertrophy is suggestive of mosaicism, which would account for variability among other features including acanthosis nigricans, hypotonia, and facial dysmorphisms. Two previously published cases of *AKT2* mutation were found to be mosaic for the variant,⁷ and notably, two siblings inherited the variant from their unaffected father who was found to carry the variant at low level of mosaicism in his sperm.⁵ Mosaicism was not detected in our patient's peripheral blood leukocytes or skin fibroblasts, although it cannot be excluded at other tissues.

The variable occurrence of developmental delay is also notable, as this outcome is potentially preventable. Unfortunately, etiologic determination of our patient's

developmental delay is confounded by MRI findings consistent with perinatal asphyxia secondary to shoulder dystocia. These abnormalities are unlikely the consequence of her activating *AKT2* mutation, as normal brain MRIs have been documented in five individuals with the same mutation, four of whom have developmental delay or intellectual disability.^{4,5,7,8} Nevertheless, hypoglycemia is likely contributory to her delay given her presentation with hypoglycemic seizures and initial challenges obtaining glycemic control. Previous studies of children with congenital hyperinsulinism suggest development is adversely impacted by both hypoglycemic duration and severity, emphasizing the need for prompt recognition and treatment.¹⁵

At present, the mainstay of treatment is nutritional support with frequent, carbohydrate-rich feeds. Our patient initially required a markedly elevated GIR of 15 mg/kg/min in addition to intermittent dextrose boluses for breakthrough hypoglycemia. Although GIR is reported inconsistently, this exceeds the GIR of 3–5 mg/kg/min described in three previous cases.^{7,8} Current management is nevertheless comparable to other cases, with a GIR of 4–5 mg/kg/min provided by intermittent nasogastric feeds including uncooked cornstarch during the day and a continuous feed overnight.⁷ While this approach provides glycemic control, previously described limitations include obesity secondary to excess caloric intake.⁷

The metabolic and quality of life implications of frequent feeding make anti-hypoglycemic agents an attractive therapeutic option (Table 3). Consistent with previous reports,^{5,7} diazoxide and octreotide were ineffective in our patient as these agents target upstream

insulin release, as opposed to downstream signaling.¹³ Due to its action on this pathway, sirolimus was trialed in a sibling pair with activating *AKT2* mutations. The frequency of hypoglycemic episodes and carbohydrate need were reduced; however, overnight fasting was extended only up to 4 h.⁵ Although no serious adverse effects occurred, use of sirolimus in congenital hyperinsulinism and PIK3CA-related overgrowth spectrum has been associated with severe infectious and hematologic complications, including sepsis and anemia requiring blood transfusion.^{16,17} Sirolimus was only modestly effective in children with congenital hyperinsulinism, further highlighting the need for novel therapeutic approaches.¹⁷

An enticing option is WMHMS, which is approved for children >2 years with glycogen storage disease (GSD) in Canada. WMHMS is a slow-release carbohydrate, shown to provide improved glycemic control with less gastrointestinal discomfort than uncooked cornstarch.⁹ Despite its purported benefits, WMHMS did not improve fasting blood glucose compared to uncooked cornstarch in a 6-month-old-male with an activating *AKT2* mutation (Table 3).⁸ However, this result should be interpreted cautiously as expression of pancreatic amylase is substantially reduced in infancy, impairing starch digestion.¹⁸ Age-related differences in digestion could explain the contrasting improvement in fasting tolerance observed in our patient following WMHMS administration. Unfortunately, overnight hypoglycemia necessitated WMHMS discontinuation after three nights at home. Given otherwise unchanged daytime feeds, a conceivable explanation is increased energy expenditure at home, where activity is unrestricted. The family

TABLE 3 Summary of attempted treatments in individuals with c.49G>A *AKT2* mutations.

Treatment	Outcome (number of patients)	Authors
Diazoxide	No response (4)	Dushar et al., Hussain et al., Ochoa Molina et al.
Intravenous Glucagon	No response (1)	Hussain et al.
Low-protein diet	No response (1)	Hussain et al.
Octreotide	No response (3)	Dushar et al., Hussain et al., Ochoa Molina et al.
Recombinant human growth hormone	No response (1)	Hussain et al.
Sirolimus	Fasting extended from 3 to 4 h with reduced number of overnight feeds and increased morning fasting glucose (2)	Dushar et al.
Somatostatin	No response (1)	Hussain et al.
Uncooked cornstarch	Used alongside frequent feeding to maintain euglycemia (5). Excess weight gain described in one patient ⁷	Arya et al., Dushar et al., Garg et al., Hussain et al., Ochoa Molina et al.
Waxy maize heat-modified starch	No difference in glycemic control compared to uncooked cornstarch (1)	Ochoa Molina et al.

remains willing to use WMHMS and an increased dose of 5.8 g/kg was recommended, though it has yet to be attempted by the family.

Before trialing WMHMS, we suggest first achieving glycemic control with uncooked cornstarch to establish carbohydrate requirements and tolerability. Instructions for converting enteral feeds and uncooked cornstarch into an approximate dose of WMHMS are available through the manufacturer (Glycosade®, VitaFlo USA, NJ). Blood glucose should be measured hourly within the patient's established fasting window and more frequently beyond it.⁸ Response is defined by improved fasting tolerance or a reduction in the required GIR. Ultimately, individualized treatment targets are necessary given the anticipated continued absence of clinical guidelines for patients with the rare c.49G>A *AKT2* variant.

5 | CONCLUSION

We describe the ninth individual presenting with hypoketotic hypoglycemic secondary to an activating *AKT2* mutation causing autonomous activation of the downstream insulin signaling cascade. Our patient's dysmorphic features, developmental delay, and hemihypertrophy provide additional evidence of a broad phenotypic spectrum. Due to the anticipated lifelong duration of treatment, safe and tolerable options are needed. Our initial success with WMHMS indicates it is a promising option, although additional research is needed to establish dosing.

AUTHOR CONTRIBUTIONS

Madeline Parker: Resources; writing – original draft; writing – review and editing. **Daphne Yau:** Conceptualization; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

In accordance with journal policy, written informed consent was obtained from the patient's parents to publish this report.

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REFERENCES

- Hers I, Vincent EE, Tavaré JM. Akt signalling in health and disease. *Cell Signal*. 2011;23:1515-1527. doi:10.1016/j.cellsig.2011.05.004
- Fischer-Posovszky P, Tews D, Horenburg S, Debatin KM, Wabitsch M. Differential function of Akt2 and Akt1 in human adipocytes. *Mol Cell Endocrinol*. 2012;358:135-143. doi:10.1016/j.mce.2012.03.018
- Wan M, Leavens KF, Saleh D, et al. Postprandial lipid metabolism requires signaling through Akt2 independent of the transcription factors FoxA2, FoxO1, SREBP1c. *Cell Metab*. 2011;14:516-527. doi:10.1016/j.cmet.2011.09.001
- Arya VB, Flanagan SE, Schober E, Rami-Merhar B, Ellard S, Hussain K. Activating *AKT2* mutation: hypoinsulinemic hypoketotic hypoglycemia. *J Clin Endocrinol Metab*. 2014;99(2):391-394. doi:10.1210/jc.2013-3228
- Dushar M, Nowaczyk J, Pyrzak B, et al. Efficacy and safety of sirolimus therapy in familial hypoinsulinemic hypoglycemia caused by *AKT2* mutation inherited from the mosaic father. *Eur J Med Genet*. 2021;64(12):104368. doi:10.1016/j.ejmg.2021.104368
- Garg N, Bademci G, Foster J 2nd, Sıklar Z, Berberoglu M, Tekin M. MORFAN syndrome: an infantile hypoinsulinemic hypoketotic hypoglycemia due to an *AKT2* mutation. *J Pediatr*. 2015;167(2):489-491. doi:10.1016/j.jpeds.2015.04.069
- Hussain K, Challis B, Rocha N, et al. An activating mutation of *AKT2* and human hypoglycemia. *Science*. 2011;334(6055):474. doi:10.1126/science.1210878
- Ochoa Molina MF, Poggi H, De Toro V, Mendoza C, Hussain K. Facial dysmorphic features in a patient with Nonketotic hypoglycemia and a pathogenic variant in the *AKT2* gene. *AACE Clin Case Rep*. 2021;8(3):109-112. doi:10.1016/j.aace.2021.11.006
- Hijazi G, Pai N, Nagy LL, et al. Use of waxy maize heat modified starch in the treatment of children between 2 and 5 years with glycogen storage disease type I: a retrospective study. *Mol Genet Metab Rep*. 2019;21:1-6. doi:10.1016/j.ymgmr.2019.100536
- Ferrara C, Patel P, Becker S, Stanley CA, Kelly A. Biomarkers of insulin for the diagnosis of hyperinsulinemic hypoglycemia in infants and children. *J Pediatr*. 2016;168:212-219. doi:10.1016/j.jpeds.2015.09.045
- White MF. The insulin signalling system and the IRS protein. *Diabetologia*. 1997;40:S2-S17. doi:10.1007/s001250051387
- Hemmings BA, Restuccia DF. PI3K-PKB/Akt pathway. *Cold Spring Harb Perspect Biol*. 2012;4(9):a011189. doi:10.1101/csh-perspect.a011189
- Banerjee I, Salomon-Estebanez M, Shah P, Nicholson J, Cosgrove KE, Dunne MJ. Therapies and outcomes of congenital hyperinsulinism-induced hypoglycaemia. *Diabet Med*. 2019;36(1):9-21. doi:10.1111/dme.13823

14. Minic M, Rocha N, Harris J, et al. Constitutive activation of AKT2 in humans leads to hypoglycemia without fatty liver or metabolic dyslipidemia. *J Clin Endocrinol Metab.* 2017;102(8):2914-2921. doi:[10.1210/jc.2017-00768](https://doi.org/10.1210/jc.2017-00768)
15. Steinkrauss L, Lipman TH, Hendell CD, Gerdes M, Thornton PS, Stanley CA. Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. *J Pediatr Nurs.* 2005;20(2):109-118.
16. Parker VER, Keppler-Noreuil KM, Faivre L, et al. Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. *Genet Med.* 2019;21:1189-1198. doi:[10.1038/s41436-018-0297-9](https://doi.org/10.1038/s41436-018-0297-9)
17. Szymanowski M, Estebanez MS, Padidela R, et al. mTOR inhibitors for the treatment of severe congenital hyperinsulinism: perspectives on limited therapeutic success. *J Clin Endocrinol Metab.* 2016;101(12):4719-4729. doi:[10.1210/jc.2016-2711](https://doi.org/10.1210/jc.2016-2711)
18. Were FN, Lifschitz C. Complementary feeding: beyond nutrition. *Ann Nutr Metab.* 2018;73(1):20-25. doi:[10.1159/000490084](https://doi.org/10.1159/000490084)

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