Molecular Genetics and Metabolism Reports 38 (2024) 101058

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

A novel *GK* Ala469Val variant resulting in glycerol kinase deficiency with concurrent hepatoblastoma: A case report

Domenic Filingeri [a,1], Sarah Mackey [b,1], Haley Soller [c], Alissa Guarneri-Tragone [a], James Cooper [b], Oscar Escobar [a], Jirair K. Bedoyan [c,*]

[a] Division of Pediatric Endocrinology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh and University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[b] Division of Hematology-Oncology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh and University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[c] Division of Genetic and Genomic Medicine, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh and University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

ARTICLE INFO

Keywords:
Glycerol kinase deficiency
GK gene
Hepatoblastoma

ABSTRACT

Glycerol kinase deficiency (GKD) is a rare X-linked condition where glycerol cannot be phosphorylated to glycerol-3-phosphate, a key component of gluconeogenesis. Clinical presentation varies widely. We present a novel variant of the responsible *GK* in a patient with concurrent hepatoblastoma, whose course was complicated by hypoglycemia. Hepatoblastoma has not previously been described with GKD, highlighting the need for further research into GKD and its potential role in the pathogenesis of some forms of hepatoblastoma.

1. Introduction

Glycerol kinase deficiency (GKD; OMIM: 307030, GeneID: 2710) is a rare X-linked recessive disease resulting from variants in *GK*, a 23-exon gene found on the short arm of the X chromosome at position 21.2 (Xp21.2) [1]. Glycerol kinase is a key enzyme in the regulation of glycerol uptake and metabolism with generation of glycerol-3-phosphate (G3P), a crucial component in gluconeogenesis [1]. Presentation of GKD varies greatly, but hypoglycemia due to impaired gluconeogenesis is well described. GKD occurs as part of an Xp21 contiguous gene deletion syndrome or as isolated GKD [2]. The most common combination of the Xp21 contiguous gene deletion syndrome is the lack of *DMD*, *GK* and/or *NROB1*, which has been described as Complex Glycerol Kinase Deficiency (CGKD) [3,4]. Adrenal hypoplasia congenita, due to deletion of *NROB1*, is usually the first condition to appear in CGKD with symptoms of adrenal insufficiency. Depending on the size of the Xp21 contiguous gene deletion, additional deletions of *CYBB* and/or *OTC*, about 7.5 Mb from *GK*, can present with clinical symptoms of chronic granulomatosis disease and/or ornithine transcarbamylase deficiency, respectively. Here, we present a patient with GKD and hepatoblastoma. While many cases of hepatoblastoma are sporadic in nature, there are known genetic predisposition syndromes associated with hepatoblastoma, including but not limited to familial adenomatous polyposis, Beckwith-Wiedemann syndrome, glycogen storage disease (particularly GSD type I), and Trisomy 18 [5–7]. Hepatoblastoma has not previously been reported with GKD.

2. Case presentation

A 9-month-old ex-35-week gestational age male presented to the emergency room with fussiness. On exam, the patient was found to have a large heterogeneous liver mass by ultrasound, which was later confirmed by CT scan of the chest/ abdomen/pelvis, where the result was suspicious for localized hepatoblastoma. Interventional radiology-guided biopsy of the liver mass was diagnostic for hepatoblastoma with pure fetal histology. Initial alpha fetoprotein was notable for levels >61,000 ng/mL (reference range: <20) (Table 1). At 10 months-of-age, the patient hepatoblastoma treatment with cisplatin monotherapy and resection of the mass after two cycles of chemotherapy at 13 months-of-age. The patient's post-operative course was complicated by resistant hypoglycemia. Pediatric endocrinology was consulted to assist with management of hypoglycemia, which required IV dextrose at a glucose

* Corresponding author at: Division of Genetic and Genomic Medicine, Department of Pediatrics, University of Pittsburgh School of Medicine and UPMC Children's Hospital of Pittsburgh, Faculty Pavilion, 4401 Penn Avenue, Suite 1200, Pittsburgh, PA 15224, USA.
E-mail address: jbedoyan@pitt.edu (J.K. Bedoyan).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ymgmr.2024.101058
Received 13 October 2023; Received in revised form 17 January 2024; Accepted 18 January 2024
Available online 23 January 2024
2214-4269/© 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

infusion rate of 6.6 mg/kg/min with subsequent dextrose 10% (D10) to maintain euglycemia. A baseline cortisol level was robust at 33 μg/dL. Adrenocorticotrophic hormone was requested but not collected. A critical sample during his admission was obtained while euglycemic. This sample showed a robust growth hormone concentration of 29.8 ng/mL (reference range: <6) in the absence of hypoglycemia (with concomitant glucose concentration of 145 mg/dL). A genetics work-up included urine organic acids (UOA), which revealed a significantly elevated urinary excretion of glycerol, suspicious for X-linked glycerol kinase deficiency, confirmed on a repeat UOA sample (Table 1).

Another episode of hypoglycemia occurred while the patient was NPO in preparation for a port removal surgery. Given his continued hypoglycemia, a diagnostic fast was completed at 17 months-of-age. The patient was able to maintain euglycemia during the diagnostic fast for 13.5 hours before the patient's blood glucose decreased below 50 mg/dL. Critical sample labs were obtained with a concomitant glucose level of 41 mg/dL (Table 1). These results showed growth hormone at 1.3 ng/mL, insulin at 2.0 μIU/mL, C-peptide <0.2 ng/mL, cortisol at 16 μg/dL, beta hydroxybutyrate at 2.12 mmol/L (reference range: 0.02–0.27) and free fatty acids at 2.22 mmol/L (reference range: 0.6–1.5). Lactate was 1.4 mmol/L (reference range: 0.5–2.2). After obtaining the critical labs, glucagon was administered and the patient's subsequent measurements of glucose (lab and meter) continued to be low (47 mg/dL, 42 mg/dL, 47 mg/dL, 32 mg/dL, and 34 mg/dL; average 40 mg/dL), suggesting lack of response to glucagon administration (Table 1). He received a D10 bolus for blood sugar levels ~30 mg/dL with subsequent blood sugar rise to 148 mg/dL. During a second episode of hypoglycemia while fasting, repeat measurements showed elevated growth hormone (14.7 ng/mL) and beta hydroxybutyrate (2.63 mmol/L), and normal plasma amino acids.

Outpatient follow up with genetics resulted in exome sequencing at 17 months-of-age with samples from both parents used for variant segregation analysis. Exome sequencing identified a hemizygous maternally inherited variant of uncertain significance (VUS) in *GK* (hg19;chrX:30739017C > T, NM_001205019.1:c.1406C > T, p.Ala469Val in exon 18). No other causative variant(s) in disease genes related to our patient's phenotype were identified. Family history was noted for a full brother who died at 32 weeks gestational age and a half-brother sharing mother with apparent "sugar" issues, not otherwise specified, and maternal grandmother with two early spontaneous abortions. Segregation of *GK* variant in the half-brother was not evaluated.

3. Discussion

Here we present an interesting case of X-linked GKD due to a previously unknown genetic variation of *GK* in a patient with hepatoblastoma. Exome sequencing identified a hemizygous *GK* c.1406C > T; p.Ala469Val variant in our proband that was maternally inherited and classified as VUS. Multiple bioinformatic tools [SIFT, MutationTaster, LRT, DANN (score of 0.999) and REVEL (score of 0.954)] predicts this Ala to Val amino acid replacement would be damaging and the Ala469 residue is highly conserved across the vertebrate species examined. This previously undescribed variant is absent in ClinVar and from the gnomAD population dataset (0 of approximately 182,500 alleles). Based on the American College of Medical Genetics and Genomics (ACMG) guidelines for variant classification [8], this variant holds only one moderate (PM2) and two supporting (PP3 and PP4) phenotype-based criteria and would not make the cutoff for reclassification as likely pathogenic because a minimum of four supporting criteria are needed. However, we strongly postulate that this variant explains this patient's clinical GKD diagnosis with his constellation of feeding intolerance, gastroesophageal reflux disease, and hypoglycemia along with significant elevation of urinary glycerol on multiple urinary organic acids analyses. This variant has not been reported in an individual affected with a *GK*-related disorder. Furthermore, *GK* variants and GKD association with hepatoblastoma have not previously been reported.

Genetic predisposition to hepatoblastoma, hepatocellular adenoma, and hepatocellular carcinoma have been noted in inborn errors of metabolism (IEM) like GSD, urea cycle disorders such as ornithine transcarbamylase, argininosuccinic acid lyase, arginase, and citrin deficiencies, dysregulations of methionine adenosyltransferases, and hereditary tyrosinemia type 1, but not with GKD [5–7,9–16]. The pathogenesis of the rare association of hepatoblastoma and hepatocellular carcinoma with GSD and other IEM is not well understood. Previous suggested mechanisms include glucose/insulin imbalance, cellular glycogen imbalance, autophagy impairment, inflammation activation, proto-oncogene activation and activation of multiple tumor-promoting pathways, exposure to toxic metabolites such as argininosuccinic acid and/or arginine, and/or impairment of the glutathione metabolism (the major antioxidant in the liver) [17–22]. To our knowledge, this is the first report of hepatoblastoma and GKD occurring together. The possibility of dual unrelated diagnoses in our patient cannot be excluded. The hepatoblastoma could be unrelated to the patient's GKD, although his clinical course may have been complicated by the GKD diagnosis. However, further studies of this *GK* variant (Ala469Val) using *in vivo* and *ex vivo* models could delineate the downstream effects of this variant with impact on downstream signaling, impairment of autophagy, activation of tumor-promoting pathways, and/or impairment of glutathione metabolism, thus providing insight as to whether disruption of any such process(es) may have contributed to this patient's hepatoblastoma.

Table 1
Summary of relevant labs on patient with hepatoblastoma and glycerol kinase deficiency.

Age (mo)	Clinical course	AFP (ng/mL)	Serum Glucose (mg/dL)	Insulin (μIU/mL)	Cortisol (μg/dL)	GH (ng/mL)	BOHB (mmol/L)	UOA
9	Pre-chemo	61,283	101	–	–	–	–	–
10	Chemotherapy	13,168	87	–	–	–	–	–
12	Post-chemo	12,867	79	–	–	–	–	–
13	Post-chemo	–	85	–	–	–	–	–
13	Hepatectomy	–	77	–	–	–	–	–
13	POD #2	–	45 (145 after IV dextrose)	2.8	33	29.8	0.70	SEG
14	Post-Surgery	971	83	–	–	–	–	SEG
14.5	Post-Surgery	112	71	–	–	–	–	–
17	Post-surgery	–	41 (diag fast)	2.0	16	1.3	2.12	–
17	Post-surgery	–	32–47 (after glucagon)	–	–	14.7	2.63	–
20	Post-surgery	11	97	–	–	–	–	–
23	Post-surgery	8	95	–	–	–	–	–
26	Post-surgery	6	80	–	–	–	–	–

Abbreviations: AFP, alpha fetoprotein; BOHB, beta-hydroxybutyrate; chemo, chemotherapy; diag fast, diagnostic fasting study; GH, growth hormone; IV, intravenous; mo, month; POD, post-op day; ref., reference; SEG, significantly elevated glycerol; and UOA, urine organic acids. Dash implies, not done.
Reference ranges: AFP, ref. < 20 ng/mL; serum glucose, ref. 70–126 mg/dL; insulin, ref. < 17.0 μIU/mL; cortisol, diurnal peak range 3–21 μg/dL; GH, ref. < 6 ng/mL; and BOHB, ref. 0.02–0.27 mmol/L.

CRediT authorship contribution statement

Domenic Filingeri: Writing – original draft. **Sarah Mackey:** Writing – original draft. **Haley Soller:** Data curation. **Alissa Guarneri-Tragone:** Writing – review & editing. **James Cooper:** Writing – review & editing. **Oscar Escobar:** Writing – review & editing. **Jirair K. Bedoyan:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

References

[1] Available from, https://www.ncbi.nlm.nih.gov/gene/?term=2710.

[2] K.M. Dipple, Y.H. Zhang, B.L. Huang, L.L. McCabe, J. Dallongeville, T. Inokuchi, M. Kimura, H.J. Marx, G.O. Roederer, V. Shih, S. Yamaguchi, I. Yoshida, E. R. McCabe, Glycerol kinase deficiency: evidence for complexity in a single gene disorder, Hum. Genet. 109 (2001) 55–62, https://doi.org/10.1007/s004390100545.

[3] A. Sehgal, J. Stack, Complex glycerol kinase deficiency: an X-linked disorder associated with adrenal hypoplasia congenita, Indian J. Pediatr. 72 (2005) 67–69, https://doi.org/10.1007/BF02760584.

[4] C.M. Stanczak, Z. Chen, Y.H. Zhang, S.F. Nelson, E.R. McCabe, Deletion mapping in Xp21 for patients with complex glycerol kinase deficiency using SNP mapping arrays, Hum. Mutat. 28 (2007) 235–242, https://doi.org/10.1002/humu.20424.

[5] H. Chen, Q. Guan, H. Guo, L. Miao, Z. Zhuo, The genetic changes of Hepatoblastoma, Front. Oncol. 11 (2021) 690641, https://doi.org/10.3389/fonc.2021.690641.

[6] N. Shirazi, B.P. Kalra, N.K. Bhat, S. Wasim, Embryonal hepatoblastoma with co-existent glycogen storage disease in a seven-month-old child, J. Clin. Diagn. Res. 10 (2016) ED09–10, https://doi.org/10.7860/JCDR/2016/15984.7239.

[7] H.J. Jang, H.R. Yang, J.S. Ko, J.S. Moon, J.Y. Chang, J.K. Seo, Development of hepatocellular carcinoma in patients with glycogen storage disease: a single center retrospective study, J. Korean Med. Sci. 35 (2020) e5, https://doi.org/10.3346/jkms.2020.35.e5.

[8] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W.W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, H.L. Rehm, A.L.Q.A. 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. 17 (2015) 405–424, https://doi.org/10.1038/gim.2015.30.

[9] J.M. Wilson, O.A. Shchelochkov, R.C. Gallagher, M.L. Batshaw, Hepatocellular carcinoma in a research subject with ornithine transcarbamylase deficiency, Mol. Genet. Metab. 105 (2012) 263–265, https://doi.org/10.1016/j.ymgme.2011.10.016.

[10] L. Cheng, Y. Liu, W. Wang, J.L. Merritt, M. Yeh, Hepatocellular adenoma in a patient with ornithine transcarbamylase deficiency, Case Reports Hepatol. 2019 (2019) 2313791, https://doi.org/10.1155/2019/2313791.

[11] J. Baruteau, E. Jameson, A.A. Morris, A. Chakrapani, S. Santra, S. Vijay, H. Kocadag, C.E. Beesley, S. Grunewald, E. Murphy, M. Cleary, H. Mundy, L. Abulhoul, A. Broomfield, R. Lachmann, Y. Rahman, P.H. Robinson, L. MacPherson, K. Foster, W.K. Chong, D.A. Ridout, K.M. Bounford, S. N. Waddington, P.B. Mills, P. Gissen, J.E. Davison, Expanding the phenotype in argininosuccinic aciduria: need for new therapies, J. Inherit. Metab. Dis. 40 (2017) 357–368, https://doi.org/10.1007/s10545-017-0022-x.

[12] J.P. Tsang, W.L. Poon, H.M. Luk, C.W. Fung, C.K. Ching, C.M. Mak, C.W. Lam, T. S. Siu, S. Tam, V.C. Wong, Arginase deficiency with new phenotype and a novel mutation: contemporary summary, Pediatr. Neurol. 47 (2012) 263–269, https://doi.org/10.1016/j.pediatrneurol.2012.06.012.

[13] J. He, J. Zhang, X. Li, H. Wang, C. Feng, F. Fang, S. Shu, A case report: Can citrin deficiency lead to hepatocellular carcinoma in children? Front. Pediatr. 7 (2019) 371, https://doi.org/10.3389/fped.2019.00371.

[14] E.M. Imseis, J.S. Bynon, C. Thornhill, Case of hepatocellular carcinoma in a patient with hereditary tyrosinemia in the post-newborn screening era,, World J. Hepatol. 9 (2017) 487–490, https://doi.org/10.4254/wjh.v9.i9.487.

[15] M. Koo, G.S. Lipshutz, S.D. Cederbaum, C. Lassman, Biopsy-proven hepatocellular carcinoma in a 53-year-old woman with arginase deficiency, Pediatr. Dev. Pathol. 20 (2017) 517–521, https://doi.org/10.1177/1093526617697058.

[16] R.M. Pascale, C.F. Feo, D.F. Calvisi, F. Feo, Deregulation of methionine metabolism as determinant of progression and prognosis of hepatocellular carcinoma, Transl. Gastroenterol. Hepatol. 3 (2018) 36, https://doi.org/10.21037/tgh.2018.06.04.

[17] J.H. Cho, Y.M. Lee, S.H. Bae, J.Y. Chou, Activation of tumor-promoting pathways implicated in hepatocellular adenoma/carcinoma, a long-term complication of glycogen storage disease type Ia, Biochem. Biophys. Res. Commun. 522 (2020) 1–7, https://doi.org/10.1016/j.bbrc.2019.11.061.

[18] S. Gautam, L. Zhang, C. Lee, I. Arnaoutova, H.D. Chen, R. Resaz, A. Eva, B. C. Mansfield, J.Y. Chou, Molecular mechanism underlying impaired hepatic autophagy in glycogen storage disease type Ib, Hum. Mol. Genet. 32 (2023) 262–275, https://doi.org/10.1093/hmg/ddac197.

[19] P. Bannasch, D. Mayer, H.J. Hacker, Hepatocellular glycogenosis and hepatocarcinogenesis, Biochim. Biophys. Acta 605 (1980) 217–245, https://doi.org/10.1016/0304-419x(80)90005-0.

[20] S.C.S. Nagamani, S. Ali, R. Izem, D. Schady, P. Masand, B.L. Shneider, D.H. Leung, L.C. Burrage, Biomarkers for liver disease in urea cycle disorders, Mol. Genet. Metab. 133 (2021) 148–156, https://doi.org/10.1016/j.ymgme.2021.04.001.

[21] E.S. Jin, C.R. Malloy, G. Sharma, E. Finn, K.N.Z. Fuller, Y.G. Reyes, M.A. Lovell, S. C. Derderian, J.A. Schoen, T.H. Inge, M.G. Cree, Glycerol as a precursor for hepatic de novo glutathione synthesis in human liver, Redox Biol. 63 (2023) 102749, https://doi.org/10.1016/j.redox.2023.102749.

[22] A. Al-Mass, P. Poursharifi, M.L. Peyot, R. Lussier, I. Chenier, Y.H. Leung, A. Ghosh, A. Oppong, E. Possik, Y. Mugabo, R. Ahmad, R. Sladek, S.R. Murthy Madiraju, F. Al-Mulla, M. Prentki, Hepatic glycerol shunt and glycerol-3-phosphate phosphatase control liver metabolism and glucodetoxification under hyperglycemia, Mol. Metab. 66 (2022) 101609, https://doi.org/10.1016/j.molmet.2022.101609.